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[Intervention Review]

Psychological interventions for co-occurring depression and substance use disorders

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ABSTRACT

Background

Comorbid depression and substance use disorders are common and have poorer outcomes than either disorder alone. While effective psychological treatments for depression or substance use disorders are available, relatively few randomised controlled trials (RCTs) have examined the efficacy of these treatments in people with these comorbid disorders.

Objectives

To assess the efficacy of psychological interventions delivered alone or in combination with pharmacotherapy for people diagnosed with comorbid depression and substance use disorders.

Search methods

We searched the following databases up to February 2019: Cochrane Central Register of Controlled Trials, PubMed, Embase, CINAHL, Google Scholar and clinical trials registers. All systematic reviews identified, were handsearched for relevant articles.

Selection criteria

The review includes data from RCTs of psychological treatments for people diagnosed with comorbid depression and substance use disorders, using structured clinical interviews. Studies were included if some of the sample were experiencing another mental health disorder (e.g. anxiety); however, studies which required a third disorder as part of their inclusion criteria were not included. Studies were included if psychological interventions (with or without pharmacotherapy) were compared with no treatment, delayed treatment, treatment as usual or other psychological treatments.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

Seven RCTs of psychological treatments with a total of 608 participants met inclusion criteria. All studies were published in the USA and predominately consisted of Caucasian samples. All studies compared different types of psychological treatments. Two studies compared Integrated Cognitive Behavioural Therapy (ICBT) with Twelve Step Facilitation (TSF), another two studies compared Interpersonal Psychotherapy for Depression (IPT-D) with other treatment (Brief Supportive Therapy (BST) or Psychoeducation). The other three studies compared different types or combinations of psychological treatments. No studies compared psychological interventions with

no treatment or treatment as usual control conditions. The studies included a diverse range of participants (e.g. veterans, prisoners, community adults and adolescents).

All studies were at high risk of performance bias, other main sources were selection, outcome detection and attrition bias. Due to heterogeneity between studies only two meta-analyses were conducted. The first meta-analysis focused on two studies (296 participants) comparing ICBT to TSF. Very low-quality evidence revealed that while the TSF group had lower depression scores than the ICBT group at post-treatment (mean difference (MD) 4.05, 95% confidence interval (CI) 1.43 to 6.66; 212 participants), there was no difference between groups in depression symptoms (MD 1.53, 95% CI -1.73 to 4.79; 181 participants) at six- to 12-month follow-up. At post-treatment there was no difference between groups in proportion of days abstinent (MD -2.84, 95% CI -8.04 to 2.35; 220 participants), however, the ICBT group had a greater proportion of days abstinent than the TSF group at the six- to 12-month follow-up (MD 10.76, 95% CI 3.10 to 18.42; 189 participants). There were no differences between the groups in treatment attendance (MD -1.27, 95% CI -6.10 to 3.56; 270 participants) or treatment retention (RR 0.95, 95% CI 0.72 to 1.25; 296 participants).

The second meta-analysis was conducted with two studies (64 participants) comparing IPT-D with other treatment (Brief Supportive Psychotherapy/Psychoeducation). Very low-quality evidence indicated IPT-D resulted in significantly lower depressive symptoms at post-treatment (MD -0.54, 95% CI -1.04 to -0.04; 64 participants), but this effect was not maintained at three-month follow-up (MD 3.80, 95% CI -3.83 to 11.43) in the one study reporting follow-up outcomes (38 participants; IPT-D versus Psychoeducation). Substance use was examined separately in each study, due to heterogeneity in outcomes. Both studies found very low-quality evidence of no significant differences in substance use outcomes at post-treatment (percentage of days abstinent, IPTD versus Brief Supportive Psychotherapy; MD -2.70, 95% CI -28.74 to 23.34; 26 participants) or at three-month follow-up (relative risk of relapse, IPT-D versus Psychoeducation; RR 0.67, 95% CI 0.30 to 1.50; 38 participants). There was also very low-quality evidence for no significant differences between groups in treatment retention (RR 1.00, 95% CI 0.81 to 1.23; 64 participants). No adverse events were reported in any study.

Authors' conclusions

The conclusions of this review are limited due to the low number and very poor quality of included studies. No conclusions can be made about the efficacy of psychological interventions (delivered alone or in combination with pharmacotherapy) for the treatment of comorbid depression and substance use disorders, as they are yet to be compared with no treatment or treatment as usual in this population. In terms of differences between psychotherapies, although some significant effects were found, the effects were too inconsistent and small, and the evidence of too poor quality, to be of relevance to practice.

PLAIN LANGUAGE SUMMARY

Do psychological interventions work for people with both depression and substance use disorders?

What is the aim of this review?

The aim of this Cochrane Review was to find out if psychological interventions (delivered with or without pharmacotherapy) are effective for the treatment of comorbid depression and substance use disorders. Cochrane researchers collected and analysed all relevant studies to answer this question.

Key messages

No conclusions about the effectiveness of psychological interventions for the treatment of comorbid depression and substance use disorders can be made, due to the low number of studies found and very low quality of the evidence. More high-quality studies comparing psychological interventions versus no treatment, delayed treatment, treatment as usual and other psychological interventions are needed.

What was studied in the review?

Comorbidity occurs for people experiencing mental disorders when the same person has two or more mental disorders. People diagnosed with depression are more likely to have substance use disorders, and vice versa. Comorbid disorders are associated with poorer clinical, social and vocational outcomes than either disorder alone. Psychological treatments for comorbid depression and substance use disorders are available, but relatively few have been tested. These treatments target psychological (thoughts, feelings, behaviours), social (family and personal relationships), and environmental risk factors (access to drugs) for depression and substance use.

What are the main results of the review?

The review authors searched for studies and found seven randomised controlled trials involving 608 people with comorbid depression and substance use disorders published between 2003 and 2014. All seven studies were published in the USA and predominately consisted of individuals from Caucasian backgrounds. No conclusions about the effectiveness of psychological interventions delivered with or without pharmacotherapy could be made, as no studies comparing these interventions with no treatment, delayed treatment or treatment as usual were found. All seven studies compared different types or combinations of psychological treatments. Few consistent differences in depression or substance use treatment outcomes were found. No conclusions about which type of psychological intervention was most effective could be made, due to the low number of studies found and very low quality of the evidence. None of the studies reported any

harms related to receiving psychological treatment for depression and substance use disorders. All studies were funded by university and government research grants in the USA.

How up-to-date is this review?

