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D-Cycloserine Effects on Extinction of Conditioned Responses to Drug-Related Cues

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Abstract

D-cycloserine (DCS) is an *N*-methyl-D-aspartate (NMDA) receptor partial agonist that facilitates extinction of conditioned fear in animals and cue exposure therapy (CET) for fear and anxiety disorders in people. Recent preclinical and clinical studies have examined the effect of DCS on extinction of conditioned responses elicited by cues paired with administration of or withdrawal from drugs of abuse, including physiological responses, craving, withdrawal, and drug-seeking behavior. DCS facilitates extinction and blunts postextinction recovery of these responses in animal models, including place conditioning and drug self-administration, but DCS effects on CET in substance users/abusers are less robust. Some of the null effects in the clinical literature might be attributable to issues related to sample size, data characteristics, DCS administration, and participant characteristics, among others. In this review we describe the preclinical and clinical literatures on DCS modulation of extinction of addiction-related conditioned responses, consider possible limitations of the clinical studies that have been published to date, and propose ways of designing future clinical studies so as to maximize the probability of detecting a DCS effect. We also discuss concerns with regard to potential harmful effects of DCS-coupled CET in addicts and describe how these concerns might be mitigated. We conclude that it is as yet unclear whether DCS-coupled CET might be a useful approach in the treatment of addiction.

Keywords

Addiction; clinical; craving; cue exposure therapy; D-cycloserine; extinction

The long-term success rate of addiction treatments remains poor. It is estimated that 40%–60% of patients relapse within 1 year of completing a treatment program (1). Improved clinical approaches are urgently needed and likely will arise through behavioral and neurobiological research.

Among the contributors to addictive behavior are craving and withdrawal elicited by cues associated with drug use or acute withdrawal (2,3). These cues (conditioned stimuli [CS]) acquire the ability to elicit these responses (conditioned responses [CRs]) via Pavlovian

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conditioning (4). Addiction treatment programs emphasize avoidance of drug-related cues, but a more effective strategy might be to lessen the ability of the cues to elicit CRs. To this end, therapies that weaken associations between cues and drug-related states might be useful. Cue exposure therapy (CET) is based on extinction, a form of conditioning in which CRs are weakened through exposure to a CS in the absence of the event or state it formerly predicted. Results with CET as a treatment for addiction have been modest (5); however, it might be possible to strengthen CET with cognitive enhancers. Preclinical work indicates that a drug called D-cycloserine (DCS) facilitates extinction in animal models, and clinical work shows that DCS augments CET for anxiety disorders (6).

The possibility that DCS might also enhance CET for addiction is addressed in recent studies. Here we review data on DCS modulation of extinction of CRs to drug-related cues. We begin with a description of DCS and its effects on extinction of conditioned fear and drug-related CRs. We then consider the limitations of the clinical DCS/CET studies that have been conducted to date, propose ways in which future studies could be optimized, and address concerns about the use of DCS in addiction treatment. We conclude by identifying future directions.

DCS and *N*-Methyl-D-Aspartate Receptors

Glutamate is the major excitatory neurotransmitter in the mammalian brain. The *N*-methyl-D-aspartate (NMDA) receptor is one of three major types of glutamate receptors. It is a doubly gated ion channel whose activation requires both agonist binding and membrane depolarization (7). Once activated, the receptor fluxes sodium ion, calcium, and potassium ion, contributing to further membrane depolarization and activating intracellular signaling pathways. NMDA receptors are involved in synaptic plasticity, learning, and memory (8,9).

DCS is an NMDA receptor partial agonist that binds to the strychnine-insensitive glycine binding site on the NR1 NMDA receptor subunit, thereby increasing the activation probability of the receptor (10). DCS is a less efficient modulator of NMDA receptor function than the endogenous ligands glycine and D-serine, and as such its effects can be dose-dependent. At high doses DCS acts as a functional antagonist by displacing the more efficacious endogenous ligands (11), but at moderate doses DCS facilitates NMDA receptor-dependent forms of synaptic plasticity as well as learning and memory (12,13).

DCS Facilitates Fear Extinction

Fear conditioning is a form of Pavlovian conditioning in which an organism is exposed to contingent pairings of a CS (e.g., a tone) with a salient event called an unconditioned stimulus (US) (e.g., a mild electric shock) and acquires a fear CR. This basic learning process is an essential element of psychiatric disorders including phobias and posttraumatic stress disorder (14). Treatment programs for anxiety disorders seek to restore normal functioning by mitigating maladaptive fear CRs.

