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Is Behavioural Activation an Effective and Acceptable Treatment for Co-occurring Depression and Substance Use Disorders? A Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Background. Depression often co-occurs with substance use problems and is associated with poor treatment outcome. Whilst the efficacy of behavioural activation (BA) has been tested in clinical trials with substance users, outcomes have not yet been quantitatively synthesised. *Methods.* A random effects meta-analysis of the randomised clinical trial evidence base was performed. Outcomes for individual or group BA were compared against passive or active controls. Attendance and dropout rates were also compared. The grading of recommendations assessment, development and evaluation (GRADE) approach was used to assess the quality of each meta-analytic comparison. *Results.* Five trials were meta-analysed (N=195). No significant differences were found between BA and controls with regards to depression (Post-treatment: k = 5; N = 195; SMD: 0.19, CI -0.10 to 0.49; p = 0.20; GRADE = Low; Follow-up: k = 5; N = 195; SMD: -0.10, CI -0.51 to -0.30; p = 0.62; GRADE = Low) or substance use (Post-treatment: k = 4; N = 151; SMD: 0.14, CI -0.33 to -0.6; p = 0.57, GRADE = Low; Follow-up: k = 4; N = 151; SMD: 0.17, CI -0.34 to 0.69; p = 0.51, GRADE = Low) and there was little evidence of publication bias. The average session attendance rate for BA was 72%. An average dropout rate of 35% was reported for both BA and comparator conditions. *Conclusion*. BA does not emerge as a differentially efficacious treatment for comorbid depression and substance use disorders, although it does appear to be an acceptable treatment option. Confidence in the results are limited by the number and quality of the original studies and the possibility of the effect of small sample bias. Suggestions are made for improving the methodological quality and direction of future BA trials.

Keywords: Behavioral Activation, Depression, Substance Use, Reinforcement, Treatment, Meta-Analysis

Declarations of Interest: None

1. Introduction

Depression is highly prevalent amongst people who also have substance use problems (Torrens, Mestre-Pintó & Domingo-Salvany, 2015), with up to 55% of treatment-seeking substance users meeting criteria for clinically significant problems with depression (Johnson et al., 2006; McKetin et al., 2011; Teesson et al., 2004). The co-morbidity of depression and substance use disorders (SUDs) is associated with poorer health outcomes (McKay et al., 2002), lower rates of treatment completion (Tate et al., 2004), increased risk of substance use relapse (Davis et al., 2010) and eventual suicide (Blanco et al., 2012). Therefore, providing effective and efficient treatment for patients with comorbid depression and comorbid substance use problems is essential for improving health-related outcomes in this population and is a growing area of clinical research.

Pharmacological treatments for depression tend to be of limited effectiveness in people who use drugs and alcohol, with studies frequently reporting modest benefits (Iovenio et al., 2011; Nunes & Levin, 2004). Indeed, some authors have questioned whether medication actually has a role to play in the treatment of substance users with comorbid depression (Lingford-Hughes et al., 2012). In terms of psychological treatments, there is some empirical support for the delivery of cognitive behavioural therapy (CBT) for co-occurring depression and alcohol dependence (Baker et al., 2012; Hides et al., 2010; Magill & Ray, 2019, 2009; Riper et al., 2014) and co-occurring depression and cannabis dependence (Magill & Ray, 2019, 2009). However, previous narrative reviews have highlighted only modest effects of CBT on depression and substance use outcomes overall (Hides et al., 2010), even when combined with other evidence-based psychological treatments such as motivational interviewing (Riper et al., 2014). There is some preliminary and emerging evidence that 3rd wave CBT therapies such as ACT may be effective in treating comorbid depression and alcohol use disorder (Petersen & Zettle, 2009; Thekiso et al., 2015). Mindfulness-based cognitive therapy (MBCT) has been reported to improve alcohol outcomes in problematic alcohol users with co-occurring depression (Baker et al., 2010) and mindfulness-based relapse prevention (MBRP) has been found to produce superior long-term substance use outcomes compared to CBT-based relapse prevention (Bowen et al., 2014). However, research in this area

remains limited and few studies have explored mindfulness-based therapies as a treatment for co-occurring depression in patients who are accessing SUD treatment and actively using substances.

It is notable that CBT tends to produce moderate-to-large effect sizes for depression outcomes in non-substance-dependent samples (e.g., *g* = 0.71; Cuijpers et al., 2013) and smaller effect sizes when employed as a standalone treatment for people with SUDs (e.g., *g* = 0.18; Magill et al., 2019). A possible explanation for this difference is that substance using populations may find it hard to grasp and utilise the cognitive components of CBT. Indeed, patients accessing treatment for SUDs are more likely to have cognitive impairments (Bruijnen et al., 2019; Vik et al., 2004) and low literacy (Beitchman et al., 2001), which could make understanding and adhering to CBT treatment concepts more difficult. A less complex treatment that may be well-suited to people with co-occurring depression and substance use problems is behavioural activation (BA). BA is based on behaviour modification and reinforcement theory (e.g. Lewinsohn & Shaffer, 1971), which posits that depression develops when people have reduced access to contingent reward from their environment for non-depressive and functional behaviours. The typical depressive behavioural responses (e.g. avoidance and inactivity) then contribute to the maintenance of low mood, leading to what has been termed the “inactivity trap” (Elfrey & Ziegelstein, 2009). SUDs and depression are therefore maintained through the interaction of both positive (i.e. the positive feeling created by the substance) and negative (i.e. escaping or avoiding negative feelings, experiences or thoughts) reinforcement schedules. Prolonged substance use may then result in withdrawal symptoms or other additional social and financial problems, leading to the use of more substances in an attempt to cope (Pickard, 2016). The central aim of BA treatment in an SUD context is therefore to increase behavioural engagement in rewarding and valued activities, and to decrease engagement in maladaptive (e.g. avoidance or addictive) behaviours, in order to jointly alleviate depression symptoms and to reduce dependence on substances (Daughters, Magidson, Lejuez & Chen, 2016).

The evidence base for BA as a treatment for depression stems from Jacobson’s deconstruction trial (Jacobson et al., 1996), which found that activity scheduling resulted in similar improvements in depression compared to full CBT.

Further research has since extended these findings, indicating that there is no difference in efficacy between BA and cognitive therapy (Cuijpers et al., 2006; Ekers et al., 2007). There is also evidence to suggest that BA is economically advantageous, with a recent non-inferiority trial showing that BA produces equivalent outcomes to CBT at a 21% reduced treatment cost (Richards et al., 2016). BA notably requires fewer treatment competencies than CBT (Dimidjian et al., 2011) and can be delivered effectively by practitioners with minimal training and supervision (Ekers et al., 2011). The straightforward treatment principles of BA also make it feasible for delivery with a wide range of populations, including those with reduced cognitive abilities (e.g. Dimidjian et al., 2011; Jahoda et al., 2015). A recent meta-analysis of the group BA trial evidence base (Simmonds-Buckley, Kellett & Waller, 2019) showed that depression outcomes for BA were superior to passive controls and were equivalent to active therapies, with evidence of maintenance of treatment effects at follow-up for group BA.

Within this evidence base, a number of BA protocols for depression have been developed and tested and can be categorised according to four main treatment models: (1) activity scheduling to incorporate pleasant activities into daily lives (Lewinsohn et al., 1980), (2) *Self-Control Therapy* (SCT), which extended Lewinsohn's model by introducing self-monitoring strategies (e.g. activity monitoring) to better facilitate the understanding and management of relationship of depressed behaviours and mood (Rehm, 1984), (3) *Behavioral Activation Treatment for Depression (BATD;* Lejuez et al., 2001*)*, which additionally enables activation to be grounded in valued life areas (e.g. family, hobbies), and (4) *Contextual Behavioural Activation* (Martell et al., 2001) which emphasises functional analysis of avoidance and coping behaviours in managing depression symptoms.

Nevertheless, the focus and evaluation of BA for co-occurring depression and SUDs has been limited. To date, only one systematic review has examined the effectiveness of BA as a treatment for depression and substance use (Martinez-Vispo et al., 2018). This review narratively synthesized findings from 6 RCTs and 2 practice-based studies, suggesting that BA interventions led to improvements in depression symptoms in 6 studies and reductions in substance use in 7 studies. However, this review was notably limited by the inclusion of samples with subclinical depression, thus bringing into doubt the generalisability of the evidence to clinically

depressed substance users treated within routine services. Similarly, the BA intervention in one of the included studies (González-Roz et al., 2018) was delivered in combination with CBT, thereby masking the independent effect of either treatment. As the effectiveness of BA was not quantified in the previous narrative systematic review, the clinical efficacy of BA for comorbid depression and substance use disorders currently remains uncertain.

A meta-analysis is a methodologically sound approach to enable the estimation of the overall effect of an intervention across studies, allowing for a thorough assessment of the consistency of effects in order to understand generalisability (Borenstein et al., 2011). This statistically rigorous approach to the synthesis of best available evidence is generally considered to be more reliable than qualitative and narrative syntheses (Borenstein et al., 2011; Pettiti, 1999). This meta-analysis therefore aimed to address the limitations of the previous review by quantifying the effectiveness of BA for co-occurring depression and SUDs. The study sought to specifically focus on studies that have investigated the efficacy of BA compared to active and passive controls in clinical trials with working age substance users with clinically significant depression symptoms. A meta-analysis offered the opportunity to critically evaluate and statistically combine results of comparable clinical trials and in doing so increases the numbers of observations, statistical power and improves the estimates of the effect size for BA in this patient group (Walker et al., 2008). Given that there may be distinct benefits of group BA for people with substance use problems due to factors such as affiliation and strengthening commitment to recovery (Center for Substance Abuse Treatment, 2005), the study sought to examine whether the mode of delivery of BA interventions had any impact on treatment outcomes via sensitivity analyses. In the sensitivity analyses conducted, the study also sought to define any effect that the type of substance being used had on outcome and also whether the use of active versus passive controls had an effect. Finally, the study aimed also to define the acceptability of BA through reporting the average duration of treatment, number of BA sessions attended and the overall dropout rate compared to controls.

2. Methods

2.1 Study protocol

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (Protocol ID: PROSPERO 2018: CRD42018112098).

2.2. *Inclusion and exclusion criteria*

This study was limited to randomised controlled trials of BA for substance users with depression. Studies therefore had to randomise participants to either BA or a passive control or active control (i.e. alternative psychological treatment). All available randomised controlled trials (RCTs: published studies, unpublished studies and dissertations) were included. Studies included adult substance users (age $\geq$ 18 years), with clinically significant depression symptoms as measured using diagnostic interviews or validated case-finding measures. RCTs were included if they reported depression outcomes, substance use outcomes, or both. Substances included alcohol, tobacco, illicit drugs and non-prescription use of legal drugs. Substance users were defined as individuals who met at least one of the following criteria: (i) enrolled in community or inpatient addiction treatment programme, (ii) had used substances recently as assessed by a screening questionnaire (e.g. Timeline Follow-Back Method; TLFB; Sobell & Sobell, 1992), and (iii) met criteria for SUD assessed by a structured clinical interview (e.g. Structured Clinical Interview for DSM-III-R/DSM-IV-SAC; SCID-SAC; Nunes et al., 1996).