The review authors searched for studies that had been published up to February 2019.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Integrated CBT compared with Twelve Step Facilitation for co-occurring depression and substance use disorders

Integrated CBT compared with Twelve Step Facilitation for co-occurring depression and substance use disorders

Patient or population: co-occurring depression and substance use disorders

Setting:

Intervention: Integrated CBT

Comparison: Twelve Step Facilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Twelve Step Facilitation	Risk with Integrated CBT				
Depression score Assessed with: Hamilton Depression Rating Scale (HDRS) - Structured clinical interview (21 items) Scale from: 0 to 54 (higher score worse) Follow-up: end of treatment	The mean depression score ranged from 21.0 to 23.2	MD 4.05 higher (1.43 higher to 6.66 higher)	-	212 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 2} 3	
Depression score Assessed with: Hamilton Depression Rating Scale (HDRS) - Structured clinical interview (21 items) Scale from: 0 to 54 (higher score worse) Follow-up: 6 months to 12 months	The mean depression score ranged from 21.0 to 27.9	MD 1.53 higher (1.73 lower to 4.79 higher)	-	181 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 2} 3	
Percent of days abstinent Assessed with: The calendar-assisted structured interview - Time-Line Follow-Back (TLFB) for past 3-month substance use Scale from: 0 to 100 (lower score better) Follow-up: end of treatment	The mean proportion of days abstinent ranged from 93 to 90	MD 2.84 lower (8.04 lower to 2.35 higher)	-	220 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 2} 3	
Percent of days abstinent Assessed with: TLFB for past 3-month substance use Scale from: 0 to 100 (lower score better) Follow-up: 6 months to 12 months	The mean proportion of days abstinent ranged from 72 to 75	MD 10.76 higher (3.10 higher to 18.42 higher)	-	189 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{2 3} 4	

Treatment retention Assessed with: dropped out of treatment after attending an average of 1.2 sessions	Moderate	RR 0.95 (0.72 to 1.25)	296 (2 RCTs)	⊕○○○ VERY LOW ^{1 2} 3
	785 per 1,000	745 per 1,000 (565 to 981)		
Number of treatment sessions attended Scale from: 0 to 36	The mean number of Treatment Sessions Attended ranged from 19.4-22.1	MD 1.27 lower (6.10 lower to 3.56 higher)	- 270 (2 RCTs)	⊕○○○ VERY LOW ^{2 3} 5

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded two levels due to very serious risk of bias: high levels of performance bias, attrition bias and uneven medication use between groups. One study also had high risk of selection bias and unclear risk for selective reporting.

² Downgraded one level due to Imprecision: small number of trials/participants

³ Downgraded one level due to indirectness: population of predominately Caucasian male veterans

⁴ Downgraded two levels due to very serious risk of bias: high levels of selection bias, performance bias, attrition bias, unclear risk for selective reporting and uneven attendance between groups at 12-step Community Meetings

⁵ Downgraded two levels due to very serious risk of bias: mean attendance was based on a reduced sample, not those originally randomised into the study. Also high risk of selection bias, performance bias and attrition bias

Summary of findings 2. Interpersonal Psychotherapy for Depression (IPT-D) compared with Other Psychological Interventions for co-occurring depression and substance use disorders

Interpersonal Psychotherapy for Depression (IPT-D) compared with Other Psychological Interventions for co-occurring depression and substance use disorders

Patient or population: Individuals experiencing co-occurring depression and substance use disorders

Setting: any setting

Intervention: Interpersonal Psychotherapy for Depression (IPT-D)

Comparison: Other Psychological Interventions

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Other Therapeutic Interventions	Risk with Interpersonal Psychotherapy for Depression (IPT-D)				
Depression score Assessed with: Hamilton Depression Rating Scale (HDRS) - Structured clinical interview (17 and 24 items) Scale from: 0 to 54 (higher score worse) Follow-up: end of treatment		SMD 0.54 SD lower (1.04 lower to 0.04 lower)	-	64 (2 RCTs)	⊕⊕⊕⊕ VERY LOW 1 2 3	
Depression score Assessed with: Hamilton Depression Rating Scale (HDRS) - Structured clinical interview (17 items) Scale from: 0 to 54 (higher score worse) Follow-up: 3 months	The mean depression score was 15.8	MD 3.80 higher (3.83 lower to 11.43 higher)	-	38 (1 RCT)	⊕⊕⊕⊕ VERY LOW 3 4 5	
Percentage of days abstinent Assessed with: the calendar-assisted structured interview - Time-Line Follow-Back (TLFB) for past month of alcohol use Scale from: 0 to 100 (better) Follow-up: end of treatment	The mean percentage of days abstinent was 49.7	MD 2.70 lower (28.74 lower to 23.34 higher)	-	26 (1 RCT)	⊕⊕⊕⊕ VERY LOW 3 6 7	
Substance use - relapse Assessed with: self-reported heavy drinking (4+ drinks) or drug use on at least 10% of non-incarcerated days or positive urine test Follow-up: 3-months	Study population		RR 0.67 (0.30 to 1.50)	38 (1 RCT)	⊕⊕⊕⊕ VERY LOW 3 4 5	
	316 per 1,000	212 per 1,000 (95 to 474)				
Treatment retention	Study population		RR 1.00 (0.81 to 1.23)	64 (2 RCTs)	⊕⊕⊕⊕ VERY LOW 1 2 3	
	774 per 1,000	744 per 1,000 (627 to 952)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

- 1 Downgraded two levels due to serious risk of bias: high levels of performance bias due to difficulties with blinding participants and personnel, one of the studies also had high attrition bias and reported group differences in use of antidepressants and adjunctive mental health counselling
- 2 Downgraded one level due to indirectness: one of the study was based on a female prison population, the other were recruited through a medical college, neither sample is likely to be representative of broader population of individuals experience comorbid substance use and depressive disorders
- 3 Downgraded two levels due to very small sample size
- 4 Downgraded two levels due to serious risk of bias: high levels of performance bias due to difficulties with blinding participants and personnel and reported group differences in use of antidepressants and adjunctive mental health counselling
- 5 Downgraded one level due to indirectness: Female prison population unlikely to be representative of broader population of individuals experience comorbid substance use and depressive disorders
- 6 Downgraded two levels due to serious risk of bias: high levels of performance bias due to difficulties with blinding participants and personnel
- 7 Downgraded one level due to indirectness: sample recruited through a medical college, predominately White male, unlikely to be representative of broader population of individuals experience comorbid substance use and depressive disorders

BACKGROUND

Description of the condition

Comorbidity occurs for people experiencing mental disorders when the same person is diagnosed with two or more mental disorders using Diagnostic and Statistical Manual (DSM)/International Statistical Classification of Diseases and Related Health Problems (ICD) criteria (American Psychiatric Association 2000; World Health Organization 1992). People diagnosed with substance use disorders are more likely to have a depression disorder, and vice versa. High rates of comorbid substance use and depression disorders have consistently been reported in epidemiological surveys (Australian Bureau of Statistics 2007; Degenhardt 2001; EMCDDA 2013; Farrell 2001; Grant 2004; Jane-Llopis 2006; Kessler 2003). The United States National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found that individuals with alcohol or drug dependence were four and nine times more likely to experience major depression, respectively than individuals with no substance dependence (Grant 2004). Similarly in Australia, the National Survey of Mental Health and Wellbeing found that individuals with an alcohol or drug use disorder were 3 to 4 times more likely to have experienced depression, or another affective disorder, in the past 12 months compared with the general population (Teesson 2009; Teesson 2010). Within treatment settings, rates of comorbid substance use and affective disorders are even higher, with 30% to 50% of patients meeting criteria for concurrent major depression (Baker 2007a; Bulkstein 1992; Grella 2001; Hall 2009; Lejoyeux 2011; Lubman 2007; Teesson 2005). Such high rates of comorbid disorders are problematic, as they have been linked to treatment non-compliance, a more severe and chronic illness course, and an increased risk of relapse in both substance use and co-occurring mental disorders, as well as greater social and vocational impairment, poor physical health, higher risk of suicidal behaviour and greater use of health services (Australian Bureau of Statistics 2007; Davis 2008; Hasin 2002; Sullivan 2005; Šprah 2017).