One method of reducing CRs is extinction. The term “extinction” refers to both a training protocol involving exposure to the CS in the absence of the US and the outcome of that training (a decline in the CR). Extinction is not due to forgetting because it requires

nonreinforced CS exposure rather than the simple passage of time (15,16). Extinction also is not due to "unlearning." Extinguished CRs can be recovered without additional CS-US pairings through three mechanisms: reinstatement, in which extinguished CRs reappear after unsignaled US presentations (17); renewal, in which extinguished CRs reappear upon testing outside of the extinction context (18); and spontaneous recovery, in which extinguished CRs reappear over time (19).

Fear extinction is an NMDA receptor-dependent form of learning. It is blocked by NMDA receptor antagonists administered immediately before extinction training (20) and is enhanced in genetically modified mice overexpressing the NR2B NMDA receptor subunit (9). DCS facilitates fear extinction when administered before or immediately after extinction training (20) and might reduce recovery of extinguished fear, although the evidence is mixed (21,22).

DCS Facilitates CET for Anxiety Disorders

CET is an extinction-based protocol used to treat anxiety disorders. It involves exposing a patient to a feared stimulus (CS), typically in a graded fashion, until the fear CR declines. Like fear extinction in preclinical models, CET for fear and anxiety is enhanced by DCS.

The first clinical study to examine DCS-coupled CET involved patients with acrophobia (fear of heights) who underwent a standardized CET protocol in a virtual reality glass elevator (23). Patients received DCS or placebo before each of two CET sessions. During the second session the DCS group reported less fear and rode the virtual elevator to higher floors than did the placebo group. They also showed sustained benefits in long-term follow-up sessions. Subsequent studies examined the effect of DCS on CET for obsessive-compulsive disorder (24–26), social anxiety disorder (27,28), spider fear (29), and panic disorder (30,31). Overall the results have been positive. There have been some null effects (25,29), but a meta-analysis of the literature suggests significant enhancement (32).

Conditioning and Addiction

Like anxiety disorders, addiction involves conditioning. Cues associated with drug use and acute withdrawal, such as drug paraphernalia, elicit conditioned craving and withdrawal that contribute to ongoing drug use and relapse (2–4). Preclinical work in paradigms such as place conditioning and drug self-administration (SA) (33) indicates that CRs elicited by drug-related cues in animals are subject to extinction. However, CET involving exposure to drug-related cues is not particularly effective at reducing drug-related CRs in addicts (5). One strategy to potentially improve the efficacy of CET is to couple it with DCS. Preclinical and clinical studies have examined the feasibility of this approach, as described in the following sections.

DCS Effects on Drug-Related Cues

The literature on DCS-coupled extinction of drug-related CRs includes studies involving nicotine, cocaine, ethanol, morphine, and amphetamine.

Nicotine

There are no published preclinical studies on DCS modulation of extinction of nicotine-related CRs, but there are two clinical studies (Table 1). Santa Ana *et al.* (34) recruited smokers for a study modeled after the acrophobia study (23). Participants received DCS or placebo before each of two CET sessions involving handling cigarettes, ashtrays, and lighters. Galvanic skin response (GSR) and urge to smoke (craving) were measured throughout. In follow-up sessions conducted in the absence of DCS or placebo, smoking behavior was assessed as expired carbon monoxide and urinary cotinine (a nicotine metabolite), and participants reported the number of cigarettes smoked/day and completed a smoking urge questionnaire. The main finding was that DCS facilitated extinction of cue-elicited GSR and craving. There was some evidence of a DCS effect on smoking behavior, consisting of a decrease in expired carbon monoxide that was statistically significant at the first follow-up and which just missed significance at the second, but overall smoking behavior was unaffected.

