Review

Cue exposure therapy for the treatment of alcohol use disorders: A meta-analytic review

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HIGHLIGHTS

- No meta-analytic review has examined the effect of cue exposure therapy on alcohol use disorders (AUD).
- We reviewed and analyzed the effect of CET targeting AUD.
- CET showed no to small additional effects on primary outcomes and small to moderate additional effects on secondary outcomes compared to active control conditions.
- The overall quality of evidence was graded as low due to high risk of bias, inconsistency, imprecision and suspected publication bias.
- More studies with sounder methodological methods are warranted.

ABSTRACT

Cue Exposure Therapy (CET) is a behavioristic psychological approach to treating substance use disorders (SUD). Prior systematic reviews have found CET to be ineffective when targeting SUDs. The effect of this approach on alcohol use disorders (AUD) seems more promising at trial level but has yet to be systematically reviewed and quantitatively analyzed. Therefore, we aimed to examine the effectiveness of CET targeting AUD compared to active control conditions in a meta-analytic review. Following a systematic search of the literature, a total of seven controlled trials were identified. CET showed no to small additional effects on drinking intensity and drinking frequency, a small additional effect on total drinking score and a moderate additional effect on latency to relapse. Stratification and analysis of a-priori defined trial covariates revealed that CET may have an increased effect in the longer term, and that CET combined with urge-specific coping skills may be the better option for treating AUD than conventional CET. Also, CET may prove less effective when comparing it to cognitive behaviour therapy as opposed to other active control conditions. The overall quality of evidence was graded low due to high risk of bias, inconsistency, imprecision and suspected publication bias. Sounder methodological trials are needed to derive a firm conclusion about the effectiveness of CET for treating AUD.

1. Background

Cue Exposure Therapy (CET) is a behavioristic psychological approach to treating substance use disorders (SUD) whereby individuals are exposed to relevant drug cues to extinguish conditioned responses (Conklin & Tiffany, 2002; Drummond, Cooper, & Glautier, 1990; Marlatt, 1990). The approach is based on learning theory, more specifically its classical conditioning component, in which the drug itself represents an unconditioned stimulus (US) and the effects of the drug are unconditioned responses (UR). Previously neutral stimuli, such as the visual, auditive, olfactory and tactile attributes of the drug and the different contexts in which it is taken become associated with the US, after which they turn into

conditioned stimuli (CS) capable of triggering conditioned responses (CR) by frequent pairing with the UR. Through the process of associative learning, both the drug and associated stimuli can evoke similar UR and CR, which over time will elicit cue-induced cravings causing addictive behavior (Drummond, 2000; Everitt & Robbins, 2005; Pavlov & Anrep, 2003).

Learning theory predicts that drug addiction is learned through reinforcement mechanisms, and that CR can be extinguished (e.g. unlearned or weakened by new learning) by exposing afflicted individuals to relevant drug cues. With prolonged exposure, CR will gradually lose their reinforcing properties (Bouton, 2002; Drummond, 2000; Mackintosh, 1974; Myers & Davis, 2002; Pavlov & Anrep, 2003; Rescorla & Wagner, 1972; Skinner, 1938; Wise, 1988). When learning theory is operationalized through conventional CET, individuals are exposed to US or CS in vivo whilst their habitual behavior, i.e. drug use is hindered. This procedure supposedly diminishes the contingency between the US and CS, eventually leading to the extinction of CR. Hence, the goal of this approach is to extinguish learned responses to drug cues through repeated non-reinforced exposure (Drummond et al., 1990; Marlatt, 1990).

Although there is abundant experimental evidence from animal and human models in favor of extinction learning (Berridge & Kringelbach, 2008; Bouton, 2004; Everitt & Robbins, 2016; Mackintosh, 1974; Pavlov & Anrep, 2003), the extent to which the operationalization of learning theory through CET is an effective intervention for SUD has been a matter of debate for more than a decade due to inconsistent findings. Early findings provided by non-controlled studies were promising, but the current state of the art is that some studies have reported positive effects of CET (Childress, McLellan, Ehrman, & O'Brien, 1988; Childress, McLellan, & O'Brien, 1986; Franken, de Haan, van der Meer, Haffmans, & Hendriks, 1999; O'Brien, Childress, McLellan, & Ehrman, 1990), others no effect (Dawe, Rees, Mattick, Sitharthan, & Heather, 2002; Dawe et al., 1993; McLellan, Childress, Ehrman, O'Brien, & Pashko, 1986) and others have even reported opposed effects related to cravings and drug intake outcomes (Corty & McFall, 1984; Lowe, Green, Kurtz, Ashenberg, & Fisher, 1980; Marissen, Franken, Blanken, van den Brink, & Hendriks, 2007). Subsequent systematic reviews have concluded that there is no consistent evidence for the effectiveness of CET targeting SUD (Conklin & Tiffany, 2002; Martin, LaRowe, & Malcolm, 2010).

However, these reviews have compiled all abuse and dependence disorders into one SUD category, and knowledge is therefore lacking about the effectiveness of CET targeting drug-specific disorders. For instance, the effectiveness of CET for alcohol use disorders (AUD), the most prevalent and harmful of all SUDs (Nutt, King, & Phillips, 2010; Patel et al., 2016; Rehm, 2011), has yet to be systematically reviewed. In contrast to the majority of other drugs of choice, alcohol is both legal and socially accepted in most parts of the Western World leading to pervasive exposure. The massive endorsement of alcohol by the industry through advertising coupled with lenient regulation continues to play a major role in promoting social acceptance and widespread physical availability of the drug. Not only is alcohol an accompaniment to a growing array of social situations (e.g. at bars, clubs, restaurants, cafes, work gatherings, private parties etc.) but it has also become enmeshed in everyday living (e.g. through media exposure; at kiosks, supermarkets, gas stations etc.), making exposure to alcohol and related cues impossible to avoid. Therefore, it may be problematic to compile all abuse and dependence disorders into one overall SUD category.

Thus, an important dilemma is raised when applying CET specifically to the treatment of AUD. On the one hand, CET represents a controversial approach to the treatment of SUD (including AUD) seen in light of the previously mentioned lack of empirical evidence in favor of CET. On the other hand, it can be argued that CET is a rational approach to the treatment of AUD given that it aims to prepare afflicted individuals to cope with cue-induced cravings experienced during pervasive exposure to alcohol and conditioned stimuli across diverse contexts. Furthermore, in the single available meta-analysis examining the effectiveness of CET for SUD, the majority of reported effect sizes in the studies targeting AUD were clinically significant (Cohens d ≥ 0.50

(Cohen, 1988)), and none of them indicated an opposed effect (Conklin & Tiffany, 2002), which supports the second notion that CET may be a rational approach to the treatment of AUD. Although the purpose of Conklin and Tiffany's meta-analysis was not to disentangle the effects of CET on different drugs of choice and the authors therefore did not comment on drug-specific disorders, it is observable that the effects of CET targeting AUD are much more favorable than for other SUDs (Conklin & Tiffany, 2002). In addition, other researchers have emphasized the notion that CET targeting AUD may indeed have positive outcomes (Loeber, Croissant, Heinz, Mann, & Flor, 2006; Monti, 2002; Monti & Rohsenow, 2003). Nonetheless, the research on CET targeting AUD has not received much attention in the last decade, which may, in part, be due to lack of empirical evidence supporting the use of CET for treating addictive disorders.