Description of the intervention

Psychological interventions are theory-based, manualised approaches to the treatment of depression, substance use and other mental disorders. Common approaches include the following.

- Cognitive behavior therapy (CBT), a family of interventions targeting cognitions, behaviours, emotions and environmental factors which may predispose, precipitate or perpetuate comorbid depression and substance use disorders (Beck 2011). CBT approaches include cognitive therapy (CT), behaviour therapy (BT), traditional CBT approaches and ‘third wave’ approaches including acceptance and commitment therapy, dialectical behaviour therapy and mindfulness-based interventions (Hofmann 2012b; Wells 2016).
- Motivational interviewing is a psychotherapeutic approach that aims to elicit behaviour change by first exploring and resolving ambivalence about making a change (Miller 2013). A number of strategies are then utilised to enhance commitment to making the change. Motivational interviewing is commonly delivered in combination with other psychotherapies including CBT. Only studies combining motivational interviewing with CBT were included in this review.
- Interpersonal psychotherapy (IPT) is most commonly used to treat depression (Frank 2011). It focuses on the role of difficulties

in everyday interactions with others on depressive symptoms by targeting the individual's emotional responses to life stressors, role disputes and role transitions (Frank 2011; Stuart 2012).

- Contingency management is most-widely used in the treatment of substance use disorders. Based on the principles of operant conditioning, it provides incentives or rewards to encourage behaviour change (Petry 2012). Typical reward systems include the use of abstinence-based voucher programs, which increase in value with each consecutive negative drug test (Petry 2012).

How the intervention might work

Psychological interventions aim to modify individual, family, social and environmental factors that may increase risk of depression and substance use disorders (Baker 2007b). Psychological approaches vary depending on the theoretical models underpinning them, but typically target thoughts, feelings, behaviours, interpersonal relationships, social and environmental variables that may predispose, precipitate or perpetuate depression and substance use (Baker 2007b; NCCMH 2009). They can be delivered face-to-face, online, via telephone or bibliotherapy (e.g. self-help books; NCCMH 2009).

Why it is important to do this review

There have been numerous studies investigating the efficacy of psychological interventions for people experiencing depression or substance use disorders. Manualised psychological interventions, including CBT (Cuijpers 2013; Hofmann 2012a), motivational interviewing (Smedslund 2011), IPT (Cuijpers 2011) and contingency management (Benishek 2014; Prendergast 2006), have shown some promise in individually reducing symptoms related to each of these disorders. However, many of the trials excluded comorbid disorders making it difficult to ascertain the efficacy of these interventions for those experiencing both disorders. While there have been some trials examining the efficacy of these treatments within comorbid populations, the few existing meta-analyses or systematic reviews on comorbid substance use and depression have either mainly focused on pharmacological interventions (e.g. Agabio 2018; Foulds 2015; Pani 2010; Zhou 2015), have included subclinical populations for either depression and/or substance use (Babowitch 2016; Baker 2012; Hesse 2009), or did not exclusively examine randomised controlled trials (Riper 2014). There have been no systematic reviews conducted to determine which psychological intervention is most efficacious among individuals with comorbid depression and substance use disorders.

OBJECTIVES

To assess the efficacy of psychological interventions delivered alone or in combination with pharmacotherapy for people diagnosed with comorbid depression and any substance use disorder (excluding nicotine).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs)

Types of participants

Individuals (adults and adolescents) with co-occurring Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) depression and substance use disorder (excluding nicotine) derived using a structured clinical interview were included. Where possible, those with psychosis, bipolar disorder and intellectual disability were excluded as these individuals form distinct clinical groups with specific needs. Studies were included if some of the sample were experiencing another mental health disorder (e.g. anxiety); however, studies which required a third disorder as part of their inclusion criteria were not included in the review.

Types of interventions

Experimental conditions (+/- pharmacotherapy)

- CBT with and without motivational interviewing
- Cognitive therapy
- Behaviour therapy
- Contingency management
- Acceptance and commitment therapy
- Dialectical behaviour therapy
- Interpersonal psychotherapy (IPT)

Control conditions (+/- pharmacotherapy)

- No, minimal or delayed treatment
- Other psychological interventions (including studies comparing those listed above)
- Treatment as usual (defined according to study setting but typically consists of case management)

Types of outcome measures

Primary outcomes

- Depression: changes in symptom severity on a standardised questionnaire (e.g. Beck Depression Inventory (BDI) or Hamilton Depression Rating Scale (HDRS)) or presence of DSM/ICD disorder on a structured clinical interview (e.g. the Structured Clinical Interview for DSM-IV (SCID-IV)).
- Substance use: changes in the frequency (including abstinence), quantity, severity of use measured by calendar-based methods such as Timeline Follow Back (TLFB) and self-report instruments such as the Alcohol Use Disorders Identification Test (AUDIT) or presence of DSM/ICD substance use disorders.
- Treatment retention as measured by the number of participants still in treatment at the end of the study, and treatment attendance as assessed by the average number of sessions attended.

Secondary outcomes

- Functioning: changes in social, occupational/educational functioning as measured by changes on standardised measures of quality of life (e.g., World Health Organization-Quality of Life Scale) or daily functioning (e.g. Global Assessment of Functioning (GAF) scale).
- Anxiety: changes in symptom severity on a standardised questionnaire (e.g. Beck Anxiety Inventory (BAI)) or presence of

DSM/ICD disorder on a structured clinical interviews (e.g. SCID-IV).

- Global clinical severity of mental health disorders: as measured by changes on standardised instruments such as the Clinical Global Impression Scale (CGI) scale.
- Adverse effects linked to treatments delivered.

Search methods for identification of studies

Electronic searches

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

We searched the following databases up to 04 February 2019:

- the Cochrane Central Register of Controlled Trials (CENTRAL; (2019, Issue 1), in the Cochrane Library using the strategy in [Appendix 1](#);
- PubMed (from 1966 to 04 February 2019) using the strategy in [Appendix 2](#);
- Embase (from 1980 to 04 February 2019) using the strategy in [Appendix 3](#);
- CINAHL (from 1982 to 04 February 2019) using the strategy in [Appendix 4](#);
- Google Scholar, scholar.google.com (searched on 04 February 2019).

We searched the following trials registries on 25 February 2019:

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We handsearched relevant articles, systematic or meta-analytic reviews. We also searched grey literature including internal reports and conference proceedings to identify unpublished studies and we contacted the authors of these studies to obtain relevant information.

Data collection and analysis

Selection of studies

- We merged all search results (including records identified from electronic searches and other resources) into Endnote and deleted duplicate records.
- Two review authors independently examined titles and abstracts and deleted obviously irrelevant records
- Two review authors independently assessed full-text articles of the potentially relevant records identified for inclusion in the review and linked multiple reports of the same study.