Kamboj *et al.* (35) sought to extend the findings of Santa Ana *et al.* (34) in a study employing two CET sessions, each involving imaginal cues, handling cigarettes and lighters, and viewing a video of a man smoking. During the first CET session, participants completed instruments assessing mood, bodily symptoms, and tonic craving; then took DCS or placebo; then 1 hour later repeated the instruments assessing mood and bodily symptoms; and finally began cue exposure. During cue exposure, GSR was measured continuously and participants reported episodic craving periodically. The second CET session was similar to the first but omitted the mood and bodily symptom reports. Follow-up sessions were conducted in the absence of DCS or placebo and involved assessments of attention, tonic craving, and smoking behavior. Kamboj *et al.* (35) found no significant DCS effects, contrary to the findings of Santa Ana *et al.* (34). There was a trend in the first CET session toward decreased euphoria after DCS administration, but there was a trend in the opposite direction on this same measure in another study from the same group (36). There also was a trend in the second follow-up toward a reduction in one of four factors (emotionality) of the instrument assessing tonic craving.

Cocaine

The literature on DCS modulation of extinction of CRs to cocaine cues includes both preclinical and clinical studies.

Preclinical—The preclinical literature includes conditioned place preference (CPP) and SA studies (Table 2). Interestingly, the findings with the two paradigms are somewhat different.

In CPP, DCS consistently enhances extinction rate. This effect is seen with pre- or immediate postextinction but not with delayed postextinction administration, indicating that DCS modulates extinction memory consolidation (37). The DCS effects on CR recovery after extinction are inconsistent and include no effect on cocaine-primed reinstatement (38), reduced spontaneous recovery (39,40), and increased spontaneous recovery with a relatively high DCS dose (40). In one study the effect of DCS on cocaine-primed reinstatement was unclear due to limited reinstatement in the control group (39).

By contrast, in SA studies, DCS reduces CR recovery after extinction measured as context specificity of cue-induced reinstatement (41) and reacquisition rate (42). DCS effects on extinction rate are inconsistent and might be dose-dependent (42,43), species-dependent (42), and/or parameter-dependent (44). There is one report of increased cocaine-seeking behavior after DCS-coupled cue exposure (45), but this was attributed to enhanced memory reconsolidation (46) rather than an interaction with extinction.

Clinical—Price *et al.* (47) recruited cocaine-dependent but nontreatment-seeking individuals for a study examining DCS-coupled cocaine CET (Table 1). Participants received DCS or placebo before each of two CET sessions involving handling simulated cocaine, drug paraphernalia, and money, and watching a video depicting cocaine use. Heart rate (HR) and craving were assessed immediately before and at intervals throughout cue exposure. One week later participants reported craving and cocaine use in the preceding week. The major finding was that, during the first CET session, the placebo group showed an initial increase in craving that declined as the session progressed, whereas the DCS group showed an increase that persisted throughout the session. The group difference in the latter part of the session was large but did not reach statistical significance; comparisons of the DCS and placebo groups at 30, 45, and 60 min into the CET session were $p = .10$, .06, and .06, respectively. This effect was not seen in the second CET session, nor was there a group difference in the follow-up. There were no significant group differences in HR.

Alcohol

The literature on DCS modulation of extinction of CRs to alcohol cues includes both preclinical and clinical studies.

Preclinical—In CPP (48) and SA (49) studies, DCS reduced CR recovery after extinction, measured as reacquisition of ethanol CPP and ethanol-primed reinstatement of ethanol-seeking behavior (Table 2). There was no effect of DCS on extinction rate in the CPP study. There was a reduction in ethanol-seeking behavior in the SA study that might not be extinction-related because it was present from the beginning of extinction training.

Clinical—There are three published clinical studies examining DCS-coupled alcohol CET (Table 1).

Kamboj *et al.* (36) recruited nontreatment-seeking, nonalcohol-dependent participants. In each of two CET sessions, participants took DCS or placebo, then 1 hour later reported craving, mood, and bodily symptoms. Cue exposure then began and involved handling and smelling a favored drink and imagining being in a drinking environment. GSR was measured continuously and craving was assessed periodically. In a follow-up session conducted in the absence of DCS or placebo, participants reported craving, mood, and bodily symptoms and completed an attentional task. In all three sessions participants reported the amount of alcohol they had consumed in the past 2 days. There was no effect of DCS except for increased contentedness and a trend toward increased euphoria before cue exposure, which was interpreted as a mild stimulant effect. However, there was a trend in the opposite direction on the euphoria measure in another study from the same group (35).