Hence, on this background it is seems important to disentangle the effects of CET on AUD from other SUDs in a systematic review and meta-analysis.

1.1. Aims

We aimed to examine the overall effectiveness of CET targeting AUD compared to active control conditions in an explorative systematic review and meta-analysis. Using stratified analyses, we further investigated whether overall effects were influenced by the following study design characteristics: (1) type of AUD population, (2) type of CET, (3) type of comparison group, (4) treatment setting, and (5) treatment goals.

2. Methods

2.1. Protocol and registration

The present meta-analysis was conducted according to recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Collaboration, 2011). Findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The inclusion criteria and analyses were specified in advance and registered in the international Prospective Register of Systematic Reviews (PROSPERO): registration no. CRD42016036919.

2.2. Eligibility criteria

To be eligible for inclusion in this meta-analysis, a study had to meet the following criteria: (1) it was a peer-reviewed randomised controlled trial (RCT) or a controlled trial (CT) written in English; (2) it included adult participants (≥ 18) diagnosed with sub-clinical or clinical AUD; (3) it compared the effects of CET to active or non-active control groups; (4) it included a CET intervention that wasn't combined with pharmacological treatment; and (5) it measured the effect of treatment on alcohol consumption.

2.3. Electronical databases

Two authors (AIM; LS) independently performed a systematic literature search in the following bibliographic databases: MEDLINE (via PubMed), PsycINFO (via APA), EMBASE (via Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) up to the 28th January 2017.

2.4. Electronical literature search

A systematic search in the electronical databases was performed to identify all relevant studies. The search was based on key words that included subject headings and free text words describing the AUD patient group (sub-clinical and clinical samples) and the intervention (cue exposure treatment) (see Appendix 1).

2.5. Study selection

Two authors (AIM; LS) independently screened titles and abstracts of articles identified by the electronic searches and excluded obviously irrelevant studies. The same authors subsequently read the full text versions of all the remaining articles and excluded those that did not meet the inclusion criteria. The reference lists of the retrieved articles were checked for any further relevant citations. Articles identified as relevant were subjected to full analysis. Disagreements concerning the eligibility of studies were solved through discussion.

2.6. Data extraction and data-items

Two authors (AIM; CBJ) independently extracted data from the original articles and consensus about disagreements was reached through discussion.

The procedures used to calculate effect sizes for each outcome variable are in accordance with the recommendations of the Cochrane Collaboration (Collaboration, 2011).Where possible, effect sizes were calculated using number of participants (N), mean score at follow-up, and standard deviation (SD). In cases where SD was not available, SD was calculated based on standard errors (SE), confidence intervals (CI) or P-values for differences in means between the intervention and control groups. Otherwise, data were ultimately derived from figures. In cases where the exact P-value was not available but results were reported as statistically significant (e.g., P < 0.05), effect sizes were calculated using the cut-off point for reporting statistical significance (e.g., P = 0.05) applied in the individual studies.

Data relating to type of AUD population, AUD assessment instruments, study setting, number of participants in experimental and control groups, number of treatment sessions (experimental groups only), treatment goal, follow-up timeline and outcome measures were extracted. The primary outcome measure was alcohol consumption; defined as drinking days and days with heavy drinking (drinking frequency) and drinks per day (drinking intensity). Secondary outcomes were total drinking score, latency to relapse and alcohol induced cravings (cue-induced cravings).

2.7. Risk of bias in individual studies

The Cochrane risk of bias tool (CRBT) was used to assess the methodological quality of the included studies. Two authors (AIM, CBJ) independently assessed each study for risk of selection bias, performance bias, detection bias, attrition bias and reporting bias. They subsequently rated each domain as adequate (i.e. low risk of bias), inadequate (i.e. high risk of bias) or unclear (i.e. method insufficiently described). Disagreements concerning the quality of studies were solved through discussion.

2.8. Summary measures

Effect sizes were measured as standardized mean differences (SMD) by dividing the difference in treatment outcomes between the intervention and control groups by the pooled standard deviation (SD), allowing for the pooling of various continuous outcomes. Following Cohen's recommendations on the interpretations of effect sizes, we considered SMD = 0.2 as small, SMD = 0.5 as moderate, and SMD = 0.8 as large (Cohen, 1988). A negative effect size indicated a reduction in the primary and secondary outcomes. Given that Cohen's *d* is biased in small samples, the effect size was adjusted to Hedges' *g* (Hedges, 1981).

2.9. Synthesis of results

The random effects model was used for the primary meta-analysis owing to a priori expected inter-trial heterogeneity (DerSimonian & Laird, 1986). Heterogeneity was calculated as the I^2 statistic, a measure of the proportion of variation (i.e. inconsistency) in the combined estimates due

to between-trial variance. An I^2 of 0% indicates no inconsistency between the results of individual trials and an I^2 value of 100% indicates maximal inconsistency (Higgins, Thompson, Deeks, & Altman, 2003). Funnel plots were generated to examine for possible publication bias (i.e. small study bias) (Egger, Smith, Schneider, & Minder, 1997). All statistical analyses were performed using STATA V.13 (Stata Corp, Texas, USA).

2.10. Meta-analytic strategy

Firstly, we conducted meta-analyses for alcohol consumption measured at 3- and 6-month follow-ups. Insufficient data was available for this outcome at 12-month follow-up. Secondly, we conducted a meta-analysis for total drinking score at 6-month follow-up. Insufficient data was available for this outcome at 3- and 12-month follow-ups. There was insufficient data to allow us to conduct meta-analyses for latency to relapse and cue-induced cravings. Thirdly, individual studies were stratified according to characteristics at trial level, after which meta-analyses were performed fitting multiple Restricted Maximum Likelihood (REML)-based meta-regression models (Thompson & Higgins, 2002). A relevant trial-level covariate was defined a priori as a covariate that would decrease the between-trial variance (Thompson, 1994) (estimated as Tau-squared) as a consequence of inclusion in the REML statistical model (Van Houwelingen, Arends, & Stijnen, 2002).

2.11. Quality assessment

Three authors (AIM, LS and CJ) assessed and documented the overall quality of the included studies based on criteria considered within the Grading of Recommendation, Assessment, Development and Evaluation (GRADE). These included study limitations (risk of bias), inconsistency, indirectness, imprecision and publication bias. The overall evidence for each outcome was classed as high, moderate, low or very low within GRADE.

Publication bias (i.e. small-study bias) was assessed through visual inspection of funnel plots for drinking frequency and drinking intensity at 6-month follow-up. Insufficient data was available for these outcomes at 3- and 12-month follow-ups.

3. Results

3.1. Study selection

The literature search resulted in 10,652 studies. The search covered all articles in English from 1993 to 2006. Manual searches of references cited in published original studies and review articles did not yield any additional studies. After removing duplicates, a total of 5254 studies remained. The titles and abstracts of these studies were subsequently assessed leading to the exclusion of 4939 studies. Potentially eligible studies (n = 315) were reviewed in more detail. A total of 7 studies were selected. Fig. 1 illustrates the study selection process in the form of a flow chart.