In the event of a disagreement by the independent review authors, resolution followed a step-wise process. Initially the review authors discussed the disagreement to establish whether there had been an error by one of the extractors that could easily be resolved. If the disagreement remained unresolved, the next step was to contact the study authors directly and any issues that persisted would be reported explicitly in the review. At all stages of this process the presence and resolution of disagreements were recorded and

coding techniques were used to differentiate consensus data from extracted data across both review authors.

Data extraction and management

Two review authors independently extracted data using a standardised data collection checklist. We resolved any disagreements via consultation with a third review author.

The following data were extracted.

Address for correspondence.

Methods: study design, study length/number of follow-up points, setting, country of origin.

Participants: major depressive disorder/substance use disorder inclusion criteria/measure, other defining characteristics (sample size, age mean (standard deviation (SD)), sex (% male), ethnicity, other inclusion and exclusion criteria), study dates/duration (months).

Interventions: number of treatment groups, intervention type and details (content, duration in sessions/weeks), format, intervention target (depression, substance use, both), allocation (number randomised/group), number of sessions attended, fidelity, adjunctive therapy or pharmacotherapy.

Methods for: sequence generation, allocation sequence concealment and blinding.

Outcomes: depression and substance use primary outcomes (definition/measure/unit of measurement, scale (range, interpretation); treatment retention (number of participants still in treatment at the end of the study), treatment attendance (average number of sessions attended).

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. The recommended approach for assessing risk of bias in studies included in Cochrane Reviews is a two-part tool, addressing seven specific domains, including sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other source of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgments, we used the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions* adapted to the addiction field.

The domains of sequence generation and allocation concealment (avoidance of selection bias) was addressed in the tool by a single entry for each study.

We considered blinding of participants, personnel and outcome assessor (avoidance of performance bias and detection bias) separately for objective outcomes (e.g. treatment retention, attrition, participants engaged in further treatments) and self-

report and interviewer-rated subjective outcomes (e.g. depression, substance use) separately. Given that participants and personnel cannot be blinded to the type of psychological intervention being delivered, subjective outcomes were always judged at high risk of performance bias.

We assessed treatment fidelity and contamination under the 'Other bias' category, given their importance in ensuring the delivery of high-quality psychological interventions in RCT's, as well as the potential influence of concurrent out-of-study psychotherapy and pharmacotherapy treatment on study outcomes (de Bruin 2015).

See [Appendix 5](#) for details.

Measures of treatment effect

We analysed dichotomous outcomes by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed with 95% confidence interval (CI). We analysed continuous outcomes by calculating the mean difference (MD) with 95% CI and standard deviation (SD) when the studies used the same instrument for assessing the outcome. We used the standardised mean difference (SMD) and SD when the studies used different instruments. If the number and range of studies allowed it, we planned to calculate the numbers needed to treat for an additional beneficial outcome (NNT) or number needed to treat for an additional harmful outcome (NNTH), where data were homogeneous.

Unit of analysis issues

For multi-arm studies included in the meta-analyses, when one arm was considered more than once in same comparisons (e.g. two different experimental treatments compared with the same control group), we planned to combine all the relevant experimental groups into a single group and compare it with the control to avoid double-counting participants in the control groups.

If any cluster-RCTs were identified, we intended to include them in the analyses along with individual RCTs, planning to synthesise the results unless there was non-negligible heterogeneity between the trial designs. For cluster-RCTs that did not adjust for clustering, we intended to adjust the sample sizes using reported or estimated intraclass correlations (ICCs) in line with the recommendations by Higgins 2011.

Dealing with missing data

Whenever possible, we contacted the original investigators to request missing data. We made the assumptions of any methods used to cope with missing data explicit when possible, including whether the data were assumed to be missing at random, or missing values were assumed to have a particular value. The potential impact of missing data on the findings of the review are addressed in the [Discussion](#) section.

Assessment of heterogeneity

The presence of clinical, methodological and statistical heterogeneity between the included studies was assessed including: the country of origin, sample characteristics (inclusion and exclusion criteria), settings, types of treatment comparisons (including sample size, content, length of treatment), outcomes reported, measures used and length of follow-up. We analysed heterogeneity by means of the I^2 statistic and the Chi^2 test. We

regarded heterogeneity as substantial if the I^2 was greater than 50% or a P value was lower than <0.10 for the Chi^2 test for heterogeneity. Following the guidance in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011), we distinguished the following values to denote no important, moderate, substantial, and considerable heterogeneity, respectively: 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100%.

Assessment of reporting biases

If meta-analyses were conducted and number of studies allowed, we planned to use funnel plots (plots of the effect estimate from each study against the standard error (SE)) to assess the potential for bias related to the size of the trials, which could indicate possible publication bias.

Data synthesis

We combined the outcomes from the individual trials through meta-analysis where possible (comparability of intervention and outcomes between trials), using a random-effects model, because we expected a certain degree of heterogeneity between trials. If the clinical or statistical heterogeneity between trials was too high (i.e. 75% to 100%), we considered not pooling the data.

Subgroup analysis and investigation of heterogeneity

If the number and range of studies allowed it, we planned to conduct subgroup analyses for type of CBT, adults, young people, sex and type of substance used.

Sensitivity analysis

We planned to perform sensitivity analyses to assess how sensitive results were to reasonable changes in the assumptions about missing data (Higgins 2011).

'Summary of findings' tables

We assessed the overall quality of the evidence for the primary outcome variables using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system. The GRADE Working Group developed a system for grading the quality of evidence (Guyatt 2008; Guyatt 2011; Oxman 2004), which takes into account issues not only related to internal validity, but also to external validity, such as directness of results. The [Summary of findings for the main comparison](#) presents the main findings of the review in a transparent and simple tabular format. In particular, it provides key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grades of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Grading is decreased for the following reasons.

- Serious (–1) or very serious (–2) study limitation for risk of bias.
- Serious (–1) or very serious (–2) inconsistency between study results.
- Some (–1) or major (–2) uncertainty about directness (the correspondence between the population, the intervention, or the outcomes measured in the studies actually found and those under consideration in our systematic review).
- Serious (–1) or very serious (–2) Imprecision of the pooled estimate.
- Strong suspicion of publication bias (–1).

We used [GRADEpro GDT 2015](#) to import data from [Review Manager 2014](#) for the main outcomes of depression score, substance use (percentage of days abstinent, proportion of days abstinent, relapse, percentage of daily use) and treatment retention. Due to the wide variation of treatments compared, we produced one summary table per treatment comparison ([Summary of findings for the main comparison](#); [Summary of findings 2](#)).