A similar study was conducted by Watson *et al.* (50), who recruited alcohol-dependent participants. In each of three CET sessions, participants completed scales assessing anxiety, depression, and obsessive-compulsive drinking, then took DCS or placebo (sessions 1 and 2) or no tablet (session 3). Cue exposure began 2 hours later and involved seeing, handling, and smelling a favored drink. Craving, mood states, blood pressure, and HR were assessed periodically. There was no DCS effect on any measure.

Finally, Hofmann *et al.* (51) recruited heavy drinkers, some of whom were alcohol-dependent. In each of three CET sessions, participants took DCS or placebo 1 hour before cue exposure consisting of handling, smelling, and imagining consuming a favored drink. Just before cue exposure and periodically throughout, HR was measured and participants reported craving. There were two follow-up test sessions conducted in the absence of DCS which involved a brief cue exposure protocol. There were no effects of DCS other than an increase in craving in the first test session, which was significant with some statistical tests but not others. This effect is reminiscent of the finding of Price *et al.* (47) that DCS tended to increase cocaine craving, except in that study the effect was seen on-drug whereas in this study it was off-drug.

Morphine and Amphetamine

There are three preclinical studies involving morphine and amphetamine (Table 2). Lu *et al.* (52) reported no DCS effect on morphine CPP extinction rate, although there seems to be a dose-dependent facilitation early in extinction training, before floor effects emerged. DCS had no effect on morphine-primed reinstatement of CPP. Myers and Carlezon (53) found that DCS facilitates the rate of extinction of morphine withdrawal-induced conditioned place aversion. CR recovery after extinction was not measured in this study. Finally, Sakurai *et al.* (54) found that rats that received hippocampal DCS infusions before the first of four amphetamine CPP test sessions showed facilitated extinction in tests 2–4. CR recovery after extinction was not measured in this study.

Perspective on the Clinical Literature

Preclinical studies consistently report DCS facilitation of extinction, but clinical studies seem less promising. Tables 1 and 2 are formatted to indicate the valence of DCS effects: bold text indicates facilitation of extinction or reduction of CR recovery; unhighlighted text indicates no effect; and italicized text indicates increased CR recovery or enhanced reconsolidation. Crossed-out cells indicate no data. Bold predominates in Table 2 (preclinical), and of the unhighlighted cells, several are instances in which no effect was predicted (e.g., with delayed postextinction DCS administration). By contrast, Table 1 (clinical) is almost entirely unhighlighted.

This disparity is puzzling. It is possible that DCS effects on extinction of CRs to drug-related cues are limited to nonhuman animals, although this seems unlikely given the positive effects of DCS on CET for anxiety disorders. By contrast, addictive behaviors might be less sensitive to DCS if the underlying neural basis of addiction is more complex than that of anxiety disorders. Another possibility is that at least some of the null effects in the clinical literature are Type 2 errors. Issues related to sample size, data characteristics,

DCS administration, participant characteristics, and other factors arguably increase the likelihood of false negatives. Here we consider these issues and describe strategies to address them.

Sample Size and Data Characteristics

Cognitive enhancement can be difficult to demonstrate. To have a reasonable chance of detecting a DCS effect, studies should have a sufficiently large sample size for adequate statistical power; reasonably consistent data; reactivity (CRs) to drug cues in all participants at the beginning of extinction/CET, obtained if necessary through exclusion of nonresponders; and a sufficiently robust CR and slow extinction to avoid floor effects. These criteria are particularly challenging to meet in clinical studies, and not surprisingly, several of the addiction CET studies fail to meet one or more of them. For example, two of the studies (47,50) involved very small sample sizes, and in one (50) there was significant variability and floor effects due to a majority of participants exhibiting little to no CR. Future studies should strive to fulfill all of these criteria.

DCS Administration

High DCS doses might not facilitate CET for anxiety disorders (32,55,56), consistent with the dose-dependency of DCS effects on other measures (see “DCS and NMDA Receptors” section). Thus, some of the null effects in the addiction CET literature might be related to the choice of high (250 mg) (50) or borderline-high (125 mg) doses (35,36). Future clinical studies should consider the possibility of DCS dose-dependency and include more than one dose.

Long pretreatment intervals (>2 hours) might reduce DCS efficacy (32,55,56). Cerebrospinal fluid levels of DCS peak 1–2 hours after administration of a 50-mg dose (56). Because DCS facilitates extinction memory consolidation (37,57), administration should be timed such that levels peak shortly after CET sessions. In two of the addiction CET studies, DCS was administered 2 hours before the onset of CET sessions, which might have limited its efficacy (47,50). Future clinical studies should involve a pretreatment interval of no more than 1 hour or include more than one interval.