3.2. Study characteristics

Table 1 presents a summary of the study design, type of AUD population, AUD assessment instruments, treatments and outcome measures used in the reviewed studies. Five studies were conducted as randomised controlled trials and two as controlled trials, whereby participants were sequentially assigned to either experimental or control treatment conditions. Sample sizes ranged from 35 to 105 yielding a total sample size of 447. Four studies were conducted in inpatient settings and included participants with alcohol abuse or dependency (clinical sample). The remaining three studies were conducted in outpatient settings and included participants with problem drinking (subclinical sample). A total of five AUD assessment measures were used. Of the studies that relied on a clinical AUD diagnosis, three were based on DSM-III-R criteria (Association, 1987), and one on a structured clinical
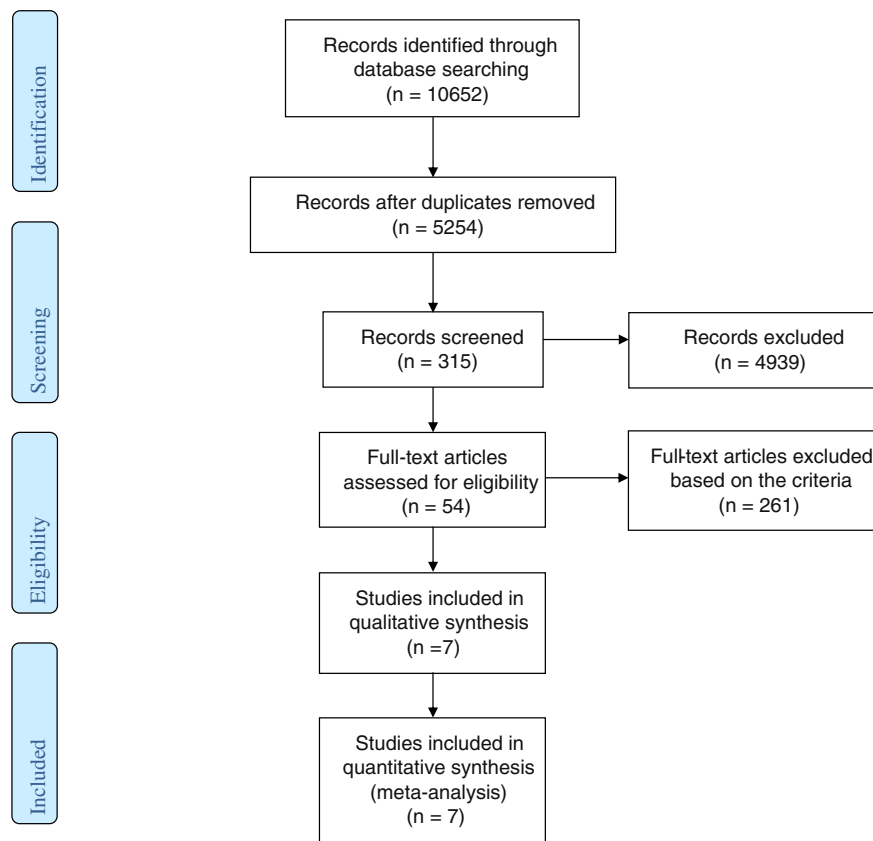
Fig. 1. Flow chart illustrating study selection process.

interview (SCID) adhering to DSM-IV criteria (First et al., 1995). These three studies also applied the Alcohol Dependence Scale (ADS) (Skinner & Allen, 1982). The remaining four studies used the Alcohol Dependence Severity Questionnaire (SADQ); one applied the traditional version (Stockwell et al., 1979), and the others a more recent community version: the Severity of Alcohol Dependence Questionnaire – Form C (SADQ-C) (Stockwell et al., 1994).

Four studies applied conventional CET and three applied CET with urge-specific coping skills training (USCS). CET conditions were compared with cognitive behavioral therapy in four studies, relaxation or meditation in two studies and daily contact with assessment in one study. Treatment goals differed among the studies; four targeted total abstinence and three targeted moderate alcohol consumption. The number of treatment sessions ranged from 6 to 16.

All seven studies applied alcohol intake as the primary outcome measure, which was assessed using different instruments. Three studies used the Timeline Follow Back (TLFB) measure (Sobell & Sobell, 1992), two used the Form 90 (Miller & del Boca, 1994; Project MATCH research Group, 1997), one used the Problem Drinking Questionnaire (PDQ) (Kavanagh et al., 1996; Sitharthan et al., 1996), and one used the Standardized Interview Method (SIM) (Drummond et al., 1990). Regarding secondary outcomes, two studies calculated total drinking score; one using the Form 90 (Dawe et al., 2002) and the other the SIM (Drummond & Glautier, 1994). Three studies assessed cue-induced cravings using both subjective and physiological measures; two used the Cue Reactivity Assessment (CRA) (Monti et al., 1987; Monti et al., 1993b), and one used non-standardized response measures (IPRM, IQ) (Drummond & Glautier, 1993, unpublished manuscript). One study assessed latency to relapse using the SIM (Drummond & Glautier, 1994).

The follow-up timeline varied greatly between studies, ranging from 1 to 12 months. However, four studies included a 3-month follow-up and all but one study included a 6-month follow-up. The study that did not include a 6-month follow-up period included an 8-month follow-up instead. Only one study included a 12-month follow-up.

3.3. Risk of bias in individual studies

Table 2 provides details of the risk of bias assessment. All seven studies were classified as having a high overall risk of bias. Regarding selection bias, two studies were judged as having a high risk and five as having an unclear risk when considering random sequence generation and allocation concealment. Five studies had a high risk of performance bias (blinding of participants and personnel) and two had an unclear risk. Detection bias (blinding of outcome assessment) was the only domain where some studies (n = 3) were judged as having a low risk. The remaining studies had a high risk (n = 1) or an unclear risk (n = 3). Attrition bias (incomplete outcome data) was a major concern with these studies, since all of them were judged as having a high risk. Reporting bias (selective reporting) was also evident, with five studies having a high risk and two an unclear risk.

3.4. Quantitative synthesis of results

3.4.1. Effects of CET on primary and secondary outcomes

Table 3 presents the results of the meta-analyses for primary and secondary outcomes by time-point.

Regarding the primary outcome measure of alcohol consumption, we could derive data for (1) drinking days and drinks per day at 3-month follow-up; (2) drinking days, days with heavy drinking and drinks per day at 6-month follow-up; and (3) days with heavy drinking and drinks per day at 12-month follow-up.

CET showed no overall effect on drinking days after 3 months ($g = 0.07$; 95%CI -0.34 to 0.49) and a small overall effect in favor of CET after 6 months ($g = -0.21$; 95%CI -0.48 to 0.06). No overall effect of CET on days with heavy drinking was observed after 6 months ($g = -0.02$; 95%CI -0.38 to 0.41). In the single study that assessed days with heavy drinking after 12 months, the SMD was reported as -0.22 (95%CI -0.64–0.21), indicating a small effect. CET showed no overall effect on drinks per day after neither 3 ($g = -0.07$; 95%CI -0.48 to

Table 1
Summary of cue-exposure treatment studies.