Studies were excluded when (a) BA treatment was combined with another structured psychotherapy (e.g. CBT); (b) samples contained child and adolescent participants; (c) the participants had subclinical depression; (d) study not published in English language; or (e) the original study did not provide sufficient data for the calculation of effect sizes. The intervention was labelled as BA when the core focus of treatment was to increase positive interactions between an individual and their environment using at least the following strategies; activity monitoring and activity scheduling. There was no limit on treatment duration, mode of delivery (e.g. group vs. 1:1) or the setting in which the BA was delivered. Comparators included any passive control, treatment as usual (TAU) or active treatment. Control comparators provided participants with either a waitlist period, TAU involving routine care in a clinical practice setting and the active comparators were alternative psychotherapies

delivered in an attempt to improve depression symptoms, including CBT and structured relaxation therapy.

2.3 Outcome Measures

2.3.1 Primary outcome

The primary outcome measure was depressive symptomatology as measured using any validated self-report measure (e.g. Patient Health Questionnaire-9; PHQ-9; Kroenke et al., 2003) or clinician-rated (e.g. Hamilton Depression Rating Scale; HAM-D; Hamilton, 1960) presented by means and SDs (continuous data). Psychotherapy trials often report multiple symptom measures and since clinician-rated measures tend to produce larger effect sizes (e.g. Cuijpers et al., 2010), an algorithm was adopted so that self-report measures took precedence over clinician-rated measures. This was in order to create a more conservative estimate of treatment effect (Borenstein et al., 2011). The clinically most commonly used and well validated self-report measure (e.g. Beck Depression Inventory; BDI; Beck, Ward, Mendelson, Mock & Erbaugh, 1961, BDI-II; Beck, Steer & Brown, 1996) was selected over other self-report measures.

2.3.2 Secondary outcomes

The secondary outcome was substance use as measured using any validated self-report scale (e.g. Severity of Dependence Scale; SDS; Gossop et al., 1995) or assessment (e.g. TLFB; Sobell & Sobell, 1992), presented by means and SDs (continuous data) or abstinent / not abstinent from substances (dichotomous data). The most commonly used substance use outcome (i.e. percent days abstinent; PDA) was selected over self-reported scale measures. For studies that reported the proportion of days that substances were used in the last month, data was converted to PDA rates. Additionally, it was of secondary interest to describe attendance and dropout rates across studies (as defined by the primary study sources). Attendance rates were based on figures reported in the individual studies. Dropout rates were calculated based on the number of patients who were reported to have dropped out of BA and control conditions in proportion to the number of patients who were randomised to each condition in the individual studies.

2.4 Search strategy for identification of studies

The following electronic databases were searched from inception to 7th June 2020: PsycINFO, PubMED and the Cochrane Register of Clinical Trials. Searches were conducted with variations (including alternative synonyms and both UK and US spellings) of the following keywords: (a) behavioural activation (including activity scheduling / monitoring); (b) depression; (c) SUDs (including various substances such as alcohol and heroin); and (d) treatment efficacy. All searches were limited to human and adult populations and English language (see Supplemental File for full search strategy). Further to this, we checked the reference lists of retrieved papers and of a previous review on this topic (Martínez-Vispo et al., 2018) to identify additional studies.

2.5 Study selection

The search returned 955 unique titles and abstracts, which were screened for eligibility by the main author (SP). The corresponding authors of all included papers and relevant study protocols were contacted via email and given 4 weeks to provide details of any other published studies or unpublished data they were aware of. This generated 1 new study, though this was a quasi-experimental study and therefore did not meet the inclusion criteria. The most common reasons for exclusion during screening of titles and abstracts were: psychological problems other than depression or SUDs and treatments that were not BA. In total, 23 full-text articles were assessed independently by 2 reviewers (SP and JD). Disagreement about the inclusion of studies was resolved by discussion. A total of 5 studies met eligibility criteria and were included in the review. Figure 1 shows the PRISMA diagram (Moher et al., 2009) for the systematic selection of studies.

2.6 Risk of bias

The methodological quality of the RCTs was assessed using the Cochrane Risk of Bias Tool (Higgins et al., 2011). Given the difficulties of blinding staff and participants

in psychotherapy trials, studies were assessed using only the following four domains: (1) sequence generation, (2) allocation concealment, (3) blind assessment and (4) data attrition. Each component was rated for high, low or unclear risk of bias and a score was given for each study based on the number of components that met criteria for low risk of bias (higher scores indicate lower risk of bias; maximum score of 4). Studies were assessed independently by the main author and an independent reviewer (PhD student). Interrater reliability was calculated using Cohen's kappa (Cohen, 1960) (whereby .21-.40 = fair agreement, .41-.60 = moderate agreement, .61 to .80 = substantial agreement, .81-1.0 = almost perfect agreement; Landis & Koch, 1977). The kappa was *k* =.83 indicating almost perfect agreement.

2.7 Quality of the meta-analysis

The grading of recommendations assessment, development and evaluation (GRADE; Dijkers, 2013) approach was also used to assess the quality of the included evidence for each meta-analytic comparison. The quality of evidence was assessed using the following six criteria: (1) study design, (2) risk of bias, (3) inconsistency of results, (4) indirectness of evidence, (5) imprecision, and (6) publication bias. The meta-analysis was graded by three reviewers (SP, SK and JD) and a consensus agreed (rated either high, moderate, low or very low quality).

2.8 Data extraction

Data from included studies were extracted by the main author (SP) using the Cochrane Collaboration Data Collection form (Higgins & Green, 2011) and checked for accuracy by a second author (SK). Data extracted included study population, study setting, participant demographics, details of the intervention and comparators, characteristics of the study methodology, outcomes and times of measurement and attendance and dropout rates. For studies where insufficient data was reported for the calculation of effect sizes, study authors were contacted by e-mail and given 4 weeks to provide the missing data.

2.9 Calculation of effect sizes

Effect sizes (ESs) were calculated based on depression and substance use outcomes reported at post-treatment and last available follow-up. Standardised mean differences (SMDs) and standard error (SE) terms were calculated for the difference between BA and each comparator condition. SMDs were calculated by subtracting the mean score of the control group from the mean score of the experimental group and dividing the result by the pooled standard deviations of the experimental and control groups for depression and substance use outcomes reported at post-treatment and last available follow-up. For dichotomous substance use outcomes (i.e. number of participants abstinent vs not abstinent) and dropout rates (i.e. percentage of dropout from BA compared to comparator conditions), the odds ratio was computed and converted to Cohen's *d* using the formula $d = LogOddsRatio \times \frac{\sqrt{3}}{\pi}$ (Borenstein et al., 2011). When a study reported separate outcomes for different substances (i.e. Carpenter et al., 2008), the means of all reported substance use outcomes were averaged for each group and the standard deviations were pooled using the variance pooling formula:

$$S_{pooled} = \sqrt{\frac{\sum_{i=1}^{K}(n_i - 1)S_i^2}{\sum_{i=1}^{K} n_i - K}}$$

Where *K* is the number of outcomes, and n_i, S_i^2 are the sample size and variance corresponding to each outcome. In this particular case, $n_1 = n_2 = \cdots = n_K$ (Borenstein et al., 2011). In order to account for the risk of small-sample bias, the *j* correction was used to convert SMDs to Hedges' *g* (Hedges & Olkin, 1985). Effect sizes were interpreted according to Cohen's criteria, whereby effect sizes of 0.8 and above are considered large, effect sizes of 0.5 are moderate and effect sizes of 0.2 are small (Cohen, 1992).

2.10 Meta-analysis

Data were synthesised using the Cochrane Collaboration RevMan program (Cochrane, 2014). A random effects model was used to account for variance between and within studies. Statistical significance was set at an alpha value of 0.05. Heterogeneity was assessed using the I^2 statistic to indicate percentage of variation.

To determine statistical significance, we calculated Cochran's heterogeneity statistic using the following formula:

$$Q = \sum_{i=1}^{k} w_i(d_i - \bar{d})^2$$

Where $w = 1/V_i$ is the weight associated to each studies (i.e. the inverse of the variance V_i), d_i is the effect size for the *i*th study, $\bar{d}$ the summary effect size and k the number of studies. In order to assess the possibility of publication bias, a Begg funnel plot graph was used and inspected for asymmetry (Begg & Mazumdar, 1994). Due to the small number of studies entered into the meta-analysis (≤ 5), more detailed subgroup or moderator analyses were not possible (Borenstein et al., 2011).

2.11 Sensitivity analyses

Given that subgroup and moderator analyses were not feasible in this review due to the small number of RCTs available (Borenstein et al., 2011), a series of exploratory random effects meta-analyses were conducted. These aimed to explore the effects of different study characteristics on depression and substance use outcomes. Three sensitivity analyses were conducted: (a) the impact of different substances of dependence on treatment outcomes; (b) the effect of mode of delivery; and (c) the impact of different comparator types on treatment outcomes. As it has previously been highlighted that active treatment comparators may not be comparable with passive controls (Karlsson & Bergmark, 2015), we only included data from studies that compared BA with TAU in these analyses.

2.12 Within-group analyses

Unbiased within-group ESs were calculated where possible for pre-post and post-treatment to last available follow-up for depression and substance use outcomes to further explore the efficacy and durability of BA. SMDs were calculated for pre-post and post-treatment to follow-up depression and substance use outcomes for BA according to the formula (Minami et al., 2008):

$$d = \left(1 - \frac{3}{4n - 5}\right) \frac{M_{post} - M_{pre}}{SD_{pre}}$$

Where *n* is the number of samples within each group and M_{pre}, M_{post} and $M_{endpoint}$ are the means for the corresponding time points.

3. Results

3.1 Study characteristics

Post-treatment outcomes from N=5 RCTs of BA contributed to the analysis, totalling N=195 participants (1:1 BA *N* =52; Group BA *N*=48; Control *N* =95). Selected characteristics of the included studies are presented in Table 1 and details of the interventions are provided in Table 2. BA interventions were delivered in group (*N*=2) and individual formats (*N*=3). Treatment duration ranged from 3-24 sessions. BA sessions typically lasted between 30-60 minutes. All BA interventions included activity monitoring and activity scheduling components, some also included values assessments (N=4), behavioural contracting (*N*=2), decisional balance exercises (*N*=2), contingency management (*N*=1) and mindfulness / relaxation exercises (*N*=1).