DCS might lose efficacy over multiple, closely spaced administrations (58,59). In the Santa Ana *et al.* (34) study—the only clinical study to report a convincing DCS effect—DCS administrations were separated by 2 weeks. In all others, inter-treatment intervals were 1–7 days. In future clinical studies DCS administrations should be separated by 2 weeks or more.

Finally, DCS might lose efficacy after chronic exposure to antidepressants (59). Some of the addiction CET studies excluded people who were taking this type of medication (34,47,51); one expressly did not exclude on this basis (50); and some were not clear about exclusion criteria (35,36). Future clinical studies should be limited to people not undergoing concurrent antidepressant treatment.

Participants

There have been some notable failures in the human fear and anxiety literature to obtain a DCS effect on extinction/CET (29,60). Because these studies are unique in that they involved subclinical populations, it has been suggested that DCS modulates CET in clinical populations only (32,55,56). The choice of a subclinical (36) or mixed clinical/subclinical sample (51) might have contributed to the lack of a DCS effect in some of the addiction/CET studies. Future clinical studies should include only participants meeting diagnostic criteria for substance dependence or examine subclinical and clinical subgroups separately.

Abstinence from drug use after CET sessions is critical. If a participant used drugs shortly after a session, this could diminish any benefit of the session by strengthening associations between cues and drug-related states through re-conditioning. Compounding the problem, the cognitive-enhancing effects of DCS might strengthen these associations further. Relapse after sessions was a potential problem in all of the addiction CET studies. In some, participants were instructed to remain abstinent after CET sessions but abstinence at this time point was not confirmed with an objective measure (34,35,50,51). In others, participants were not instructed to remain abstinent after CET sessions (36) or were hospitalized overnight after one CET session but not another (47). Future clinical studies should safeguard against relapse by instructing participants to remain abstinent after CET sessions and confirming abstinence via drug screening at an appropriate post-CET interval or hospitalizing participants overnight after CET sessions.

Finally, DCS and placebo groups should be matched in terms of history, frequency, and severity of drug use. If the DCS group had more severe substance use problems than did the placebo group, as might have been the case in two of the addiction CET studies (47,51), DCS effects might be difficult to detect.

Cognitive-Behavioral Interventions

The Santa Ana *et al.* (34) study was the only one in which participants were taught cognitive-behavioral (CBT) techniques (e.g., relaxation, decisional balance, and guided visualization of abstinence and associated benefits) to cope with craving. Whether this contributed to the positive DCS effect in this study is unclear. In humans DCS might modulate declarative learning processes more robustly than implicit learning processes (35), although putative differential interactions of DCS with different learning systems are controversial (61). Another possibility is that participants who receive CBT training are less likely to relapse after CET sessions (“Participants” section). It might be valuable to include CBT training in future clinical studies.

Response Metrics

The preclinical literature suggests that, for some drugs of abuse or response measures, DCS might facilitate extinction rate or decrease CR recovery but not both (Cocaine: Preclinical section). Thus, the timing of CR assessment in clinical studies should be considered carefully. The longest follow-up interval in the addiction CET literature is 16–17 days (35). By comparison, some of the fear and anxiety CET studies feature follow-up intervals of 1–3

months (23,27). Future clinical studies should assess DCS effects not only during and shortly after CET but also at longer posttreatment intervals.

It is important to recognize that CET (whether DCS-coupled or not) addresses only one element of a behavior that has multiple determinants, and might not have a measurable effect on substance use unless it is part of a more comprehensive treatment program. Response measures in clinical studies should be chosen carefully so as not to overlook potentially subtle behavioral effects. A narrow focus on cue-elicited CRs such as autonomic reactivity, craving, and withdrawal might be most appropriate. Null effects on substance use should not be interpreted as a broad failure of the approach.