Author	Study design	AUD[a] population	AUD assessment	Treatment setting	Exp. group (n)	Exp. group content	Con. group (n)	Con. group content	No. of sessions	Treatment goal	Outcome measures Drinking	Outcome measures Cravings	Follow-up
Monti et al., 1993a, 1993b	RCT	Clinical	DSM-III-R, CD ADS	I	22	CET + CST	18	DCA	6	A	TLFB	CRA	3, 6
Drummond & Glautier, 1994	CT	Clinical	SADQ	I	20	CET	15	RT	10	A	SIM	IPRM, IQ	1, 3, 6
Sitharthan, Sitharthan, Hough, & Kavanagh, 1997	RCT	Sub-clinical	SADQ-C	O	22	CET	20	CBT	6	MD	PDQ	–	6
Heather et al., 2000	RCT	Sub-clinical	SADQ-C	O	43	CET	48	CBT	16	MD	Form 90	–	6
Rohsenow et al., 2001	RCT	Clinical	DSM-III-R, CD ADS	I	59	CET + CST	41	M/RT	10	A	TLFB	CRA	(3), 6, 12
Dawe et al., 2002	RCT	Sub-clinical	SADQ-C	O	39	CET	37	CBT	8	MD	Form 90	–	8
Loeber et al., 2006	CT	Clinical	SCID, ADS	I	31	CET + CST	32	CBT	9	A	TLFB	–	1, 2, 3, 4, 5, 6

Abbreviations: A = abstinence; AA = alcohol abuse; AD = alcohol dependence; ADS = alcohol dependence scale (Skinner & Allen, 1982); AUD = alcohol abuse or dependence; CBT = cognitive behavior therapy; CD = clinical diagnoses; Con. = control; CRA = cue reactivity assessment (Monti et al., 1987; Monti et al., 1993b); CST = Coping Skills Training; CT = controlled trial; DCA = daily contact with assessment; Exp. = experimental; I = inpatient; Form 90 (Project MATCH Research Group, 1997); IPRM = idiosyncratic physiological response measure; IQ = idiosyncratic questionnaire; M/RT = meditation/relaxation techniques; MD = moderate drinking; O = outpatient; PDQ = Problem Drinking Questionnaire (Kavanagh, Sitharthan, & Sayer, 1996; Sitharthan, Kavanagh, & Sayer, 1996); RCT = randomised controlled trial; RT = relaxation techniques; SADQ = severity of alcohol dependence questionnaire (Stockwell, Hodgson, Edwards, Taylor, & Rankin, 1979); SADQ-C = severity of alcohol dependence questionnaire – form C (Stockwell, Sitharthan, McGrath, & Lang, 1994); SCID = Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995). SIM = standardized interview method (Drummond, Thom, Brown, Edwards, & Mullan, 1990); TLFB = timeline follow-back (Sobell & Sobell, 1992).

0.34) nor 6 months (g = − 0.16; 95% CI − 0.52 to 0.19). In the single study that assessed drinks per day after 12 months, the SMD was reported as − 0.22 (95%CI − 0.64 to 0.21), indicating a small effect.

Fig. 2 presents forest plots illustrating the effects of CET on drinking days and drinks per day at 6-month follow-up.

Regarding secondary outcomes, a small overall effect was shown in favor of CET on total drinking score (g = − 0.21; 95%CI − 0.78 to 0.37). In the single study that assessed latency to relapse, the SMD was reported as − 0.68 (95%CI − 1.40 to 0.04), indicating a moderate effect. Two studies reported no effect of CET on cue-induced cravings (Monti et al., 1993a; Rohsenow et al., 2001). However, there was insufficient data to allow us to calculate an overall effect size for subjective and physiological cravings. Another study assessed baseline cravings as a predictor of drinking outcomes and did not find any association (Drummond & Glautier, 1994).

3.4.2. Sub-group analyses of the effects of CET on drinking frequency and drinking intensity

The included studies shared characteristics in such a manner that we could form the following subgroups: (1) included a sub-clinical population, outpatient treatment and a moderation-oriented treatment goal (SOM), (2) included a clinical sample, inpatient treatment and an abstinence-oriented treatment goal (CIA), (3) applied CET without USCS and cognitive behavioral therapy as a comparison (CCC); and (4) applied CET with urge-specific coping skills and other comparisons (CUOC). Details of the subgroup analyses are presented in Table 4.

Type of CET and comparisons had the largest impact on the between-trial variance, together explaining 15.1% in relation to drinking days and 40.1% in relation to drinks per day. None of the other covariates explained heterogeneity.

3.5. Quality assessment

Table 5 provides a summary of the quality assessment for primary and secondary outcomes measured at 6-month follow-up. The quality of evidence was graded as very low for drinking frequency, drinking intensity and total drinking score.

Publication bias was evaluated for studies that assessed the effects of CET on drinking days and drinks per day at 6-month follow-up. Both funnel plots presented in Fig. 3 are asymmetrical, which could potentially indicate publication bias.

We judged the quality of evidence to be very low for studies that assessed the effects of CET on drinking frequency (only drinking days; n = 2) and drinking intensity (n = 2) at 3-month follow-up. Reasons for downgrading the quality of evidence to very low were mainly due to very serious risk of bias and serious imprecision.

Overall, we are very uncertain about the estimates provided by the studies included in this meta-analysis.

4. Discussion

This is the first meta-analysis to examine the effectiveness of CET for treating AUD. CET showed no to small additional effects on primary outcomes and small to moderate additional effects on secondary outcomes compared to control conditions. The overall quality of evidence was graded as very low due to high risk of bias, inconsistency, imprecision and suspected publication bias.

Earlier systematic reviews found no consistent evidence in favor of CET targeting SUD (Conklin & Tiffany, 2002; Martin et al., 2010). Despite the fact that Conklin and Tiffany (2002) concluded in their meta-analysis that 'cue exposure failed to prove efficacious in treating addiction' (p. 159), they reported clinically significant effect sizes for the majority of CET trials targeting AUD (Conklin & Tiffany, 2002; Martin et al., 2010). Although the effect sizes in our study resemble those reported by Conklin and Tiffany, we were unable to replicate the exact numbers, and we generally found smaller effects of CET on AUD

Table 2
Risk of bias in the individual studies.

Domain	Monti et al., 1993a	Drummond & Glautier, 1994	Sitharthan et al., 1997	Heather et al. 2000	Rohsenow et al., 2001	Dawe et al., 2002	Loeber et al., 2006
Selection bias							
Random sequence generation	?	−	?	?	?	?	−
Allocation concealment	?	−	?	?	?	?	−
Performance bias							
Blinding of participants and personnel	−	−	−	?	−	?	−
Detection bias							
Blinding of outcome assessment	?	−	?	+	+	+	?
Attrition bias							
Incomplete outcome data	−	−	−	−	−	−	−
Reporting bias							
Selective reporting	−	−	−	−	−	?	?
Overall risk of bias	−	−	−	−	−	−	−

+ = low risk of bias, − = risk of bias, ? = unclear.

compared to coinciding studies (Drummond & Glautier, 1994; Monti et al., 1993a; Rohsenow et al., 2001; Sitharthan et al., 1997). Furthermore, since the publication of Conklin and Tiffany's meta-analysis, new controlled studies have been published reporting no additional effects of CET on alcohol consumption outcomes (Dawe et al., 2002; Loeber et al., 2006), which obviously decreases the overall effect sizes found in our study.

Even though the present meta-analysis showed small additional effects in favor of CET at best, there is little doubt that more positive results are reported in CET studies specifically targeting AUD compared to those targeting other SUD's (Corty & McFall, 1984; Dawe et al., 1993; Lowe et al., 1980; Marissen et al., 2007; Niaura et al., 1999; Raw & Russell, 1980). In addition, stratification and analysis of a priori defined covariates revealed that CET may have an increased effect in the longer term, and that type of CET (conventional CET vs. CET with USCS) and type of comparisons (CBT vs. other comparisons) explained much of the between trial variance.