BA was compared to active treatments in 2 studies and passive controls in 3 studies across 10 comparisons. The active treatment comparisons were structured relaxation therapy (Carpenter et al., 2008) and CBT-based guided self-help (Delgadillo et al., 2015). Structured relaxation therapy was delivered in a group format, while CBT-based guided self-help was delivered via individual therapy. In the control comparisons, BA was compared with TAU (*N*=3). In studies conducted in outpatient treatment, TAU was contact time matched to the BA interventions during the study period (*N*=2). For inpatient treatment, the BA intervention was delivered in addition to TAU (*N*=1). Participants were recruited from clinical settings in four studies (outpatient *N*=3, inpatient *N*=1) and the community on one study. Substances of dependence included nicotine (*N*=2), illicit drugs (*N*=1) and illicit drugs and alcohol (*N*=2). In all studies and across all conditions, participants had access to pharmacological treatments for substance use (e.g. OST, NRT) and depression. Depression was identified by clinical interview (*N* =4) or self-report (*N* =1).

Depression outcomes were measured via self-report in all studies, as well as clinician-rated in two studies. The BDI-II was the most commonly employed self-report outcome measure for depression (*N* =4), and the HAM-D was the most commonly employed clinician-rated measure (*N*=2). Substance use outcomes were measured via self-report using the TLFB in all studies and outcomes were biologically verified in 4/5 studies. Follow-up duration ranged between 4-30 weeks.

3.2 Acceptability of BA

The average session attendance rate for BA was 72% (range 48.3%-100%). The average attendance rate for active comparator conditions was 56% (range 48.1%-100%) and the average attendance rate for passive comparators was 86% (range 75%-100%). Insufficient information was provided to calculate specific attendance rates for BA in Delgadillo et al. (2015) study; however, only 34.8% of participants attended at least one session and the average number of sessions attended was 3.13. In the comparator condition the attendance rate was 48.1%. The attendance rate in Bercaw's (2007) study was 100% in both conditions, as failure to attend one session resulted in dropout. In the remaining studies, attendance rates ranged from 48-91% for BA interventions and 64-84% for comparator conditions. The highest attendance rate for BA was reported in the Daughters et al. (2008) inpatient study and this was also the only study in which the BA attendance rate was higher than the comparator (91% versus 84% respectively). An outpatient smoking study reported an equivalent attendance rate of 75% in both arms (MacPherson et al., 2010). The remaining study was conducted in outpatient addictions treatment and reported lower attendance rates in both arms, with a rate of 48% for BA and 64% in the comparator condition (Carpenter et al., 1998). Overall, the average dropout rate for BA was 35% (range 9-65%), while the average dropout rate for active comparator conditions was 39% (range 25-52%) and the average dropout rate for passive comparators was 32% (range 9-51%). BA dropout rates tended to be lower than comparators, with the lowest BA dropout rate reported in the Daughters et al. (2008) study. The highest dropout rate was reported in Carpenter et al.'s (1998) study which was conducted in outpatient addictions treatment and also reported the lowest attendance rate for BA.

3.3 Risk of bias

Of the *N*=5 studies included, methodological quality ranged from 1-2 quality standards met (maximum was 4); therefore, overall study quality was moderate. Most studies provided sufficient information to assess that there was a low risk of bias from randomisation, however some studies lacked a complete description of randomisation procedures (Daughters et al., 2008; MacPherson et al., 2010). One study reported using an independent administrator to inform researchers of participants' treatment allocation (Delgadillo et al., 2015). However, most studies did not provide sufficient information to assess risk of bias relating to allocation concealment. Some studies reported using research assistants who were blind to the participants' treatment condition when collecting outcome data (Daughters et al., 2008; MacPherson et al., 2010). Other studies either did not provide enough information on the blinding of researchers collecting participant data (Bercaw, 2007; Carpenter et al., 2008), or indicated that researchers collecting data were not blind to participants' treatment condition (Delgadillo et al., 2015). Due to the nature of conducting research in addiction treatment settings, there were high levels of attrition in most studies. One study addressed this by conducting completer analyses (Bercaw, 2007), however most studies either did not provide adequate information on how they addressed missing data (*N*=2), or used methods that carry an increased risk of bias, such as last observation carried forward (Carpenter et al., 2008; Delgadillo et al., 2015).

3.4 Meta-analysis of BA versus comparators; GRADE results

Meta-analytic comparisons were performed to examine the aggregated effect of BA versus controls on (1) Depression and (2) Substance use outcomes at post-treatment and last available follow-up. GRADE assessments (Dijkers, 2013) are reported for each comparison to indicate the quality of evidence. All comparisons were based on evidence from RCTs so started as high quality evidence. Across the meta-analyses, few issues were found with heterogeneity or publication bias, but there were some issues with regards to study limitations, indirectness of evidence and imprecision. All comparisons were downgraded two levels due to the small

number of studies, risk of bias, differing control groups and differences in follow-up time-points and lengths.

3.5 Effects of BA on depression outcomes

3.5.1 Post-treatment and follow-up comparisons

All studies were included in a random effects meta-analysis of BA versus controls for post-treatment depression outcomes (*k* = 5; N = 195). One of these studies did not assess participants until 12 weeks after BA treatment had finished (Delgadillo et al., 2015; *N* = 50). The pooled SMD presented in Figure 2 indicated that BA was not associated with differential improvements in post-treatment depression symptoms (Figure 2; SMD = 0.19; 95% confidence interval (CI) -0.10 to 0.49; Z = 1.28, *p* = 0.20; GRADE = Low). Between-study variation was non-significant indicating homogeneity between studies (I^2 = 0%; Q = 2.65, *p* = 0.61). Inspection of the funnel plot suggested there was some evidence of publication bias for this outcome (see Figure 3), however statistical testing using Egger's regression indicated no significant asymmetry in study distribution (B = -3.2, t(4) = -1.23, *P* = 0.30).

Five treatment arm comparisons evaluated the effects of BA versus controls on depression outcomes at follow-up (*k* = 5; *N* = 195), though one of these studies only provided post-treatment data (Carpenter et al., 2008; *N* = 38). The pooled SMD indicated that BA was not associated with significant improvements in depression symptoms at follow-up when compared to controls (Figure 2; SMD = -0.10; 95% confidence interval (CI) -0.51 to 0.30; Z = 0.50; *p* = 0.62; GRADE = Low). Between-study variation was significant indicating a small to moderate level of heterogeneity between studies (I^2 = 45%; Q = 11.61, *p* < 0.05). Inspection of the funnel plot revealed no evidence of publication bias for this outcome (see Figure 4) and Egger's regression indicated no significant asymmetry in study distribution (B = -3.1, t(4) = -0.62, *P* = 0.58).

3.5.2 S*ensitivity analyses*

For post-treatment depression outcomes, results of sensitivity analyses indicated that neither substance type (*k*=2; *N*=63; SMD = 0.15; 95% confidence interval (CI) -0.44 to 0.73; Z = 0.50; *p* = 0.62), mode of BA delivery (*k*=2; *N*=86; SMD = 0.15; 95% confidence interval (CI) -0.30 to 0.60; Z = 0.66; *p* = 0.51) nor type of comparator (*k*=3; *N*=107; SMD = 0.07; 95% confidence interval (CI) -0.32 to 0.47; Z = 0.35; *p* = 0.73) affected the size of the effect for post-treatment depression outcomes (see Figure 5).

For follow-up depression outcomes, sensitivity analyses indicated that group BA delivery (*k*=2, *N*=86; SMD = -0.49; 95% confidence interval (CI) -0.94 to -0.04; Z = 2.15; *p* < 0.05) and passive control comparators (*k*=3; *N*=107; SMD = -0.45; 95% confidence interval (CI) -0.85 to -0.05; Z = 2.22; *p* = < 0.05) were associated with significant overall effects in favour of BA. Substance type (Figure 3; *k*=2; *N*=63; SMD =- 0.46; 95% confidence interval (CI) -0.97 TO 0.05; Z = 1.78; *p* = 0.08) did not significantly affect the size of the effect for depression outcomes at follow-up (see Figure 5).

3.5.3 *Within-group Effect Sizes for depression outcomes*

The pre-post standardised mean ES for the full BA sample indicated an overall reduction in depression symptoms from pre-treatment to post-treatment (*N* = 100; SMD = -0.57; 95% confidence interval (CI) -0.79 TO -0.36). Studies that did not report both post-treatment and follow-up outcomes were excluded from post-treatment to follow-up analyses (Carpenter et al., 2008; Delgadillo et al., 2015). The post-treatment to follow-up standardised mean ES for the remaining BA sample indicated an overall reduction in depression symptoms from post-treatment to last available follow-up (*N* = 59; SMD = -0.49, confidence interval (CI) -0.76 to -0.22).

3.6 Effects of BA on substance use outcomes

3.6.1. Post-treatment and follow-up comparisons

All studies reporting substance use outcomes were included in a random effects meta-analysis of BA versus controls for post-treatment substance use

outcomes (*k* = 4; N = 151). One of these studies did not assess participants until 12 weeks after BA treatment had finished (Delgadillo et al., 2015; *N* = 50). The pooled SMD indicated that BA was not associated with significant improvements in post-treatment substance use outcomes compared to controls (Figure 5; SMD = 0.14; 95% confidence interval (CI) -0.33 to 0.6; Z = 0.57; *p* = 0.57; GRADE = Low). Between-study variation was non-significant indicating homogeneity between studies (I^2 = 37%; Q = 5.89, *p* = 0.12). There was some evidence of publication bias for this outcome based on inspection of the funnel plot (see Figure 6), however Egger's regression indicated no significant asymmetry in study distribution (B = -0.67, t(3) = -0.18, *P* = 0.88).

Four comparisons evaluated the effects of BA versus controls on substance use outcomes at follow-up (*k* = 5; *N* = 151). One of these studies only reported post-treatment substance use outcomes (Carpenter et al., 2008; *N* = 38). The pooled SMD indicated that BA was not associated with significant improvements in follow-up substance use outcomes compared to controls (Figure 5; SMD = 0.17; 95% confidence interval (CI) -0.34 to 0.69; Z = 0.65; *p* = 0.51; GRADE = Low). The studies were homogeneous (I^2 = 35%; Q = 4.81, *p* = 0.18). There was no evidence of publication bias for this outcome based on inspection of the funnel plot (see Figure 7) and Egger's regression indicated no significant asymmetry in study distribution (B = -0.84, t(3) = -0.37, *P* = 0.75).

3.6.2 Sensitivity Analyses

For post-treatment substance use outcomes, results of sensitivity analyses indicated that neither substance type nor type of comparator (*k*=2; *N*=63; SMD = 0.02; 95% confidence interval (CI) -0.64 to 0.68; Z = 0.06; *p* = 0.95) affected the size of the effect for substance use outcomes (see Figure 8). It was not possible to conduct a sensitivity analysis for mode of delivery as one of the two studies that delivered BA in a group format did not report post-treatment substance use outcomes (Daughters et al., 2008).