Concerns

DCS-coupled CET for addiction has some potential to be harmful. For example, CET could provoke relapse in abstinent participants because it involves exposure to cues that elicit craving and withdrawal. If DCS enhances cue-elicited craving (47,50), relapse might be even more likely. In nonabstinent participants, drug use shortly after CET sessions could be counterproductive for other reasons (“Participants” section). Even in the absence of relapse, DCS could enhance memory reconsolidation rather than extinction (45,62), which would have the effect of strengthening rather than weakening cue-drug associations. These concerns are all valid; however, there are ways to address them, some of which we have already described. To avoid relapse after CET sessions, studies could be restricted to inpatients or involve a short-term hospital stay (“Participants” section). It might also be valuable to incorporate CBT training to facilitate coping with craving (Cognitive-Behavioral Interventions section). To avoid DCS modulation of reconsolidation, CET protocols should result in measurable within-session extinction, indicating that the extinction “trace” rather than the reconsolidation “trace” is dominant (63). DCS also could be given immediately after CET sessions rather than before, because DCS modulates extinction memory consolidation (37,57). An added benefit of this approach is that DCS could be given selectively after “good” sessions (i.e., those in which measurable extinction occurred), thereby avoiding concerns about reconsolidation and minimizing the number of DCS administrations (32,64).

Future

Future preclinical work should address issues directly relevant to clinical application of DCS and advance basic understanding of DCS mechanisms. Specific goals include clarifying whether DCS has differential effects on extinction rate versus CR recovery; identifying brain region(s) where DCS effects are mediated (37,41,54); and exploring the neurobiology of extinction of drug-related CRs (33), which could facilitate development of new putative cognitive enhancers for CET (65).

The modest DCS effects in the addiction CET studies that have been conducted to date should not discourage continuing clinical work. First, there is ample justification for this approach in the preclinical addiction and clinical anxiety literatures. Second, the existing clinical studies have weaknesses that complicate interpretation of null effects. Clinical studies designed to mitigate these limitations arguably will be more likely to identify a

positive DCS effect should one exist. If not, null effects could comfortably be attributed to a true lack of effect rather than Type 2 error.

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Table 1

Clinical Literature on DCS-Coupled CET for Addiction

Participants	CET Protocol	Groups[a]	Time of DCS Admin
Nicotine			
Men and women; ages 18–55 yrs; smoked at least 10 cigarettes/day for previous yr; smoked ~24 yrs on average; not taking measures to quit; abstained for at least 11 hours before CET sessions; instructed to abstain for at least 4 hours after CET sessions	Handling cigarettes, ashtrays, and lighters	DCS 50 mg (n = 8), placebo (n = 10)	1 hour pre-CET sessions
Men and women; ages 18–65 yrs; smoked at least 15 cigarettes/day; nicotine-dependent; not taking measures to quit; abstained for 2 hours before CET sessions; instructed to abstain for 2 hours after CET sessions	Imagining craving scenarios; handling cigarettes and lighters; video depicting a man smoking	DCS 125 mg (n = 13), placebo (n = 13)	~1 hour pre-CET sessions
Cocaine			
Men and women; at least 18 yrs old; met DSM-IV criteria for cocaine dependence; nontreatment-seeking; abstinent for at least 24 hours before all sessions	Handling paraphernalia, simulated cocaine, and money; video depicting cocaine use	DCS 50 mg (n = 5), placebo (n = 5)	2 hours pre-CET sessions
Alcohol			
Men and women; ages 18–65 yrs; heavy drinkers; nontreatment-seeking; did not meet criteria for alcohol dependence; abstinent for at least 12 hours before all sessions	Imaginal cues; handling and smelling favored alcoholic drink	DCS 125 mg (n = 19), placebo (n = 17)	1 hour pre-CET sessions
Men and women; >18 yrs old; DSM-IV diagnosis of alcohol dependence; in treatment (inpatient or outpatient); abstinent for minimum of 2 weeks; experiencing alcohol craving	Graded CET: seeing a picture of favored drink; seeing a bottle or can of favored drink; opening drink; pouring drink and raising to lips without sipping	DCS 250 mg (n = 7), placebo (n = 7)	2 hours pre-CET sessions 1 and 2
Men ages 21–50 yrs; heavy drinkers; nontreatment-seeking; instructed to remain abstinent for study period; exhibited craving to alcohol cues at intake	Seeing a glass of favored drink; handling drink; smelling drink; imaginal cues	DCS 50 mg (n = 10), placebo (n = 10)	1 hour pre-CET sessions 1–3