Regarding long-term treatment effectiveness, we found no additional effects of CET on neither drinking frequency nor drinking intensity after 3 months, no additional effect on drinking frequency but a

small additional effect on drinking intensity after 6 months, and a small additional effect on both drinking frequency and drinking intensity after 12 months. It is important to note that only one study included a 12-month follow-up, therefore it is not possible to draw any firm conclusions regarding long-term treatment effects. However, in support of our tentative findings, Monty and co-workers reported similar results after 12 months in an RCT combining CET with urge-reducing pharmacotherapy (Monti et al., 2001). If these results are replicable, it may be that CET is well-suited for long-term alcohol relapse prevention.

Stratification and analysis of type of CET therapy revealed that CET combined with USCS may be more effective than conventional approaches. Typically, the coping strategies used to reduce cue-induced cravings during alcohol exposure are derived from CBT, e.g. thinking of positive and negative consequences associated with drinking etc. (Marlatt & Donovan, 2005; Marlatt & Gordon, 1985). The distinguishing feature of CET combined with USCS is that USCS are supposed to be used when alcohol cues are present and conditioned responses are elicited, so that responses to alcohol and associated stimuli can be extinguished. Indeed, a recent study found that the use of USCS during CET improved drinking outcomes (Dolan, Rohsenow, Martin, & Monti, 2013).

Table 3
Effect of CET on primary and secondary outcomes by time-point.

	Hedges random effects model			Heterogeneity test (Q statistic)
	No. of studies	Pooled SMD	Pooled CI	I²
Primary outcomes				
3 month follow-up				
Frequency: drinking days	2	− 0.07	− 0.34–0.49	0.0
Intensity: drinks per day	2	− 0.07	− 0.48–0.34	0.0
6 month follow-up				
Frequency: drinking days	5	− 0.21	− 0.48–0.06	24.3
Frequency: days with heavy drinking	2	− 0.02	− 0.38–0.41	36.9
Intensity: drinks per day	6	− 0.16	− 0.52–0.19	63.9
12 month follow-up				
Frequency: days with heavy drinking	1	–	–	–
Intensity: drinks per day	1	–	–	–
Secondary outcomes				
6 month follow-up				
Composite alcohol score	2	0.21	− 0.78–0.37	49.0
Latency to relapse	1	–	–	–

A: Drinking days

B: Drinks per day

Fig. 2. Forests plots illustrating the effect of CET, (B) drinks per day at 6 months follow-up is rather unclear.
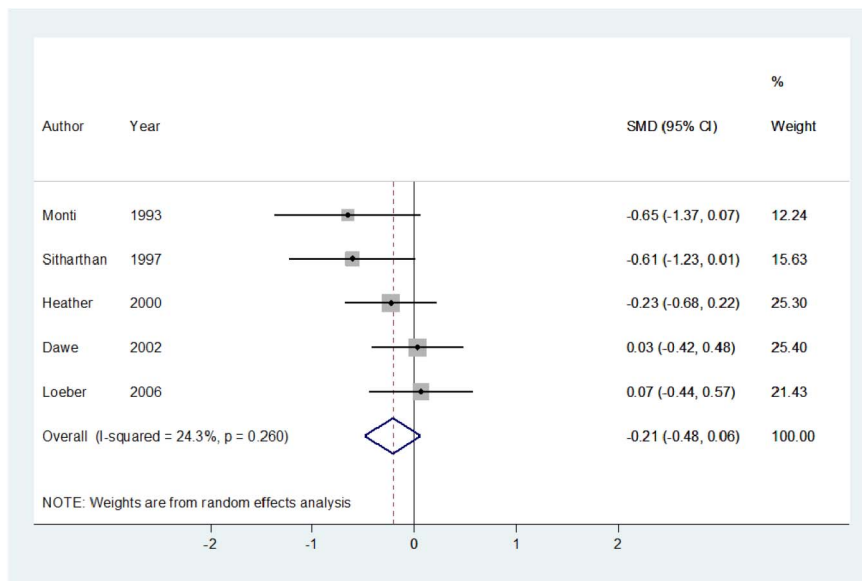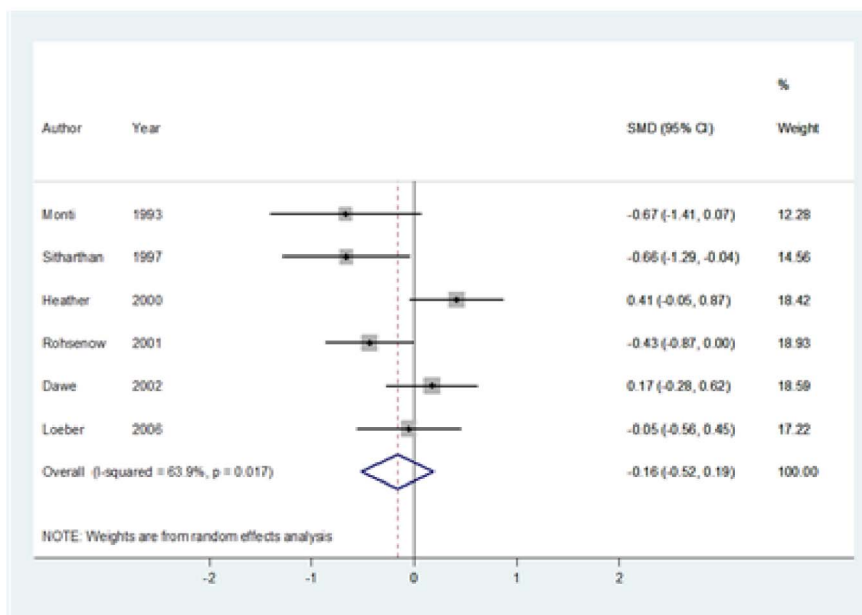
Comparison treatments featured in the included studies consisted of CBT, RMT or daily contact with assessment. Our results indicated that CET is less effective when compared to CBT as opposed to other active comparisons. This finding is not surprising given that there is ample evidence to suggest that CBT is an effective treatment for AUD, and there is more uncertainty about the use of RMT (Berglund et al., 2003; Health, Health, & Excellence, 2011a; Magill & Ray, 2009; Miller & Wilbourne, 2002). Therefore, it may be difficult to demonstrate effects of CET on AUD when comparing this approach to well-established effective interventions, such as CBT.

In addition, CBT has much in common with CET, especially when combined with USCS. CBT often comprises CET when targeting other psychiatric disorders (Barkowski et al., 2016; Cuijpers et al., 2016; Tolin, 2010). However, the literature suggests that these treatments are segregated when targeting SUD/AUD, perhaps due to the lack of empirical evidence supporting the use of CET for treating addictive disorders. When these methods are segregated, the difference between CET and CBT is the in vivo exposure element featured in CET. To our knowledge, no studies have compared CET with USCS to conventional CBT, which is why it is difficult to disentangle the effects of type of CET from comparison treatments. However, Kavanagh et al. (2006) performed an RCT on patients with alcohol abuse or dependence allocated to receive either CBT alone or CBT with CET as an add-on intervention. Results indicated that the addition of conventional CET to CBT did not reduce alcohol outcomes (Kavanagh et al., 2006). Thus, a research question that may be of interest is whether CET combined with USCS increases the effectiveness of CBT. It may be necessary to provide USCS during CET to prepare individuals with AUD to cope with cravings experienced due to pervasive exposure to alcohol and associated stimuli across diverse contexts.