For substance use outcomes at follow-up, results indicated that neither type of substance nor type of comparator (*k*=2; *N*=63; SMD = 0.08; 95% confidence interval (CI) -0.78 to 0.95; Z = 0.19; *p* = 0.95) affected the size of the effect for substance use

outcomes (see Figure 8). It was not possible to conduct a sensitivity analysis for mode of delivery as one of the two studies that delivered BA in a group format did not provide any data on substance use outcomes (Daughters et al., 2008).

3.6.3 Within-group Effect Sizes

Studies that did not report substance use outcomes (Daughters et al., 2008) or reported odds ratios for substance use outcomes (Bercaw, 2007; MacPherson et al., 2010) were excluded from pre-post analyses as means and standard deviations were not available to calculate the ES. The pre-post standardised mean ES for the remaining BA sample indicated an overall reduction in substance use from baseline to post-treatment (*N* = 41; SMD = 1.26; 95% confidence interval (CI) 0.85 to 1.66). Post-treatment to follow-up analyses were not feasible due to studies either not reporting any substance use outcomes (Daughters et al., 2008), reporting only pre-treatment to follow-up data (Delgadillo et al., 2015), or reporting odds ratios for substance use outcomes (Bercaw, 2007; MacPherson et al., 2010).

3.7 *Fail-safe N calculations*

Fail-safe *N* calculations were computed using Rosenthal's *N* (Rosenthal, 1979) to determine the number of RCTs that would need to be conducted to find a significant effect of BA based on the current evidence base. For both depression and substance use outcomes, results indicated that a further 10 trials would need to be conducted in order to find any significant effect of BA in this population.

4. Discussion

This review examined the efficacy of BA for co-occurring depression and SUDs via a systematic review and meta-analysis of the clinical trial evidence base. Given that there are few evidence-based treatments for co-occurring depression and SUDs (Baker et al., 2012; Hides et al., 2010), the objective of this analysis was to offer a quantitative summary as to the potential efficacy of BA for patients presenting with these comorbid problems. This was the first meta-analysis of BA for depression and

co-morbid SUDs and so complemented and updated a previous systematic review (Martinez-Vispo et al., 2018).

4.1 Summary of BA outcomes

Overall, results did not provide support for the differential effectiveness of BA as a treatment for co-occurring depression and SUDs. BA had no distinctive significant effects on depression or substance use outcomes compared to passive and active controls at post-treatment or follow-up. The direction of results at post-treatment was in favour of controls rather than BA which is in contrast to the conclusions drawn from a previous narrative review (Martinez-Vispo et al., 2018). However, standardised mean ESs indicated that BA was associated with improvements in depression and substance use outcomes within the pooled BA sample.

For depression and substance use outcomes, studies varied with regards to favouring BA over comparators in the computation of the total effect. For depression outcomes, studies addressing nicotine dependence (Bercaw, 2007; MacPherson et al., 2010) and the study conducted in an inpatient drug and alcohol treatment setting (Daughters et al., 2008) were found to produce the largest ESs in favour of BA at post-treatment and follow-up. These studies were notably conducted with patients who might be expected to have a lower complexity profile in terms of situational and lifestyle factors. Therefore, these findings appear to be consistent with research conducted with non-dependent samples indicating that patients with less complex profiles (in terms of various biological, behavioural and situational factors) tend to exhibit better depression outcomes after psychological treatment compared to those with more complex profiles (Delgadillo et al., 2017). For substance use outcomes, there did not appear to be any distinctive similarities between the two studies with the largest ESs at post-treatment and follow-up (Delgadillo et al., 2015; MacPherson et al., 2010).

For follow-up depression outcomes, ESs in favour of BA were notably larger in studies that delivered group BA and compared against passive comparators for depression outcomes and this observation was supported by evidence from sensitivity analyses. These findings tend to mirror those obtained from reviews of CBT for co-occurring depression and SUDs, which found that although there is

support for CBT over passive control conditions, there is little evidence that CBT is superior when compared to other psychotherapies (e.g. Hides, Samet & Lubman, 2010). For substance use outcomes, there was no evidence from individual studies or sensitivity analyses that effect sizes in favour of BA were larger in studies that addressed nicotine dependence, delivered BA in a group format or compared against passive controls. The lack of significant findings for substance use outcomes in this review is in contrast to a large RCT of BA conducted with non-depressed SUD patients, which found that BA was associated with a significantly higher likelihood of abstinence up to 12 months' post-treatment compared to an active comparator (Daughters et al., 2018). It seems possible that the small sample sizes of studies included in this review may have reduced their ability to detect any significant effects.

4.2 Acceptability of BA

On average, dropout rates were lower for BA interventions than for comparator conditions, suggesting that BA is an acceptable treatment for patients with co-occurring depression and SUDs. This finding is consistent with a recent meta-analysis of group BA conducted with non-substance-dependent samples (Simmonds-Buckley, Waller & Kellett, 2018). Attendance rates were notably higher in studies addressing nicotine dependence (Bercaw, 2007; MacPherson et al., 2011) and the study conducted in an inpatient addictions treatment centre (Daughters et al., 2008). This may reflect the lower complexity profiles of participants in these studies given that the attendance rate in comparator conditions was also higher compared to studies conducted in outpatient drugs and alcohol treatment (Carpenter et al., 2008; Delgadillo et al., 2015). It could also point to the importance of mode of delivery, as attendance rates in BA and comparator conditions were generally higher in studies that delivered treatments in a group format (Daughters et al., 2008; MacPherson et al., 2011). Higher attendance rates for BA were associated with larger ESs for depression outcomes, indicating that treatment engagement is important for reducing depressive pathology in this population.

4.3 The BA approach

All of the BA interventions delivered in the included studies were classified as "complex BA" due to their inclusion of treatment components beyond the core BA elements of activity scheduling and monitoring. Most were based on the 'BATD' treatment model (Lejuez et al., 2001), except for the intervention in Delgadillo and colleagues' (2015) study which was derived from 'contextual BA' (Martell et al., 2001). Nevertheless, there was considerable variability between the BA interventions, particularly the length of treatment, which was found to range from 3-24 sessions.

The study which delivered the highest number of BA sessions in this review was found to have the least significant results in favour of BA (Carpenter et al., 2008). This finding is consistent with a previous meta-analysis of CBT for SUDs which found that interventions with a higher number of treatment sessions were associated with lower ESs for substance use outcomes (Magill & Ray, 2009). However, studies that reported the greatest ESs in favour of BA for depression outcomes in this review delivered BA in 8-10 sessions (Daughters et al., 2008' MacPherson et al., 2010) and the study which reported the greatest ES in favour of substance use outcomes delivered BA in 12 sessions (Delgadillo et al., 2015). A previous study of MBCT also found that 10 sessions of therapy were more effective than a single session for improving substance use outcomes in people with co-occurring depression and alcohol use problems (Baker et al., 2010). It therefore seems unlikely that number of treatment sessions is the most important factor influencing BA outcomes in this population.

The study that was based exclusively on the BATD treatment model (comprising $\leq$ 3 treatment components) (Macpherson et al., 2010) notably had greater ESs in favour of BA for both depression and substance use outcomes at follow-up, while the study based on Contextual BA had the greatest ES in favour of BA for substance use outcomes at follow-up (Delgadillo et al., 2015). The former findings are consistent with evidence that more intensive, complicated interventions may be unsuitable for the needs of patients with co-occurring depression and SUDs due to a higher prevalence of cognitive deficits (e.g. Vik et al., 2004) and attention problems (e.g. Kessler et al., 2006). The findings from Delgadillo and colleagues' (2015) study challenge this idea because contextual BA includes components such as formulation and functional analysis of avoidant patterns. However, BA participants

only attended 3/12 sessions on average, therefore it is likely that most participants did not receive the more complex aspects of the intervention in any case. The comparatively low BA attendance rates observed in the two studies conducted in Community Drug and Alcohol Treatment (CDAT) (Carpenter et al.,2008, Delgadillo et al., 2015) suggest that briefer, less complex forms of BA may be a more suitable option for this specific patient group.

There is also evidence to suggest that BA may be more effective when delivered in a group format. Studies that delivered group BA were found to have higher attendance rates and greater ESs for depression (Daughters et al. 2008; MacPherson et al., 2010) and substance use outcomes (MacPherson et al., 2010). Indeed, previous studies have demonstrated the efficacy of group BA in improving depression outcomes in non-dependent samples (Simmonds-Buckley, Kellett & Waller, 2019), as well as substance use outcomes in non-depressed SUD patients (Daughters et al., 2018). The benefits of group therapy in addiction treatment are well-established (Galanter, Hayden, Castañeda & Franco, 2005) and this mode of delivery may enhance engagement with BA through social processes such as interpersonal learning, peer support and identification (Ahmed, Abolmagd, Rakhawy, Erfan & Mamdouh, 2010). These appear to be the 'common factors' that are present across group based approaches to treatment in complex client groups including feeling connected, communication and a sense of belonging (Bledin, Loat, Caffrey, Evans, Taylor & Nitsun, 2016). However, there is some evidence to suggest that group therapy may be less effective for patients with a higher level of complexity (Moggia, Lutz, Arndt & Feixas, 2020). It is therefore unclear whether group BA would be suitable for depressed SUD patients with more complex profiles, such as those who are actively using substances and accessing CDAT.

4.4 Limitations

Results of this review should be interpreted with caution, primarily due to the small number of studies and small sample sizes in the original studies. This may have reduced power to detect a significant effect and impacted on the accuracy of the confidence intervals and heterogeneity tests (Borenstein et al., 2011). None of the included studies reported sample size calculations. Based on the current

analyses, an RCT investigating BA as a treatment for co-occurring depression and SUDs would need to recruit at least 786 participants (393 in each group) in order to detect a small effect in favour of BA (Cohen, 1992). This would notably present a considerable challenge to researchers given the difficulties of recruiting SUD participants to trials in addiction treatment centres (e.g. Ashery & McAuliffe, 1992; Melberg & Humphreys, 2010).

Some issues were also noted regarding variability in the measurement and reporting of substance use outcomes. Indeed, in contrast to depression outcomes which were all reported based on standardised self-report measures of recent depressive symptoms, reporting of substance use outcomes varied markedly between studies. Studies addressing nicotine dependence reported point prevalence abstinence (PPA) from 1-week (Bercaw, 2007) up to 30-weeks (MacPherson et al., 2010). Bercaw (2007) also reported continuous abstinence from the quit date. Studies addressing illicit drug and alcohol use reported PDA in the past month (Delgadillo et al., 2015) and percentage of days that different substances were used in the last month (Carpenter et al., 2008). With regards to the latter, this was particularly problematic as the separate substance use outcomes had to be pooled in order to calculate the ES for this review. Thus, even though Carpenter et al. (2008) found a significant effect of BA for opiate use, the ES for this study in the present review favoured the comparator, which was likely due to the lack of significant findings for benzodiazepine and cocaine use. It can be difficult to reliably measure outcomes for patients who are using illicit drugs and alcohol. Rates of polysubstance use are high (Connor et al., 2013) and PDA (as well as PPA for smoking) does not reflect reductions in the amount of substances used if the patient is still using substances daily.