RESULTS

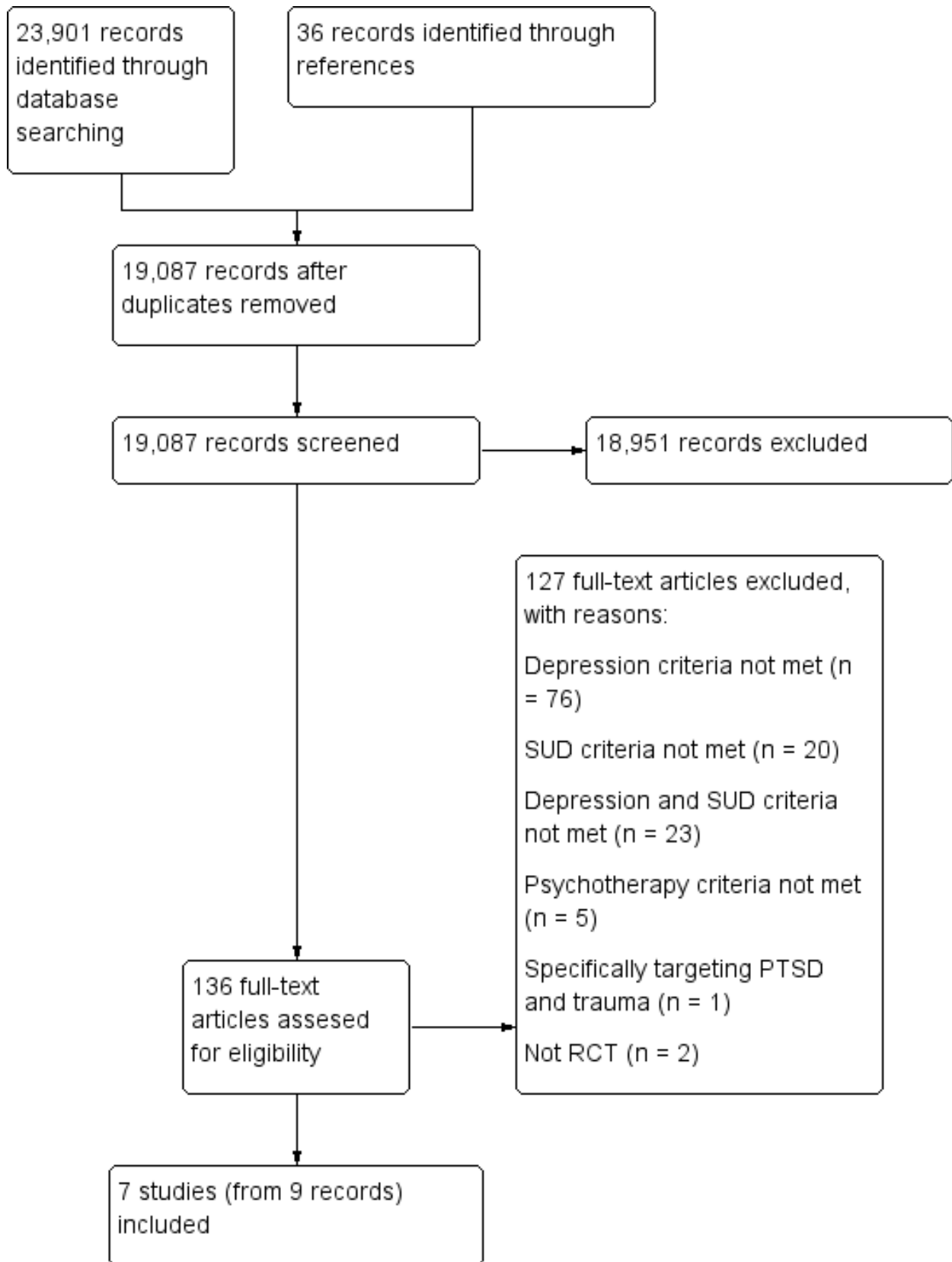
Description of studies

Results of the search

We identified 23,901 records through database searching and 36 from other sources. After removing duplicates, we were left with 19,087 unique references for analysis. We excluded 18,951 on the basis of title and abstract. We retrieved 136 articles in full text for more detailed evaluation, 127 of which were excluded for not meeting the inclusion criteria.

We included seven studies (from nine articles) that satisfied all criteria required for inclusion in the review. See [Figure 1](#).

Figure 1. Study flow diagram.



For substantive descriptions of studies see the [Characteristics of included studies](#) and [Characteristics of excluded studies](#) tables

Included studies

Seven studies enrolling a total of 608 participants were included (Beutler 2003; Brown 2006; Carpenter 2008; Johnson 2012; Lydecker 2010; Markowitz 2008; Rohde 2014).

Country: all included studies were conducted in the USA.

Participant characteristics: the studies were conducted with a variety of patient groups including veterans (Brown 2006; Lydecker 2010); adults (Beutler 2003; Carpenter 2008; Markowitz 2008); adolescents (Rohde 2014); and incarcerated females (Johnson 2012). The average age ranged from 16.4 to 48.8 years. All studies had samples with a majority of Caucasians (61% to 81%). The proportion of males ranged from 57% to 92%. One study enrolled females only (Johnson 2012).

While all study participants had comorbid DSM-IV depression and substance use disorders there was considerable variability in the disorder types included. Several studies included participants with major depression disorders only (Brown 2006; Johnson 2012), two included participants with major depressive disorder/dysthymia only (Carpenter 2008; Lydecker 2010), one included dysthymia only (Markowitz 2008), and the others included any depression disorder (Beutler 2003; Rohde 2014).

Two studies included participants with any substance abuse or dependence (Johnson 2012; Rohde 2014), the two veterans studies included individuals with alcohol, cannabis and/or stimulant dependence (Brown 2006; Lydecker 2010), and the three remaining studies included alcohol abuse or dependence only (Markowitz 2008), stimulant (cocaine or methamphetamine) dependence only (Beutler 2003), or opiate dependence only (Carpenter 2008).

Settings: six studies were conducted in outpatient settings, including two in dual diagnosis treatment services for veterans (Brown 2006; Lydecker 2010). One study was conducted among incarcerated females (Johnson 2012).

Types of comparisons: no studies that compared psychological interventions (alone or combined with pharmacotherapy) with delayed treatment, treatment as usual or no treatment control conditions met inclusion criteria; nor did any studies comparing combined psychological and pharmacological interventions with other psychological interventions. All seven studies included for review compared different types of psychological treatments.

Four studies provided group therapy (Brown 2006; Carpenter 2008; Lydecker 2010; Rohde 2014), two individual therapy (Beutler 2003; Markowitz 2008), and one study provided group therapy followed by individual therapy (Johnson 2012).

Five studies compared CBT with other psychological interventions for comorbid depression and substance use disorders.

- Two studies compared 24 weeks (36 sessions) of group-based integrated CBT (ICBT) versus Twelve Step Facilitation (TSF) in veterans accessing a dual diagnosis outpatient clinic with a DSM-IV major depressive disorder and co-occurring alcohol, cannabis and/or stimulant dependence (n = 90 Brown 2006; n = 206 Lydecker 2010).

- One study compared 24 weeks (24 sessions) of group-based Behavioral Therapy for Depression in Drug Dependence (BTDD) versus 24 weeks of a group-based structured Relaxation Intervention (REL) among 38 treatment-seeking outpatients with DSM-IV opiate dependence and major depressive disorder/dysthymia (Carpenter 2008).
- One study compared 1418 weeks (16-20 sessions) of Cognitive Therapy (CT) with Narrative Therapy (NT) and Prescriptive Therapy (PT) among 40 patients seeking outpatient care with a DSM-IV depression disorder and stimulant dependence (Beutler 2003).
- One study compared three methods for integrating CBT and Functional Family Therapy (FFT) in 170 adolescents with a comorbid DSM-IV depression and substance use disorder seeking substance use treatment (Rohde 2014). Participants received 24 weeks (24 sessions) of either the adolescent Coping With Depression (CWD) followed by FFT (CWD/FFT), FFT followed by CWD (FFT/WD) or integrated CWD and FFT care (CWD+FFT).