Stratification by type of AUD population (sub-clinical vs. clinical), treatment setting (inpatient vs. outpatient) and treatment goal (moderation-oriented vs. abstinence-oriented) did not influence the effects of CET and explained little variance in relation to drinking outcomes. In

Table 4
The effects of CET on drinking frequency and intensity by subgroups.

	No. of studies	Hedges random effects model	Heterogeneity test (Q statistic)	Hedges random effects model	Heterogeneity test (Q statistic)
		P SMD (CI)	I²	OP SMD (CI)	I²
Subgroup: Population, treatment setting and treatment goal					
Frequency: drinking days					
SOM	3	− 0.22 (− 0.55–0.11)	25.6	− 0.21 (− 0.48–0.06)	25
CIA	2	− 0.25 (− 0.95–0.45)	61.2		
Frequency: days with heavy drinking					
SOM	1	–	–	0.02 (− 0.38–0.41)	36.9
CIA	1	–	–		
Intensity: drinks per day					
SOM	3	0.01 (− 0.56–0.58)	73.7	− 0.16 (− 0.52–0.19)	63.9
CIA	3	0.34 (− 0.66–0.22)	8.7		
Subgroup: Type of CET and comparisons (CET vs. CBT or CET + USCS vs. other comparisons)					
Frequency: drinking days					
CCC	4	0.15 (− 0.41–0.13)	–	− 0.21 (− 0.48–0.62)	24.3
CUOC	1	–	–		
Frequency: days with heavy drinking					
CCC	1	–	–	0.02 (− 0.38–0.41)	36.9
CUOC	1	–	–		
Intensity: drinks per day					
CCC	4	0.01 (− 0.40–0.41)	61.7	− 0.16 (− 0.52–0.19)	63.9
CUOC	2	− 0.50 (− 0.87–0.12)	0.00		

accordance with treatment guidelines, the included studies assessed either subclinical samples in outpatient settings using a moderation-oriented treatment goal or clinical samples in inpatient settings using an abstinence-oriented treatment goal (Connor, Haber, & Hall, 2016; Health, Health, & Excellence, 2011b). It has been suggested that clinical populations with severe levels of alcohol dependency may profit more from CET than clinical populations with lower or moderate levels because they possibly have experienced a greater number of association trials between drug-associated stimuli and drug intake (Drummond, 2000; Loeber et al., 2006). Consequently, these patients have a higher level of cue-reactivity. To examine this hypothesis, Loeber et al. (2006) stratified their clinical sample into individuals with lower vs. higher levels of alcohol dependency and found that those with higher levels showed significant improvement on alcohol consumption outcomes compared to those with lower levels (Loeber et al., 2006). The time is not ripe yet to conduct a meta-analytic stratification on AUD severity profiles since so few studies have tested

clinical samples. Nonetheless, it may be that CET is better suited for individuals with a more severe AUD profile.

Although we could not assess cue-induced cravings in this meta-analysis, the two included studies reporting on this outcome found no effect in favor of CET. This contrasts with studies showing decreased levels of subjectively and objectively measured cue-induced cravings following alcohol exposure (e.g. MacKillop & Lisman, 2008; Stasiewicz, Brandon, & Bradizza, 2007; Vollstadt-Klein et al., 2011). However, these studies did not assess whether reduction in cravings influenced alcohol consumption, which was the primary outcome of interest in this meta-analysis. Although it has been reported that individuals with AUD experience fewer cue-induced cravings compared to individuals with other SUDs (Carter & Tiffany, 1999), which could decrease the power of detecting an effect, one would expect to see a reduction in cue-induced cravings in the two abovementioned studies, given that they both reported positive findings in relation to drinking outcomes (Monti et al.,

Table 5
Quality assessment for primary and secondary outcomes at 6 months follow-up.

Quality assessment							Summary of findings			
No. of studies	Study design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Publication bias	No. of patients		Relative effect (95% CI)	Quality
							CET	Control		
Primary alcohol outcomes										
Frequency: drinking days (follow-up: mean 6 months)										
5	Randomised trials	Very serious	Serious	Not serious	Serious	Suspected	157	155	SMD − 0.21 (− 0.48 lower to − 0.06 higher)	Very low
Frequency: days with heavy drinking (follow-up: mean 6 months)										
2	Randomised trials	Very serious	Serious	Not serious	Serious	Suspected	98	78	SMD − 0.02 (− 0.38 lower to − 0.41 higher)	Very low
Intensity: drinks per day (follow-up: mean 6 months)										
6	Randomised trials	Very serious	Serious	Not serious	Serious	Suspected	216	196	SMD − 0.16 (− 0.52 lower to − 0.19 higher)	Very low
Secondary alcohol outcomes										
Total drinking score (follow-up: mean 6 months)										
2	Randomised trials	Very serious	Serious	Not serious	Serious	Suspected	59	52	SMD − 0.21 (− 0.78 lower to − 0.37 higher)	Very low
Latency to relapse (follow-up: mean 6 months)										
1	Randomised trials	Very serious	–	Not serious	–	–	20	15	SDM − 0.68 (− 1.40 lower to − 0.04 higher)	–

[a] See CROB for risk of bias in individual studies.

A: Drinking days
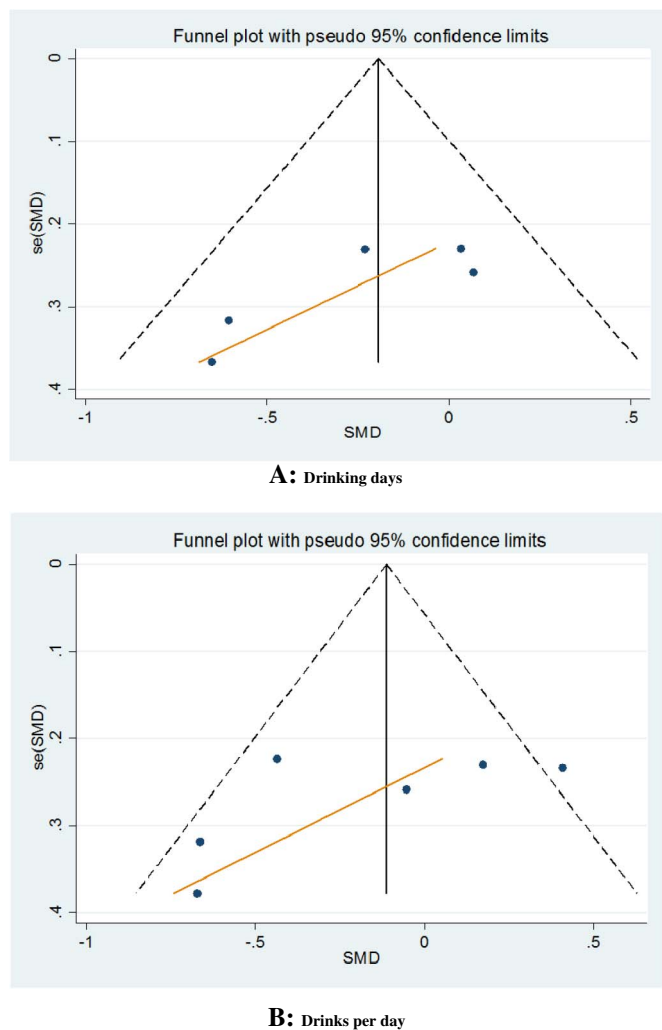

B: Drinks per day

Fig. 3. Funnel plots for (A) drinking days and (B) drinks per day at 6 months follow-up.