Moreover, there was a lack of consistency with regards to the number and duration of follow-ups which made it somewhat difficult to aggregate and compare findings between studies in this review. Nevertheless, evidence from within-group analyses suggested that BA led to improvements in depression symptoms both before and after treatment had finished. Indeed, previous research on CBT for substance use has found evidence of “sleeper effects”, whereby reductions in substance use continued to increase up to 1-year follow-up (e.g. Carroll et al., 1994). The longest follow-up period of the studies included in this review was 30 weeks, at

which point the effects of BA on both depression and smoking outcomes were indeed reported to be superior to standard treatment (MacPherson et al., 2010). In studies addressing illicit drug and alcohol use, there were no significant differences in depression (Carpenter et al., 2008; Delgadillo et al., 2015) or substance use (Carpenter et al., 2008) outcomes reported between BA and comparators at 24-week follow-up, however one of these studies only provided data for post-treatment outcomes (Carpenter et al., 2008). The other study only reported follow-up data for outcomes measured 12 weeks after BA treatment had finished therefore it was not possible to calculate standardised mean ESs from post-treatment to follow-up (Delgadillo, 2015). It is therefore possible that longer follow-ups would reveal significant overall effects of BA that extend beyond those of comparative treatments.

4.5 Future research

Additional RCTs with larger samples and multiple follow-up points over a longer period would allow for a more accurate estimate of the effectiveness and durability of BA for co-occurring depression and SUDs. These studies should compare individual and group BA in different populations of SUD patients to explore the potential influence of patient complexity, as well as any social processes that may contribute to the effectiveness of group BA. It would also be beneficial for studies to compare individual and group BA with other active treatments, particularly emerging 3rd wave therapies such as ACT and MBCT which have received remarkably little attention as a treatment for this comorbidity. This would establish whether there are any distinct benefits of individual and group BA compared to other potentially efficacious treatments. More comprehensive, high-quality studies would also allow for more detailed meta-analyses looking at subgroups and moderators in order to identify specific factors that contribute to the effectiveness of BA and multiple follow-ups over longer periods would enable exploration of identified sleeper effects (e.g. Carroll et al., 1994).

Due to power analyses not being routinely reported in the trials analysed here, all future trials should report a power analysis in their methods and whether recruitment targets were subsequently achieved in their results. All studies need to routinely report attendance rates for sessions and dropout rates and adverse event rates.

Studies also need to be more consistent and specific in how substance use outcomes are reported, particularly in drug and alcohol treatment settings where the substances used varies within samples. Measures of PDA and PPA appear to the most commonly used substance use outcomes and should continue to be reported as standard in order to ensure between-study consistency and associated benchmarking. In drug and alcohol treatment settings, it is important to provide a general measure of PDA based on participants' primary substance, though it may also be useful to report outcomes for different substances individually to allow exploration of BA's effects on the use of different substances (e.g. Carpenter et al., 2008). However, given that PDA and PPA measures may not necessarily reflect the full extent of a patient's progress, it may also be beneficial for studies to additionally report changes in psychological dependence to substances using a standardised self-report measure (e.g. Severity of Dependence scale; Gossop et al., 1995). This would facilitate a more comprehensive view of efficacy in relation to substance use outcomes.

5. Conclusion

The current evidence does not support the dissemination of BA to treat co-occurring depression and SUDs, despite this being an apparently acceptable intervention. BA appears to improve depression and substance use outcomes overall, but there is no evidence that it is more effective compared to other treatments. Preliminary analyses indicate that BA may be more effective for improving depression outcomes when it is compared to passive controls and delivered in a group format. Based on data from the studies included in this review, fail-safe N calculations indicate that a further 10 RCTs would be needed to overturn the above conclusion (Rosenthal, 1979). These additional RCTs would need to recruit a higher volume of participants and adopt multiple follow-ups over longer periods in order to detect any significant effect of BA and then assess its durability. Future RCTs should aim to compare the effectiveness of group and individual BA in different populations of SUD patients, as well as compare BA with other treatments in order to establish differential effectiveness. BA may still hold promise as a treatment for co-occurring depression and SUDs. However, there is currently unconvincing evidence that implementing BA in routine

practice is associated with distinct improvements in key outcomes for patients with this comorbidity.

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Figure 1: PRISMA flowchart depicting the process of searching, screening and selecting studies

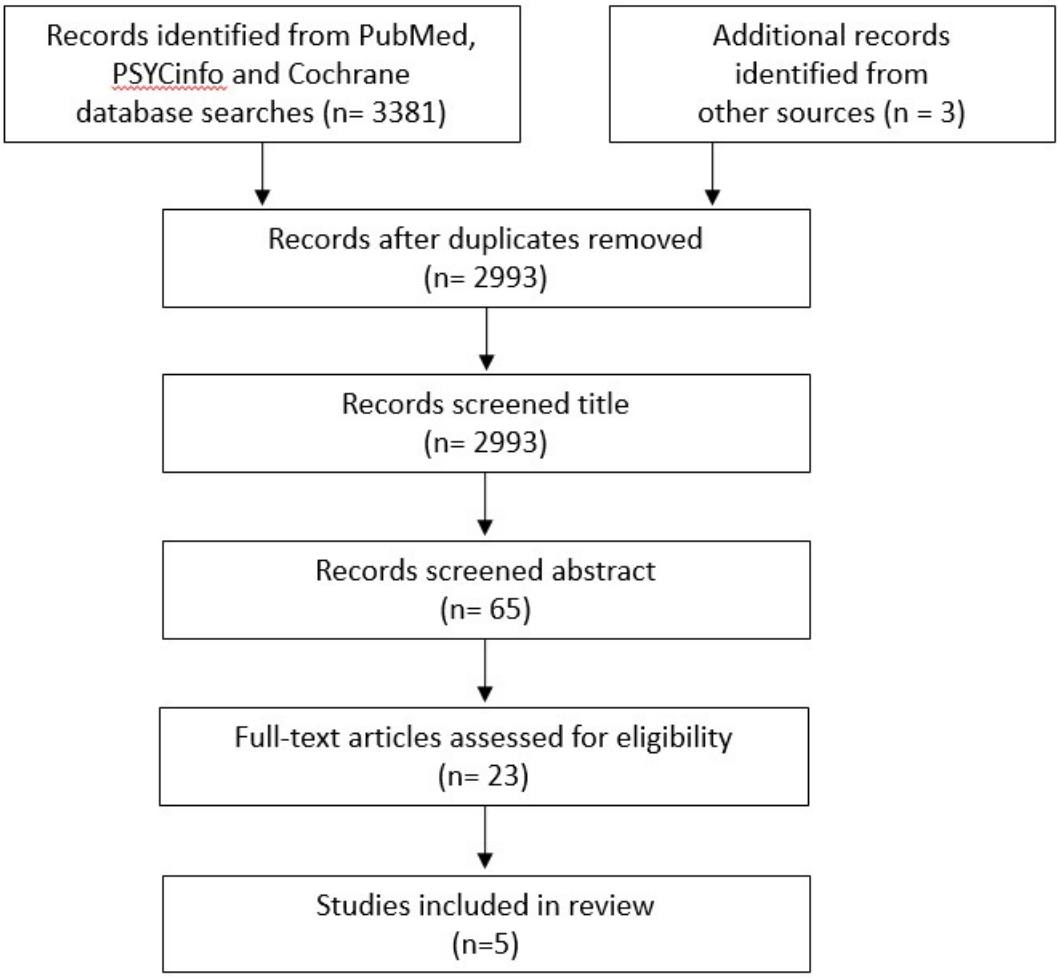


Figure 2: Effects of BA versus controls on depression outcomes

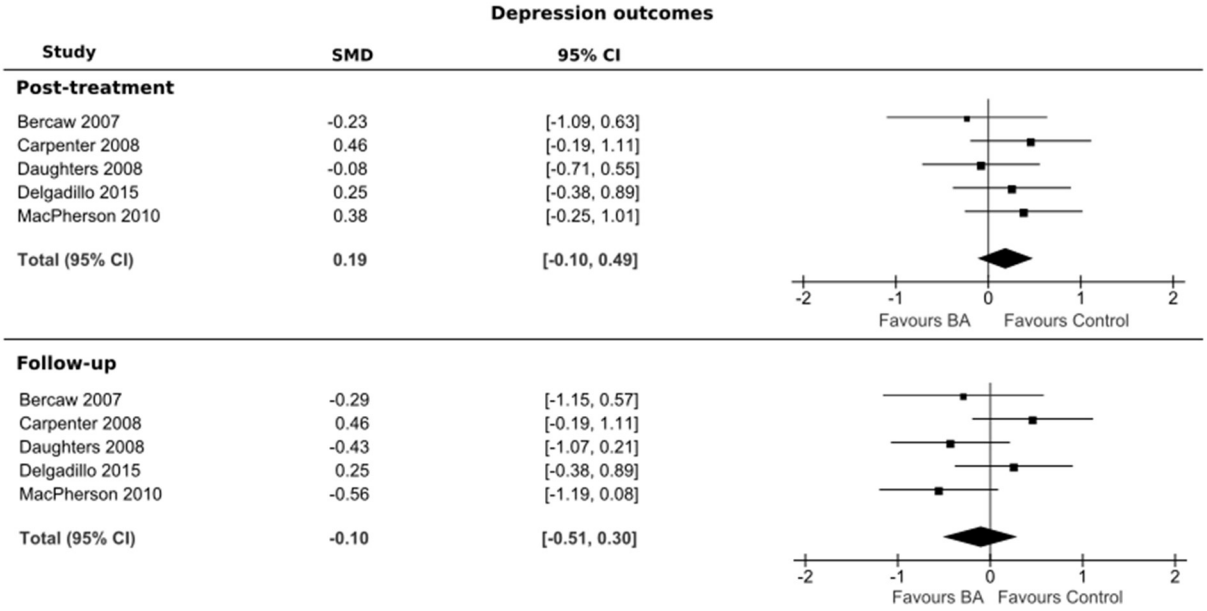


Figure 3: Funnel plot for BA versus control on post-treatment depression outcomes