Two studies compared IPT for depression (IPT-D) with other psychological interventions.

- A pilot study compared 16 weeks (16-18 sessions) of individual IPT-D versus Brief Supportive Therapy (BST) in 26 adults seeking outpatient care with DSM-IV dysthymia and secondary alcohol use disorder (Markowitz 2008).
- A second study compared eight weeks (24 sessions) of group IPT-D with a psychoeducation group for co-occurring mental health and substance use disorders (PSYCHOED) among 40 incarcerated females with DSM major depressive disorder and substance abuse or dependence. Both treatment groups also received three individual sessions at pre, mid and post the group intervention, as well as treatment as usual for substance use and mental health problems (Johnson 2012).

Outcomes

The depression and substance use outcomes reported differed across studies, as detailed in the [Characteristics of included studies](#) table. All but one study used a version of the Hamilton Depression Rating Scale (HDRS, Hamilton 1960), a clinician-rated measure of the frequency of depression symptoms in the past week. The original version (Hamilton 1960) contained 17 items, but current versions range from 17 to 29 items (Hamilton 1980; Williams 1988). Items are scored on a 3- or 5-point scale. Total scores for depression are usually derived from the original 17 items on a 3-point scale and range from zero to 51 points, with scores from 7 to 17 indicating mild depression, from 18 to 24 indicating moderate depression, and above 24 indicating severe depression.

Three studies also included the Beck Depression Inventory (BDI) (Beck 1961; Beck 1978; Beck 1996), a self-report measure of the frequency of depression symptoms in the previous two weeks. Rohde 2014 used the Child Depression Rating Scale-Revised (CDRS-R, Poznanski 1995), a 17-item clinician-rated measure of depressive symptomatology in six- to 12-year olds, which is also widely used in adolescents.

All studies used the Timeline Followback method (TLFB; Miller 1994; Sobell 1980; Sobell 1992) to assess substance use outcomes. This calendar-based method assesses the frequency and quantity of substance use, including the number of days abstinent over

a specified timeframe. Both the timeframe (30 to 90 days) and definition of substance use outcome measures (mean percentage days abstinent, proportion of days abstinent, square root of percentage of daily substance use) varied across studies. One study used the alcohol and drug index score of the Addiction Severity Index (ASI; Beutler 2003).

Definitions of treatment retention varied across studies. Four studies reported the mean number of treatment sessions attended (Brown 2006; Carpenter 2008; Lydecker 2010; Rohde 2014). Three studies reported the percentage of participants who dropped out of treatment but the definitions of dropout varied. Beutler 2003 defined treatment as missing three or more consecutive sessions out of the 20 sessions. Markowitz 2008 reported the percentage of participants who failed to complete treatment, but it is unclear how this was defined. Johnson 2012 defined treatment dropout as missing more than two out of 24 sessions by choice.

No studies reported information on any of the secondary outcome variables specified in the original Cochrane Review research protocol, including functioning, quality of life, anxiety symptoms or disorders or the global clinical severity of mental health disorders. No adverse effects linked to treatments delivered were reported.

Follow-up

All studies reported post-treatment outcomes. Three studies conducted three-month follow-ups (Brown 2006; Johnson 2012;

Lydecker 2010), three conducted six-month follow-ups (Beutler 2003; Brown 2006; Lydecker 2010; Rohde 2014), and two conducted 12-month follow-ups (Lydecker 2010, Rohde 2014).

Excluded studies

We excluded 127 articles from 124 studies for not meeting the inclusion criteria. Overall 76 articles (from 75 studies) were excluded because they did not meet the depression criteria, 20 articles (from 19 studies) were excluded because they did not meet the substance use criteria, 23 articles (from 22 studies) were excluded because they did not meet both the depression and substance use criteria, two studies were excluded because they were not RCTs, one study was excluded because it focused depression and substance use in the context of Posttraumatic Stress Disorder and Trauma, and five studies were excluded because they did not meet psychotherapy criteria (three of these studies focused on the use of technology as an adjunct to therapy, not actual differences between therapies; and the remaining two studies randomised pharmacological treatments, without randomising psychological therapies) See Figure 1 for further details.

Risk of bias in included studies

The seven included studies were evaluated by the review author's using Cochrane's 'Risk of bias' tool (see Appendix 5). The results are summarised in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

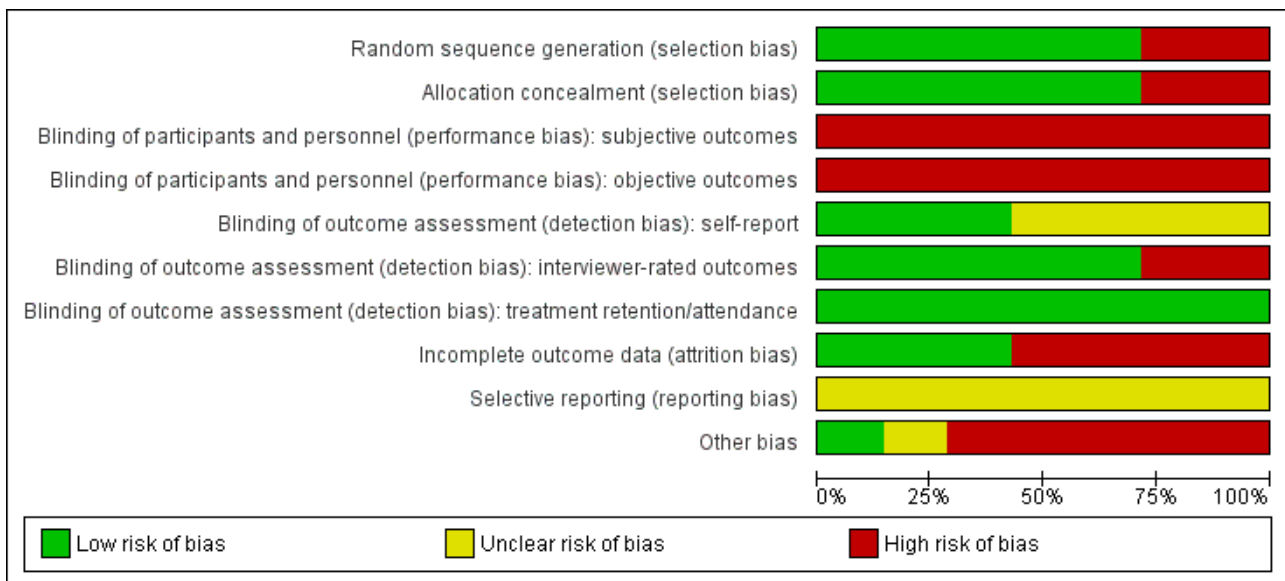


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): subjective outcomes	Blinding of participants and personnel (performance bias): objective outcomes	Blinding of outcome assessment (detection bias): self-report	Blinding of outcome assessment (detection bias): interviewer-rated outcomes	Blinding of outcome assessment (detection bias): treatment retention/attendance	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Beutler 2003	+	+	-	-	?	+	+	-	?	-
Brown 2006	-	-	-	-	+	+	+	-	?	-
Carpenter 2008	+	+	-	-	?	-	+	-	?	?
Johnson 2012	+	+	-	-	+	+	+	+	?	-
Lydecker 2010	-	-	-	-	+	-	+	+	?	-
Markowitz 2008	+	+	-	-	?	+	+	-	?	+
Rohde 2014	+	+	-	-	?	+	+	+	?	-

Allocation

Random sequence generation: all of the included studies were described as RCTs. Five studies were judged at low risk of selection bias: one study used concealed random draws (Beutler 2003) and four used independent computer-based randomisation to generate the sequence allocation (Carpenter 2008; Johnson 2012; Markowitz 2008; Rohde 2014). Two studies used sequential allocation of consecutively-admitted patients (Brown 2006; Lydecker 2010) and were judged to be at high risk of selection bias due to the use of a non-random sequence generation process. All but one study (Beutler 2003), checked the success of randomisation by comparing the group allocations on baseline variables.