1993a; Rohsenow et al., 2001). Moreover, one of the studies performed an additional analysis that included only urge reactors and found similar results to the overall analysis (Monti et al., 1993a). This finding challenges the theoretical assumption that cue-induced cravings can cause addictive behavior (e.g. Drummond, 2000; Niaura, 2000), particularly if it can be corroborated by future studies.

Conklin & Tiffany propose that a number of threats to extinction learning (derived from animal models) may help explain why CET does not achieve better effects in humans (Conklin & Tiffany, 2002). These are (1) the renewal effect, (2) spontaneous recovery, (3) reinstatement, and (4) failure to extinguish the most salient conditioned cues. The *renewal effect* occurs when a CS is paired with an US in one context (CC: conditioning context) and is then extinguished in a different context (EC: extinction context). A return to the original CC will renew responding to the target stimulus. In line with this notion, renewal should be attenuated if CS responding is extinguished in the context or multiple contexts where the original CS–US pairing occurred. (Bouton, 2004; Bouton & Ricker, 1994; Chelonis, Calton, Hart, & Schachtman, 1999; Gunther, Denniston, & Miller, 1998). To our knowledge, there have been no studies done on the effects of CET on alcohol consumption conducted in in vivo conditioning contexts. However, when it comes to alcohol cues, individuals with AUD will be exposed to multiple conditioning contexts between CET sessions, at least when it concerns outpatient treatment. Studies investigating extinction learning across multiple contexts in clinical samples of AUD individuals have so far not demonstrated renewal of cue-induced cravings, indicating that alcohol

cues may be rather generalizable (James MacKillop & Lisman, 2008; Stasiewicz et al., 2007). Hence, the renewal effect could indeed be generalized from the EC (e.g. alcohol treatment setting) to other CCs (e.g. the supermarket or at home) from session to session. Contact with the treatment system between CET sessions is likely to be important as individuals may be at increased risk of relapse when confronted with alcohol cues across CCs.

Whereas the renewal effect is contingent upon contextual changes, the *spontaneous recovery effect* occurs when extinguished responses re-emerge upon re-exposure to the CS following the passage of time after extinction learning (Pavlov & Anrep, 2003; Rescorla, 1997, 2004; Robbins, 1990). To overcome spontaneous recovery, consideration should be taken to the temporal spacing of cue-exposures both within (frequency of and amount of time between cue exposures) and between (amount of time between each exposure session) sessions. However, temporal spacing was not considered in the studies comprising this meta-analysis. Within-session spacing was not applicable as most studies only actively exposed patients to alcohol cues in vivo once, i.e. they were asked to focus on alcohol and its attributes (e.g. sight of the bottle, smell and in cases where the treatment goal was moderate drinking, taste). Between-session spacing was not described in detail and varies greatly between the included studies; the frequency of sessions ranged from 6 to 16 and the time interval between them was poorly specified. Moreover, it is impossible to know whether patients were exposed to alcohol cues outside the treatment setting.

Reinstatement occurs when responding to an extinguished CS re-emerges because of post-extinction exposure to an US. Although it is not common for individuals with SUD to experience non-contingent re-exposure to drugs, it may nevertheless decrease the effectiveness of CET (e.g. Carroll & Comer, 1996; De Wit, 1996). For example, an individual with AUD may drink cough medicine, eat something that contains a high amount of ethanol or take benzodiazepines. Such substances are expected to produce similar effects to alcoholic beverages as they target the same gabaminergic neurotransmitter system. This type of re-exposure can reinstate learned responding to extinguished drug cues, which is like experiencing a more voluntary lapse or relapse in cases where abstinence is the treatment goal. On this basis, CET targeting AUD should not be effective when moderate drinking is the treatment outcome. Contrary to this argument, our stratification analysis revealed that treatment goal explained little variance in drinking outcomes. However, this could be due to other shared study characteristics (type of comparison group, AUD population and treatment setting), therefore the question of whether CET is less effective when targeting moderate drinking compared to abstinence remains undetermined.

In considering the final threat to extinction: *Failure to extinguish the most salient conditioned cues*, it is important to highlight that the effects of CET on drug use can also be explained in terms of instrumental conditioning (e.g. Everitt, Dickinson, & Robbins, 2001; Mansfield & Cunningham, 1980). Drug cues may not only operate as CS but also discriminant stimuli (DS) for drug administration. For instance, the attributes of an AUD individual's favorite beverage (CS) may elicit CR by frequent pairing with alcohol effects. At the same time, the beverage may serve as a DS, setting the occasion for drinking behavior, which is then positively reinforced by the effects of alcohol. Therefore, even if conditioned responses to bottle cues are extinguished, the instrumental act of drinking may remain intact. If this behavior is not extinguished, it is unlikely that extinguishing classically conditioned responses will be sufficient to eliminate drug use (Conklin & Tiffany, 2002). Hence, moderating or hindering alcohol intake during CET may on this background not be enough to extinguish instrumental conditioning. Rather, individuals with AUD (and other SUDs) should be exposed to non-reinforced instrumental conditioning using drug antagonists or placebos to increase the effectiveness of CET. Administering antagonists that pharmacologically block or counteract drug effects prior to drug intake will not elicit UR or CR, and will result in non-reinforcing drug use. Regarding alcohol, an antagonist directly linked to ethanol has yet to be discovered.

However, Naltrexone (an opiate antagonist) and Acamprosat (unknown mechanism of ligand action) are often used to decrease the rewarding effects of alcohol, and have indeed shown promising results in relation to AUD (albeit not in connection with administering CET), and more so in the short term (Bouza, Magro, Muñoz, & Amate, 2004; Srisurapanont & Jarusuraisin, 2005). It may be of interest to combine this type of treatment with CET targeting AUD, particularly if it proves to produce better effects in relation to long-term relapse prevention. In contrast to animals, humans will be aware of experimental manipulations involving medication and will anticipate the rewarding effects evoked by alcohol when medication is not taken. This may represent a serious shortcoming of pharmacological CET approaches. The same could be argued for different placebo approaches (e.g. using alcohol free beer).

New initiatives inspired by fear extinction learning have shown preliminary promise in weakening CR by enhancing new learning. For instance, the antibiotic medication D-cycloserine (partial *N*-methyl-D-aspartate (NMDA) receptor agonist), which is involved in learning and memory (Kelley, 2004; Peters & De Vries, 2012), has been shown to facilitate the extinction of cue-induced cravings and alcohol intake (Kiefer et al., 2015; MacKillop et al., 2015). Coupled with the use of other pharmacological agents, this may increase the effectiveness of CET in the future (Everitt, 2014; Kiefer et al., 2015).

Taken together, threats to extinction learning can inform future research on the effects of CET targeting AUD, although some threats may be more relevant than others. Pervasive exposure to alcohol cues in the western world constitutes a constant challenge for renewal and spontaneous recovery, which can potentially facilitate extinction learning across time and context, hereby making them less likely to influence the effectiveness of CET targeting AUD compared to other drugs of choice. In contrast, reinstatement could potentially decrease the effectiveness of CET targeting AUD since ethanol can be found in everyday products other than alcoholic beverages.