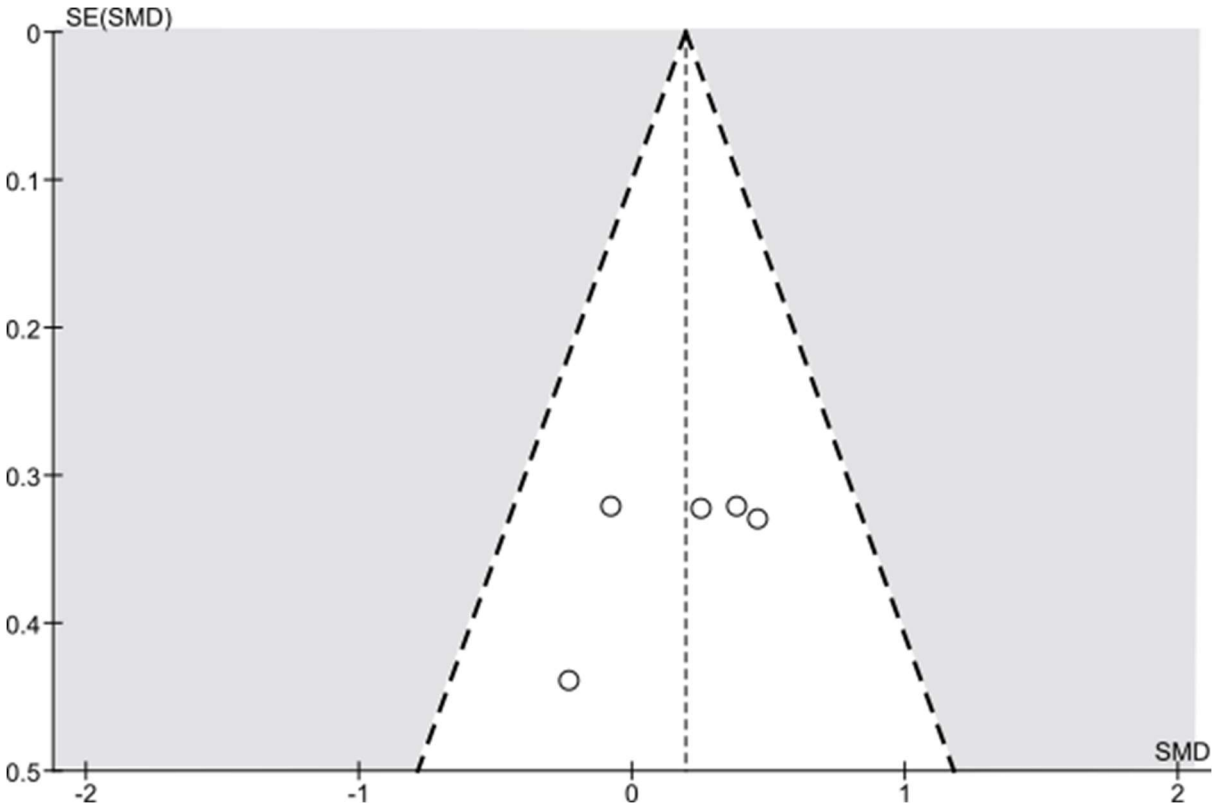


Figure 4: Funnel plot for BA versus control on follow-up depression outcomes

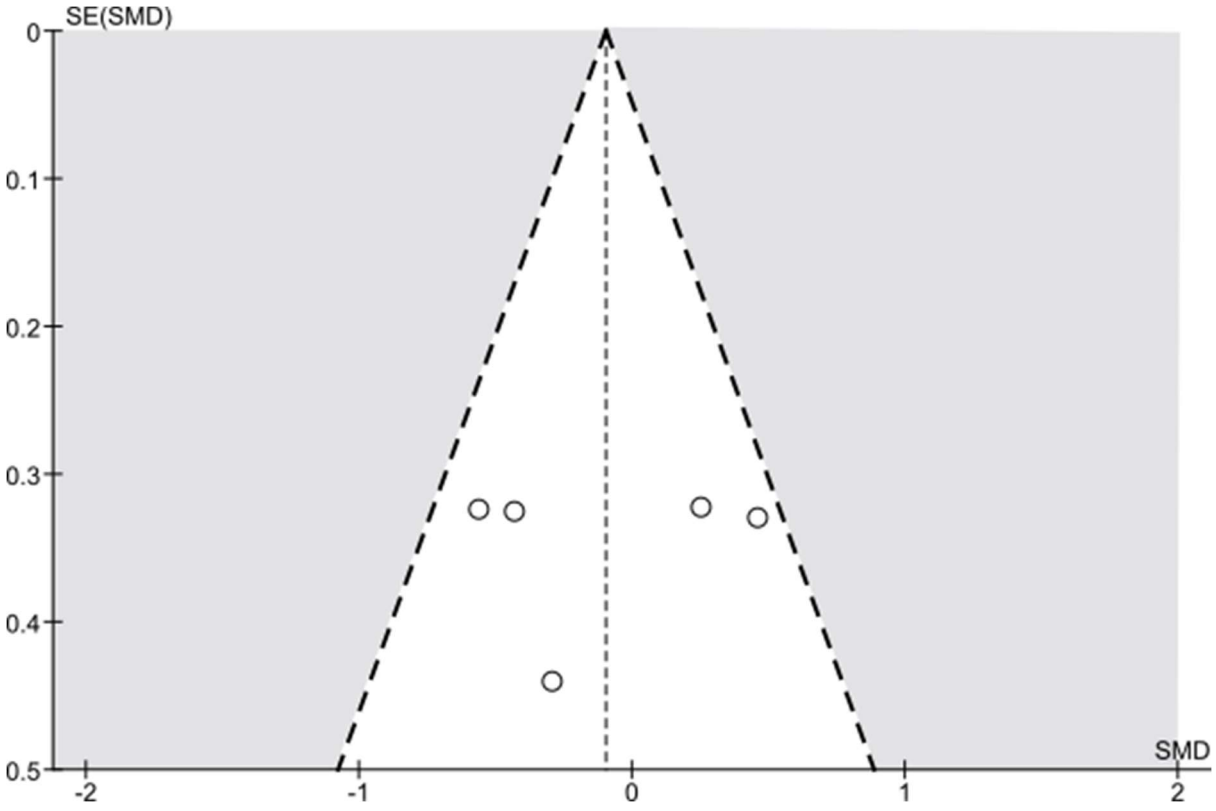
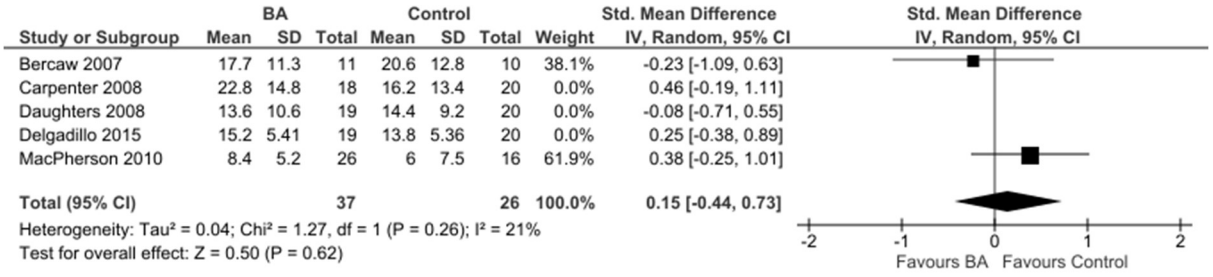


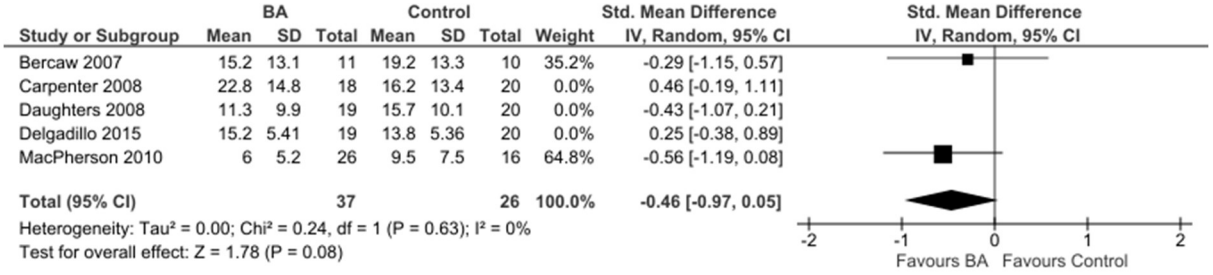
Figure 5: Sensitivity analyses for post-treatment and follow-up depression outcomes

1. Comparisons of studies conducted with nicotine dependent samples only

Post-Treatment Depression

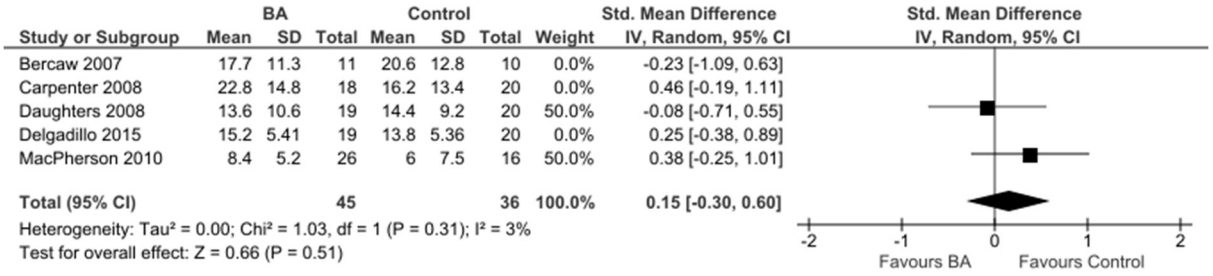


Follow-up Depression

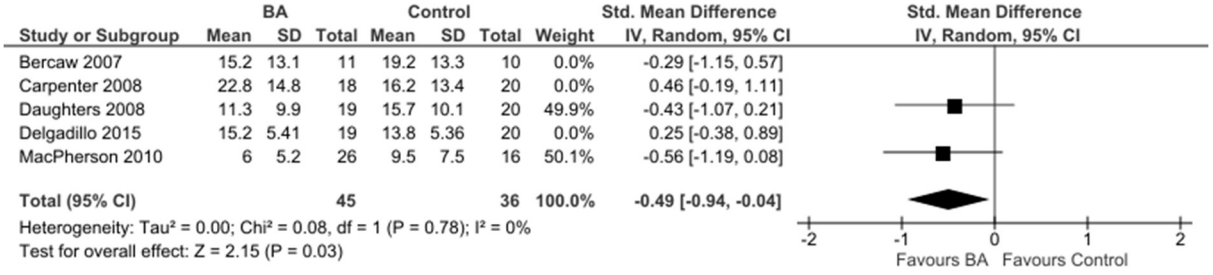


2. Comparisons of studies that delivered group BA

Post-Treatment Depression



Follow-up Depression

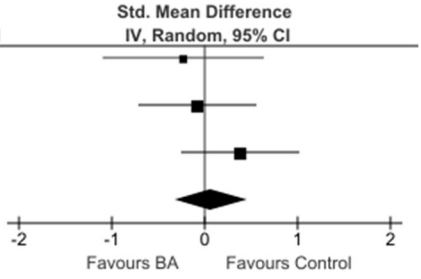


3. Comparisons of studies that employed passive controls

Post-Treatment Depression

Study or Subgroup	BA Mean	BA SD	BA Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bercaw 2007	17.7	11.3	11	20.6	12.8	10	21.1%	-0.23 [-1.09, 0.63]
Carpenter 2008	22.8	14.8	18	16.2	13.4	20	0.0%	0.46 [-0.19, 1.11]
Daughters 2008	13.6	10.6	19	14.4	9.2	20	39.5%	-0.08 [-0.71, 0.55]
Delgadillo 2015	15.2	5.41	19	13.8	5.36	20	0.0%	0.25 [-0.38, 0.89]
MacPherson 2010	8.4	5.2	26	6	7.5	16	39.4%	0.38 [-0.25, 1.01]
Total (95% CI)			**56**			**46**	**100.0%**	**0.07 [-0.32, 0.47]**