Allocation concealment: five studies were judged at low risk of bias (Beutler 2003; Carpenter 2008; Johnson 2012; Markowitz 2008; Rohde 2014). Two studies were judged at high risk of bias (Brown 2006, Lydecker 2010) because a consecutive allocation was used.

Blinding

Performance bias: no study blinded therapists to the treatment allocation, as this is not possible in psychological trials. Only one study attempted to blind participants to their group allocation, and checked but did not report the success of this blinding process (Beutler 2003). Thus, all studies were rated at high risk of performance bias, due to the subjective nature of the depression and substance use outcomes. These studies were also rated at high risk for performance bias for the treatment retention/attendance variable, as despite the objective nature of this outcome, knowledge of the treatment allocation may influence participant's treatment engagement, participation and attendance.

Detection bias: five of the seven studies were at low risk of detection bias for interviewer-rated outcomes, due to the use of outcome assessors blind to treatment allocation. Two studies which did not blind the outcome assessors were judged to be at high risk of detection bias (Carpenter 2008; Lydecker 2010). All four studies that reported self-report outcomes were rated at unclear risk of detection bias (Beutler 2003; Carpenter 2008; Markowitz 2008; Rohde 2014). While participants were not blind to treatment allocation and self-report measures may be impacted by self-presentation bias or client insight, it is unlikely that any such risk of bias will vary by treatment condition. There was insufficient information to determine whether the individuals who collected information on treatment attendance/completion were blind to treatment allocation in all studies. However, this objective outcome measure is unlikely to be influenced by lack of blinding, and all seven studies were judged to be at low risk of detection bias on this outcome variable.

Incomplete outcome data

Treatment retention/attendance: less than 50% of participants completed treatment or attended half of the allocated treatment sessions (in at least one group) in four studies (Beutler 2003; Brown 2006; Carpenter 2008; Lydecker 2010). Between-group differences in the number of sessions participants completed were reported in two studies (Beutler 2003; Rohde 2014).

Outcome assessments: high risk of attrition bias (defined as $\geq 50\%$ in at least one group) was found in three studies at post-treatment (Beutler 2003; Brown 2006; Carpenter 2008) and two studies at

follow-up (Beutler 2003; Brown 2006). One study in which one of the treatment groups had double the attrition rate at post-treatment was considered high-risk (Markowitz 2008). Attrition rates were typically between 20% and 30% in two other studies (Lydecker 2010; Rohde 2014) and one study among incarcerated females reported zero attrition (Johnson 2012).

Missing data/Intent-to-treat (ITT) analysis: three studies used the last observation carried forward (LOCF) method to manage missing data (Beutler 2003; Carpenter 2008; Markowitz 2008) and one imputed missing data, using Markov Chain Monte Carlo multiple imputation (Rohde 2014). All but one study used ITT analyses (Brown 2006). This study also excluded treatment dropouts (attended < 8 treatment sessions) and participants who missed two or more follow-up assessments from the analyses and was judged to be at very high risk of attrition bias.

Selective reporting

Risk of selective reporting was unclear in all seven studies, as none of them had a published study protocol available. However, the results of all planned analyses using the outcome listed in the methods section are reported in the manuscripts. Two studies did not conduct or report the results of endpoint analyses at all follow-up points. Trajectory, but not endpoint analyses were conducted (three-month follow-up (Brown 2006; Lydecker 2010) or nine-month follow-up (Lydecker 2010).

Other potential sources of bias

Fidelity ratings

All seven trials conducted fidelity ratings of the interventions, but only two were performed by independent raters (Johnson 2012; Markowitz 2008). Two studies controlled for therapist allegiance and contamination effects by using separate teams of therapists to deliver the different interventions (Beutler 2003; Markowitz 2008), but it was unclear if either study tested for contamination effects. One study routinely monitored therapist belief in and satisfaction with the treatment model selected and found this was comparable across the treatment groups (Beutler 2003). Risk of bias due to poor treatment fidelity was unclear in the other four studies, although Brown 2006 tested for therapist effects between and within treatment groups and reported it had no impact on the primary depression and substance use outcome variables. While all studies reported information on the number of treatment dropouts or treatment sessions attended, only one controlled for this variable in the analyses (Lydecker 2010).

Concurrent treatment

Only one study (Markowitz 2008) had concurrent pharmacotherapy as an exclusion criterion. None of the remaining studies reported on medication dose or adherence. For those that reported on pharmacotherapy, the main medication prescribed was antidepressants, with 22% to 98% of participants being prescribed an antidepressant during treatment (Brown 2006; Johnson 2012; Lydecker 2010; Rohde 2014), compared with only 1.1% to 2.7% of participants using medication to treat substance use (Johnson 2012; Lydecker 2010). The exception to this is the one study that included people with methadone-maintained opiate dependence (Carpenter 2008). Few studies reported on the type or number of antidepressants prescribed, though when these were listed selective serotonin reuptake inhibitors (SSRIs) or

atypical antidepressants (Brown 2006) and lithium, aripiprazole, or quetiapine (Johnson 2012) were described as the most commonly used antidepressants. Only one study stratified the randomisation based on antidepressant use (Carpenter 2008). Five studies compared differences in antidepressant use between the treatment groups or controlled for antidepressant use in their analyses (Brown 2006; Carpenter 2008; Johnson 2012; Lydecker 2010; Rohde 2014), with two studies reporting significant differences between groups in use of antidepressants (Johnson 2012; Lydecker 2010).

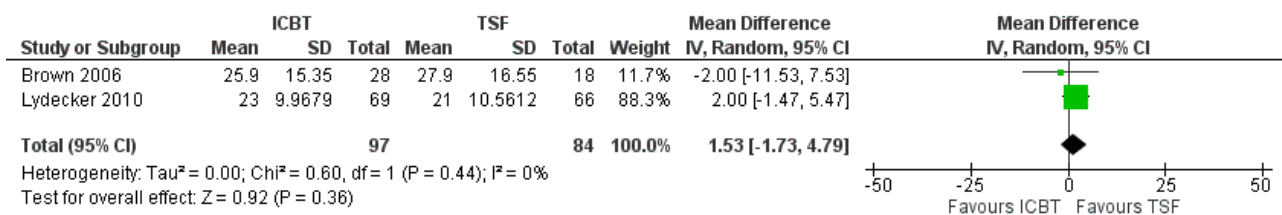
One study had concurrent non-study psychotherapy as an exclusion criterion (Markowitz 2008). A further two studies excluded people attending other psychotherapy beyond 12-Step Community Addiction Meetings (Brown 2006; Lydecker 2010). It was unclear whether participants were permitted to attend adjunctive psychotherapy in two studies (Beutler 2003; Carpenter 2008), and the risk of other bias was high in the remaining two studies, as participants attended adjunctive therapy and attendance at this therapy was not consistent between the treatment arms (Johnson 2012; Rohde 2014).