4.1. Limitations

It should be noted that even though we applied a rigorous search strategy and study selection procedures, relatively few studies on the effects of CET targeting AUD were available The identified studies were heterogeneous in terms of the included population, treatment approaches and applied methodology. Limited data were available, particularly at 3- and 12-month follow-ups, and only a couple of studies assessed percentage of days with heavy drinking, which is the most clinically relevant outcome for alcohol treatments as it reflects drinking to intoxication. Finally, inconsistency and high risk of bias in the studies limit the degree of certainty we can place in our estimates.

Appendix 1 Search strategy

5. Conclusion

Overall, CET showed no to small additional effects on the primary outcome of alcohol consumption. Small additional effects were observed after 6 and 12 months, suggesting that CET may increase in effectiveness over time. Regarding secondary outcomes assessed at 6-month follow-up, CET had a small additional effect on total drinking score and a moderate additional effect on latency to relapse. Stratification and analysis of a priori defined trial covariates revealed that CET combined with USCS may be the better option for treating AUD compared to conventional CET. However, since relatively few CET studies targeting AUD were available and that these were judged as providing very low quality evidence, sounder methodological trials are necessary to draw any firm conclusions about the effectiveness of CET targeting AUD.

6. Future directions

Our findings raise some important questions for future research. Overall, there is a need for more high quality RCT studies assessing the effects of CET targeting AUD using percentage of days with heavy drinking as the primary outcome measure. Further research is especially warranted to investigate: (1) the effectiveness of CET targeting different alcohol severity profiles; (2) the long-term effectiveness of CET; (3) whether the in vivo exposure element in CET adds to the effectiveness of CBT; (4) whether CET combined with USCS is more effective than conventional CET; (5) whether extinction learning can be increased during CET by (a) targeting different threats to extinction, and (b) adding cognitive enhancing pharmacological agents (e.g. D-cyclocerine) to the treatment.

Author disclosure

Statement 2: **Contributors**
Authors AIM, CJ, and BN designed the study. Author AIM and LS conducted literature searches and identified the included studies. Authors AIM and CJ extracted the data and CJ conducted the statistical analyses. AIM, CJ and LS conducted the quality assessment. Author AIM wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.
Statement 3: **Conflict of interest**
No conflicts of interest to declare.

FACET 1		FACET 2	
Cue exposure therapy		Clinical and sub-clinical AUD samples	
MEDLINE (via Pubmed)			
Behavior Modification	Psychological Desensitization	Alcohol Related Disorder	Alcohol-Dependents
Behavior Modifications	Psychological Desensitization	Alcohol Related Disorders	Alcohol Dependent
Behavior Modification	Systematic Desensitization Therapy	Alcohol-Related Disorder	Individual
Behavior Modifications	Systematic Desensitization Therapy	**Alcohol-Related Disorders**	Alcohol Dependent
Behavior Training	Systematic Desensitization Treatment	**[mesh]**	Individuals
Behavior Training	Systematic Desensitization Treatment	Alcohol Induced Disorder	Alcohol-Dependent
Behavior Therapy [**mesh**]	Flooding Therapy	Alcohol Induced Disorders	Individual
Behavior Therapy	Flooding Therapies	Alcohol-Induced Disorder	Alcohol-Dependent
Behavioral Therapy	Exposure Therapy	**Alcohol-Induced Disorders**	Individuals
Behavior Therapies	Exposure Therapies	**[mesh]**	Ethanol Dependence
Behavior Therapies	Conditioning Therapy	**Alcoholism** [**mesh**]	Alcohol Abuse
Behavioral Therapies	Conditioning Therapies	Alcohol Use Disorder	Ethanol Abuse

Behavior Treatment
Behavior Treatment
Behavioral Treatment
Psychologic Desensitization
Psychologic Desensitization [**mesh**]

Alcohol Use Disorders
Alcohol Addiction
Alcohol Addictions
Alcohol Dependence
Alcohol Dependent
Alcohol Dependents
Alcohol-Dependent

Alcohol Misuse
Harmful Use of Alcohol
Chronic Alcoholic
Intoxication
Chronic Alcoholism
Alcoholic
Alcoholics [**mesh**]
Alcoholic Individual
Problem Drinker
Problematic Drinker

PsychINFO (via APA)

Behavior Modification [**subject heading**]
Behavior Modifications
Behavior Modification
Behavior Modifications
Behavior Training
Behavior Training
Behavior Therapy [**subject heading**]
Behavior Therapy
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Behavior Therapies
Behavioral Therapies
Behavior Treatment
Behavior Treatment
Behavioral Treatment
Psychologic Desensitization
Psychologic Desensitization

Psychological Desensitization
Psychological Desensitization
Systematic Desensitization Therapy
Systematic Desensitization Therapy
Systematic Desensitization Treatment
Systematic Desensitization Treatment [**subject heading**]
Flooding Therapy
Flooding Therapies
Exposure Therapy [**subject heading**]
Exposure Therapies
Conditioning Therapy
Conditioning Therapies

Alcohol Related Disorder
Alcohol Related Disorders
Alcohol-Related Disorder
Alcohol-Related Disorders
Alcohol Induced Disorder
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Alcohol-Induced Disorder
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Alcoholism [**subject heading**]
Alcohol Use Disorder
Alcohol Use Disorders
Alcohol Addiction
Alcohol Addictions
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Alcohol Dependents
Alcohol-Dependent

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Alcohol Dependent
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Individual
Alcohol-Dependent
Individuals
Ethanol Dependence
Alcohol Abuse [**subject heading**]
Ethanol Abuse
Alcohol Misuse
Harmful Use of Alcohol
Chronic Alcoholic
Intoxication
Chronic Alcoholism
Alcoholic
Alcoholics
Alcoholic Individual
Problem Drinker
Problematic Drinker

EMBASE (Via OVID)

Behavior Modification [**subject heading**]
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Behavior Modification
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Behavior Training
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Behavior Therapy [**subject heading**]
Behavior Therapy
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Behavior Therapies
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Behavior Treatment
Behavior Treatment
Behavioral Treatment
Psychologic Desensitization
Psychologic Desensitization

Psychological Desensitization
Psychological Desensitization
Systematic Desensitization Therapy
Systematic Desensitization Therapy
Systematic Desensitization Treatment
Systematic Desensitization Treatment [**subject heading**]
Flooding Therapy
Flooding Therapies
Exposure Therapy [**subject heading**]
Exposure Therapies
Conditioning Therapy
Conditioning Therapies

Alcohol Related Disorder
Alcohol Related Disorders
Alcohol-Related Disorder
Alcohol-Related Disorders
Alcohol Induced Disorder
Alcohol Induced Disorders
Alcohol-Induced Disorder
Alcohol-Induced Disorders
Alcoholism [**subject heading**]
Alcohol ADJ2 Disorder
Alcohol ADJ2 Disorders
Alcohol Addiction
Alcohol Addictions
Alcohol Dependence
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Individuals
Ethanol Dependence
Alcohol Abuse [**subject heading**]
Ethanol Abuse
Alcohol Misuse
Harmful ADJ3 of Alcohol
Chronic Alcoholic
Intoxication
Chronic Alcoholism
Alcoholic
Alcoholics
Alcoholic Individual
Problem Drinker
Problematic Drinker

Cochrane Central Register of Controlled Trials = MEDLINE search.
Bold words = subject headings; Not bold = text words.

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