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)



Follow-up Depression

Study or Subgroup	BA Mean	BA SD	BA Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bercaw 2007	15.2	13.1	11	19.2	13.3	10	21.4%	-0.29 [-1.15, 0.57]
Carpenter 2008	22.8	14.8	18	16.2	13.4	20	0.0%	0.46 [-0.19, 1.11]
Daughters 2008	11.3	9.9	19	15.7	10.1	20	39.3%	-0.43 [-1.07, 0.21]
Delgadillo 2015	15.2	5.41	19	13.8	5.36	20	0.0%	0.25 [-0.38, 0.89]
MacPherson 2010	6	5.2	26	9.5	7.5	16	39.4%	-0.56 [-1.19, 0.08]
Total (95% CI)			**56**			**46**	**100.0%**	**-0.45 [-0.85, -0.05]**

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)

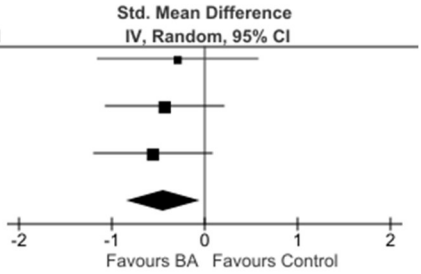
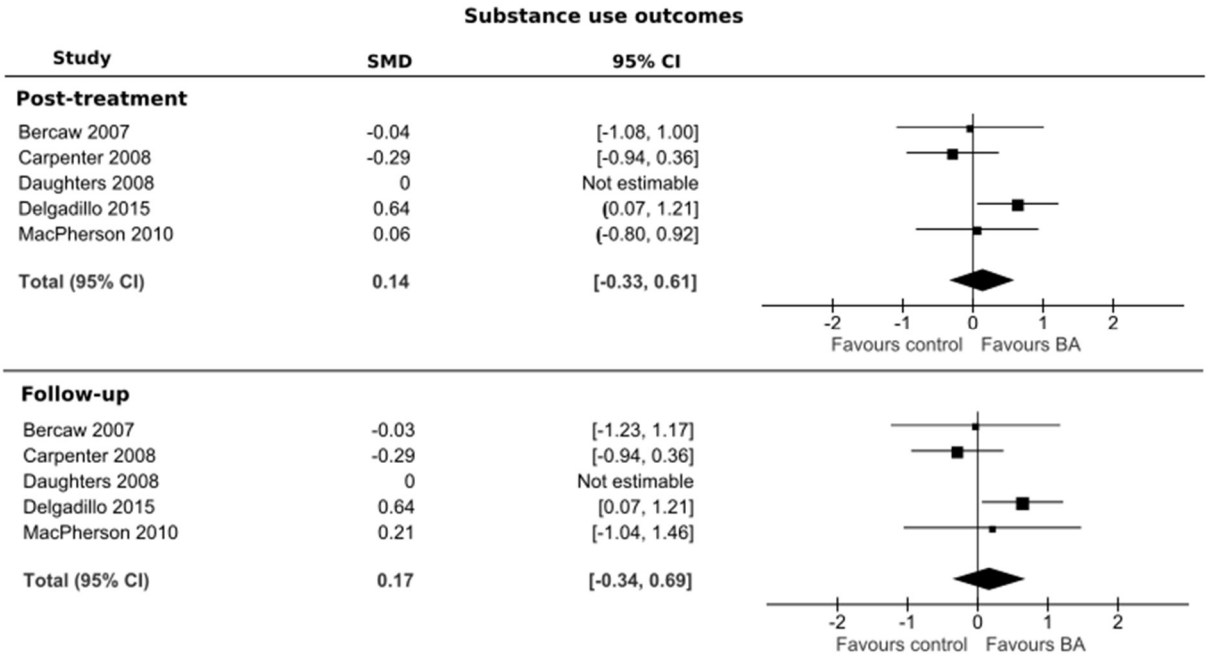


Figure 6: Effects of BA versus controls on substance use outcomes



Note: Substance use outcome is PDA/PPA: Positive values indicate more days abstinent in the BA conditions compared to controls

Figure 7: Funnel plot for BA versus controls on post-treatment substance use outcomes