Measurement Time Point	Measure	DCS Effect	Reference
CET session 1 (week 1)	Skin conductance	NE	Santa Ana *et al.* (34)
	Cue-induced urge to smoke	**Facilitated extinction**	
Follow-up 1 (week 2)	Number of cigarettes smoked	NE	
	Smoking urges questionnaire	NE	
	Urinary drug screen (cotinine)	NE	
	Expired CO	**Reduced**	
CET session 2 (week 3)	Skin conductance	**Facilitated extinction**	
	Cue-induced urge to smoke	**Facilitated extinction**	
Follow-up 2 (week 4)	Number of cigarettes smoked	NE	
	Smoking urges questionnaire	NE	
	Urinary drug screen (cotinine)	NE	
	Expired CO	**Reduced (trend)**	

Measurement Time Point	Measure	DCS Effect	Reference
CET session 1	Attentional bias task	NE	Kamboj *et al.* (35)
	Mood and bodily symptoms (baseline)	**Decreased euphoria (trend)**	
	Tonic craving (baseline)	NE	
	Episodic craving (CET)	NE	
	Skin conductance (CET)	NE	
CET session 2	Tonic craving (baseline)	NE	
	Episodic craving (CET)	NE	
	Skin conductance (CET)	NE	
First follow-up (2–3 days after CET session 2)	Attentional bias task	NE	
	Tonic craving	NE	
Second follow-up (by telephone; 14 days after first follow-up)	Number of cigarettes smoked	NE	
	Tonic craving	**Reduced emotionality (trend)**	
	Time since last cigarette	NE	
CET session 1 (day 1)	Craving (baseline)	NE	Price *et al.* (47)
	HR (baseline)	NE	
	Craving (CET)	*Increased (trend)*	
	HR (CET)	NE	
CET session 2 (day 2)	Craving (baseline)	NE	
	HR (baseline)	NE	
	Craving (CET)	NE	
	HR (CET)	NE	
One week follow-up	Craving	NE	
	Cocaine use	NE	
CET sessions 1 and 2: postplacebo or -DCS (baseline)	Craving, mood, bodily symptoms	*Increased contentedness and trend toward increased euphoria*	Kamboj *et al.* (36)
CET sessions 1 and 2: during/after CET	Craving	NE	
	Skin conductance	NE	
	Alcohol consumed in past 2 days	NE	
Follow-up	Alcohol consumed in past 2 days	NE	
	Attentional bias task	NE	
CET sessions 1 and 2 and follow-up	Craving	NE	Watson *et al.* (50)
	Physiological resp (BP, HR)	NE	
	Mood states	NE	
CET sessions 1–3 (days 1, 4, and 8)	Craving	NE	Hofmann *et al.* (51)
	HR	NE	

Measurement Time Point	Measure	DCS Effect	Reference
Test session 1 (day 11)	Craving	*Increased*[b]	
	HR	NE	
Test session 2 (day 15)	Craving	NE	
	HR	NE	

Bold text indicates facilitation of extinction or reduction of conditioned response (CR) recovery. Unhighlighted text indicates no effect.

Admin, administration; BP, blood pressure; CET, cue exposure therapy; CO, carbon monoxide; DCS, D-cycloserine; HR, heart rate; NE, no effect; resp, response.

[a] Numbers indicate number of participants finishing all phases of study.

[b] Statistically significant with some statistical tests but not others.

Table 2

Preclinical Literature on DCS-Facilitated Extinction of CRs to Drug-Related Cues

Drug of Abuse	Paradigm	Species	CS	Extinction Protocol	DCS Dose	Time of DCS Admin	Effect Extinction	Recovery	Reference
Cocaine	CPP	Rats	Context	Repeated test	15 mg/kg	Immed post-ext	**Facilitated**	~~	Botreau *et al.* (37)
						4 hours post-ext	NE	~~	
					10 μg/side (BLA)	Immed post-ext	**Facilitated**	~~	
		Mice	Context	Repeated test	15 mg/kg	Immed pre-ext	**Facilitated**	NE (cocaine-primed reinst)	Kelley *et al.* (38)
		Rats	Context	Repeated test	15 mg/kg	Immed post-ext	**Facilitated**	?	Paolone *et al.* (39)
				Re-confine	15 mg/kg	Immed post-ext	**Facilitated**	**Reduced SR**	
		Mice	Context	Re-confine	15 mg/kg	Immed post-ext	NE	**Reduced SR**	Thanos *et al.* (40)
					30 mg/kg	Immed post-ext	**Facilitated**	*Increased SR*	
	SA	Rats	Resp-cont cue	Noncontingent cues; resp prevented	10 μg/side (BLA)	20 min pre-reactivation	*Increased drug-seeking; reconsolidation effect*	~~	Lee *et al.* (45)
		Rats	Resp-cont cues	Noncontingent cues; resp prevented	15 mg/kg	Immed post-ext	~~	**Reduced context specificity of cue-induced reinst**	Torregrossa *et al.* (41)
					10 μg/side (NAc)	Immed post-ext	~~	**Reduced context specificity of cue-induced reinst**	
					10 μg/side (LA)	Immed post-ext	~~	NE	
					10 μg/side (hipp)	Immed post-ext	~~	NE	
					10 μg/side (IL)	Immed post-ext	~~	NE	
					10 μg/side (PL)	Immed post-ext	~~	NE	
		Rats	Resp-cont cue	Resp-cont cue but not cocaine	15 mg/kg	30 min pre-ext	NE	**Impaired reacquisition**	Nic Dhonnchadha *et al.* (42)
					30 mg/kg	30 min pre-ext	**Facilitated**	**Impaired reacquisition**	
					30 mg/kg	Immed post-ext (with handling)	NE	**Impaired reacquisition**	
					30 mg/kg	6 hours post-ext	NE	NE	

Drug of Abuse	Paradigm	Species	CS	Extinction Protocol	DCS Dose	Time of DCS Admin	Effect Extinction	Recovery	Reference
		Squirrel monkeys	Resp-cont cue	Resp-cont cue but not cocaine	3 mg/kg	30 min pre-ext	NE	**Impaired reacquisition**	
					10 mg/kg	30 min pre-ext	NE	**Impaired reacquisition**	
		Rats	Resp-cont cue	Resp-cont cue but not cocaine	15 mg/kg	Immed post-ext	NE	~~	Thanos *et al.* (43)
					30 mg/kg	Immed post-ext	**Facilitated**	~~	
		Mice	Resp-cont cue	Resp-cont cue but not cocaine	15 mg/kg	Immed post-ext	**Facilitated**	~~	Thanos *et al.* (44)
					30 mg/kg	Immed post-ext	**Facilitated**	~~	
				Resp had no programmed consequences	15 mg/kg	Immed post-ext	NE	~~	
					30 mg/kg	Immed post-ext	NE	~~	
Ethanol	CPP	Mice	Floor texture	Repeated test	30 mg/kg	Immed pre-ext	NE	**Impaired reacquisition**	Groblewski *et al.* (48)
					60 mg/kg	Immed pre-ext	NE	**Impaired reacquisition**	
	SA	Rats	Resp-cont cue	Resp-cont cue but no ethanol	5 mg/kg	1 hour pre-ext	?	**Impaired ethanol-primed reinst**	Vengeliene *et al.* (49)
Morphine	CPP	Mice	Context	Re-confine	7.5 mg/kg	Pre-ext	NE	NE	Lu *et al.* (52)
					15 mg/kg	Pre-ext	NE	NE	
					30 mg/kg	Pre-ext	**Facilitated**	NE	
	CPA (morphine withdrawal)	Rats	Context	Re-confine	15 mg/kg	Immed pre-ext	**Facilitated**	~~	Myers and Carlezon (53)
Amph.	CPP	Rats	Context	Repeated test	10 μg (hipp)	20 min pre-ext	**Facilitated**	~~	Sakurai *et al.* (54)

Bold text indicates facilitation of extinction or reduction of CR recovery. Unhighlighted text indicates no effect. Italicized text indicates increased CR recovery or enhanced reconsolidation. Crossed-out cells indicate no data. Question marks indicate findings that are difficult to interpret.

Admin, administration; Amph., amphetamine; BLA, basolateral amygdala; CPA, conditioned place aversion; CPP, conditioned place preference; CS, conditioned stimulus; ext, extinction; hipp, hippocampus; IL, infralimbic cortex; immed, immediately; LA, lateral amygdala; NAc, nucleus accumbens; PL, prelimbic cortex; reinst, reinstatement; resp-cont, response-contingent; SA, self-administration; SR, spontaneous recovery; other abbreviations as in Table 1.