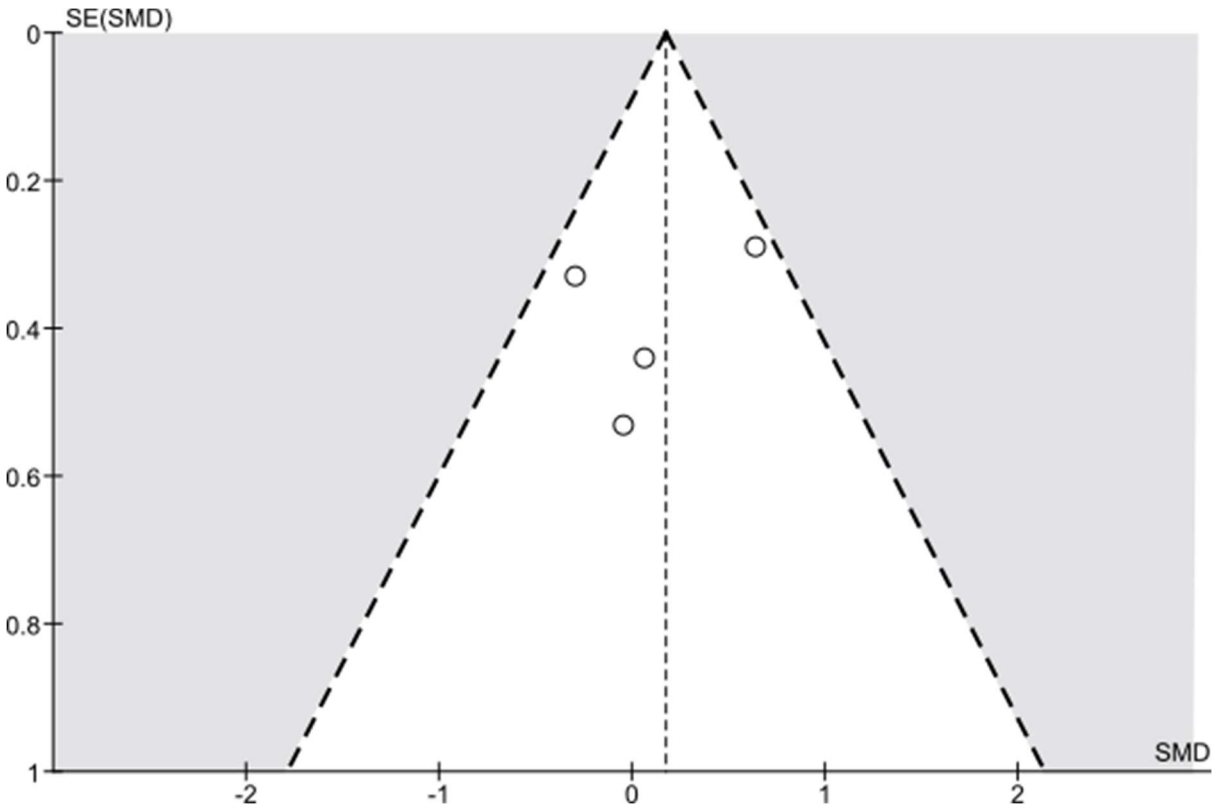


Figure 8: Funnel plot for BA versus control on follow-up substance use outcomes

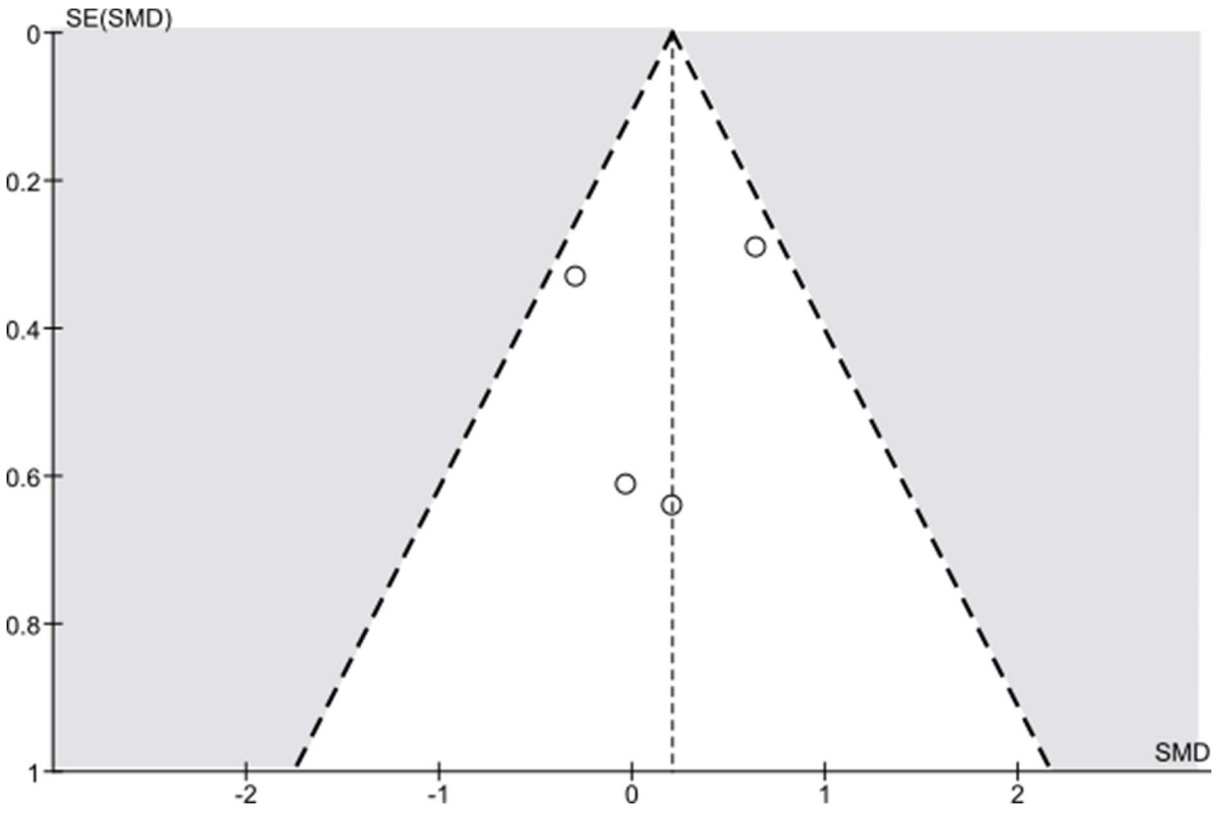
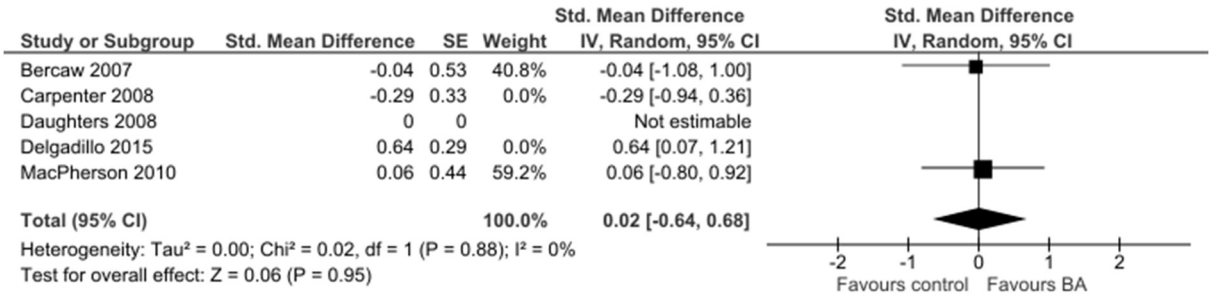


Figure 9: Sensitivity analyses for post-treatment and follow-up substance use outcomes

1. Comparisons of studies conducted with nicotine dependent samples and passive control comparators only (same sample)

Post-Treatment Substance Use



Follow-up Substance Use

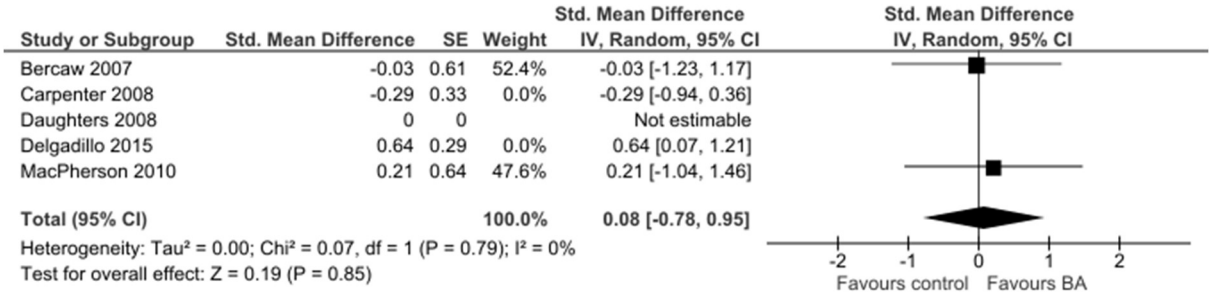


Table 1. Study characteristics of the trials treating co-occurring depression and substance use disorders

Study	*Clinical setting and country*	*Substance of dependence*	*Aims*	*Inclusion criteria*	*Exclusion Criteria*	*Sample size (N)*	*Mean age (SD)*	*Sex % Female*	*Measures used (highlighted if meta-analysed)*	*Follow-up (weeks)*	*Risk of bias score (0-4)*
Bercaw et al., (2007)	Clinical (Outpatient), USA	Tobacco	Development and investigation of a brief the BA-based smoking intervention Life Enhancement Treatment for Smoking (LETS-Quit).	(1) Baseline BDI-II score > 12, (2) Regular smoker (10+ cigarettes per day), (3) Aged 18-65, (4) Strong desire to quit smoking (≥7 on 0-10 scale)	(1) Schizophrenia diagnosis, (2) Past-month illicit drug or alcohol abuse	26	48 (SD)	14%	BDI-II, TLFB	5	2
Carpenter et al., (2008)	Clinical (Outpatient), USA	Illicit Drugs	To test the efficacy of BTDD vs. REL for DSM-IV depressive disorders and substance abuse	(1) Current DSM-IV major depression or dysthymic disorder; (2) Stable methadone dose (no changes in prior two weeks) of ≥60 ml.	NR	38	40 (SD)	42.1%	HAM-D, BDI-II, TLFB	24	1
Daughters et al., (2008)	Clinical (Inpatient), USA	Illicit Drugs	To test the efficacy of integrating a brief behavioural	(1) Minimum of 18 years of age, (2) met DSM-IV criteria for substance	(1) Not meeting all inclusion criteria, (2) Taking psychotropic medication for ≤3	44	42.1	37.2%	BDI-II, HAM-D	4	1

			intervention for depression into standard substance abuse treatment	dependence for past year, (3) Completed >= 2 weeks in the inpatient treatment center and detoxification prior to entry into the center, (4) No less than 60 days of treatment, (5) A score at least in the moderate range on the BDI-II, (6) ability to speak and read English sufficiently.	months, (3) Meet criteria for psychotic disorder						
Delgadillo et al., (2015)	Clinical (Outpatient), UK	Illicit Drugs & Alcohol	To examine the feasibility of a 12-session face-to-face BA intervention compared to a CBT-based guided self-help intervention for depression	(1) ≥1 month registered with CDAT service; (2) Clinically significant depression symptoms as defined by the PHQ-9; (3) Mild-to-moderate symptoms of alcohol/drug dependence as defined by SDS	(1) Not meeting all inclusion criteria, (2) Meeting criteria for psychotic, bipolar or severe anxiety disorder, (3) Abstinent from psychoactive substances for at least 4 weeks	50	37.2 (SD)	32%	PHQ-9, TLFB	24	2
MacPherson et al., (2010)	Community, USA	Tobacco	To examine BA as a treatment	(1) Age18–65; (2) current	(1) BDI-II score less than 7, (2)	68	43.8 (SD)	48.5%	BDI-II, TLFB	30	2

	for smoking cessation and depression vs. ST.	regular smoker (≥1 year); (3) Smoking ≥10 cigarettes/day; (4) BDI-II ≥10; (5) No current DSM-IV disorder assessed by the SCID-NP.	Current Axis I disorder as assessed by the SCID-NP, (3) Current use of psychotropic medication, (4) Current participation in psychotherapy, (4) Physical concerns contraindicating the use of nicotine patch, (5) Current use of smoking cessation pharmacotherapy, (6) Current use of smokeless tobacco products

Note: Abbreviations: NR: Not Reported, LETS-QUIT: Life Enhancement Treatment for Substance Use, BDI-II: Beck Depression Inventory-II, TLFB: Timeline Followback Method, BTDD: Behavioral Therapy for Depression in Drug Dependence, REL: Structured Relaxation Intervention, HAM-D: Hamilton Rating Scale for Depression, LETS Act!: Life Enhancement Treatment for Substance Use, BA: Behavioural Activation, CBT: Cognitive Behavioural Therapy, PHQ-9: Patient Health Questionnaire-9, BATS: Behavioral Activation Treatment for Smoking

Table 2. Details of BA interventions delivered in the trials, controls used and associated dropout rates

Study	*Type of BA [Complexity]*	*BA treatment*	*Control conditions*	*No. Of sessions (duration in minutes)*	*BA attendance rate vs comparator attendance rate*	*BA dropout rate vs comparator dropout rate*
Bercaw, 2007	BATD [Complex]	LETS-QUIT: (1) Activity Monitoring, (2) Activity Scheduling ,(3) Values Assessment, (4) Behavioural Contracting	ST: (1) Smoking Cessation Advice, (2) Functional Analysis of Thoughts and Behaviour, (3) Progressive Muscle Relaxation Exercises	LETS-QUIT: 3 (180) ST: 3 (180)	100% vs 100%	26.7% vs 9.09%
Carpenter, 2008	BATD [Complex]	BTDD: (1) Activity Monitoring, (2) Activity Scheduling, (3) Values Assessment, (4) Contingency Management	REL: (1) Progressive muscle relaxation exercises, (2) Autogenic relaxation exercises, (3) Visual imagery exercises	BTDD: 24 (NR) REL: 24 (NR)	48.3% vs 63.8%	50% vs 25%
Daughters, 2008	BATD [Complex]	LETS Act!: (1) Activity Monitoring, (2) Activity Scheduling, (3) Values assessments, (4) Behavioural Contracting, (5) Decisional Balance, (6) Mindfulness / Relaxation Exercises	TAU: (1) Relapse prevention, (2) Functional analysis of thoughts and behaviour, (3) Stress management, (4) Anger management, (5) Life skills, (6) AA / NA support groups	BA: 6 (270) TAU: NR	90.91% vs 84.21%	9% vs 36.36%
Delgadillo, 2015	Contextual BA [Complex]	BA: (1) Activity Monitoring, (2) Activity Scheduling, (3) Values Assessments, (4) Decisional Balance	GSH: (1) Guided self-help based on CBT principles	BA: 12 (60) GSH: 1 (60)	NR vs 48.1%	65.2% vs 51.9%
MacPherson, 2010	BATD [Complex]	BATS: (1) Activity Monitoring, (2) Activity Scheduling, (3) Values Assessments	ST: (1) Smoking Cessation Advice, (2) Functional Analysis of Thoughts and Behaviour, (3) Coping Skills, (4) Identifying Social Support, (5) Progressive Muscle Relaxation Exercises	BATS: 8 (480) ST: 8 (480)	75% vs 75%	25.7% vs 51.52%

Note: Abbreviations: NR: Not Reported, LETS-QUIT: Life Enhancement Treatment for Substance Use, BATD: Behavioural Activation Treatment for Depression, BTDD: Behavioral Therapy for Depression in Drug Dependence, LETS Act!: Life Enhancement Treatment for Substance Use, BA: Behavioural Activation, BATS: Behavioral Activation Treatment for Smoking, REL: Structured Relaxation Intervention, CBT: Cognitive Behavioural Therapy, SC: Supportive Counselling