Effects of interventions

See: [Summary of findings for the main comparison Integrated CBT compared with Twelve Step Facilitation for co-occurring depression and substance use disorders](#); [Summary of findings 2 Interpersonal Psychotherapy for Depression \(IPT-D\) compared with Other Psychological Interventions for co-occurring depression and substance use disorders](#)

Due to the heterogeneity of outcomes, only two small meta-analyses could be conducted, followed by a narrative review of the remaining studies. See [Summary of findings for the main comparison](#) for Integrated Cognitive Behavioural Therapy (ICBT) versus Twelve Step Facilitation (TSF); [Summary of findings 2](#) for Interpersonal Psychotherapy for Depression (IPT-D) versus other psychological treatments.

Figure 4. Comparison 1 Integrated CBT vs Twelve Step Facilitation, Outcome: Depression at 6-12 months



Substance use

See: [Analysis 1.3](#); [Analysis 1.4](#).

The meta-analysis consisting of two studies (296 participants) that compared ICBT to TSF, suggested no substantial difference between the groups in proportion of days abstinent in the past three months, as assessed by the Timeline Follow Back (TLFB), at immediately

Primary outcomes reported include depression score, substance use and treatment retention/adherence. No studies reported information on any of the secondary outcome variables specified in the original Cochrane Review research protocol (Hides 2011), including functioning, quality of life, anxiety symptoms or disorders or the global clinical severity of mental health disorders. No adverse effects linked to treatments delivered were reported.

1. Integrated Cognitive Behavioural Therapy (ICBT) versus Twelve Step Facilitation (TSF)

Two studies with 296 participants compared ICBT to TSF (Brown 2006; Lydecker 2010). Both studies recruited veterans experiencing alcohol, cannabinol and/or stimulant dependence and a major depressive diagnosis. Participants were predominately white males with a mean age of 48.3 (standard deviation (SD) = 7.8). Assessments were completed at post-treatment and at three months, and six months later. Only one of the two studies assessed outcomes at 12 months post-treatment (Lydecker 2010).

See: [Summary of findings for the main comparison](#).

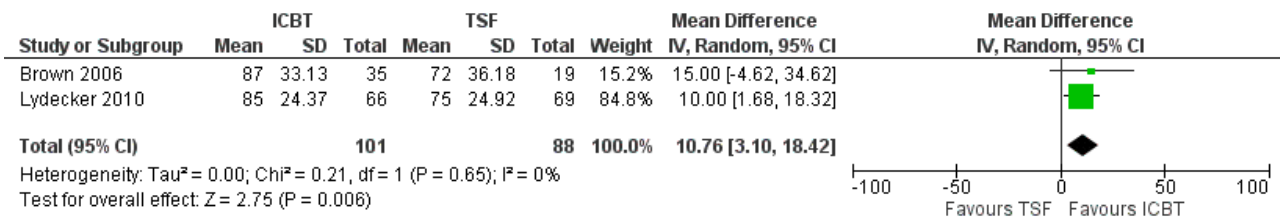
Depression

See: [Analysis 1.1](#) ; [Analysis 1.2](#).

The meta-analysis examining depression score at post-treatment and at follow-up consisted of 296 randomised participants. The meta-analysis suggested that the ICBT group had higher depression scores, compared with the TSF group, at post-treatment (mean difference (MD) 4.05, 95% confidence interval (CI) 1.43 to 6.66; 2 studies, 212 participants; [Analysis 1.1](#)), however, there did not appear to be any difference between the groups at six- to 12-month follow-up (MD 1.53, 95% CI -1.73 to 4.79; 2 studies, 181 participants; [Analysis 1.2](#); [Figure 4](#)) follow-up. Heterogeneity was of no importance (I² = 0%, P = 0.91; I² = 0%, P = 0.44), respectively.

post-treatment (MD -2.84, 95% CI -8.04 to 2.35; 2 studies, 220 participants; [Analysis 1.3](#)). At six- to 12-month follow-up, the ICBT group experienced on average 10.76% more days abstinent (95% CI 3.10 to 18.42; 2 studies, 189 participants; [Analysis 1.4](#)) compared with the TSF group ([Figure 5](#)). Heterogeneity was of no importance in either analysis (I² = 0%; P = 0.39; I² = 0%; P = .65), respectively.

Figure 5. Comparison 1 Integrated CBT vs Twelve Step Facilitation, Outcome: Percentage of Days Abstinent at 6 to 12 months.



Treatment attendance and retention

See: [Analysis 1.5](#); [Analysis 1.6](#)

The meta-analysis consisting of two studies (296 participants) that compared ICBT to TSF, revealed no substantial difference between the groups in treatment retention (RR 0.95, 95% CI 0.72 to 1.25; 2 studies, 270 participants; [Analysis 1.5](#)) or attendance (MD -1.27, 95% CI -6.10 to 3.56; 2 studies, 296 participants; [Analysis 1.6](#)). Heterogeneity was substantial for both analyses (I² = 74%, P = 0.05; I² = 67%, P = 0.08).

2. Interpersonal Psychotherapy for Depression (IPT-D) versus other psychological treatments

Two studies with 64 participants compared IPT-D with other psychological treatments, one examining Brief Supportive Psychotherapy, with a sample of patients experiencing major depression/dysthymia and secondary alcohol abuse/dependence drawn from a medical college (n = 26; [Markowitz 2008](#)); and the other examining psychoeducation, with a sample of participants experiencing major depression and a substance use disorder (including alcohol, cocaine, opiate, marijuana and sedatives/hypnotics) drawn from a female prison (n = 38; [Johnson 2012](#)). Both

samples were predominantly female (63%- to 100%), mostly white, with an average age of 36.4 (SD = 9.9).

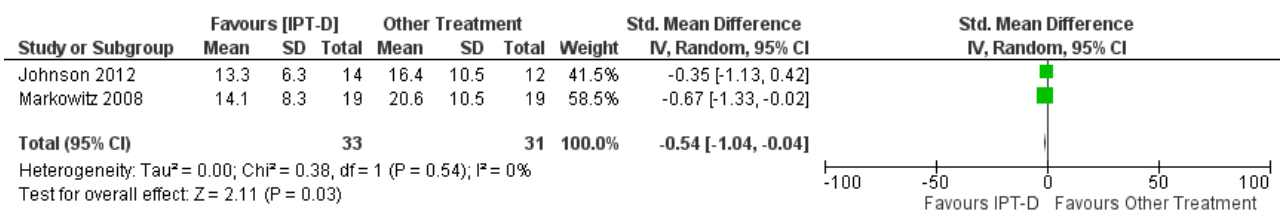
See: [Summary of findings 2](#).

Depression

See: [Analysis 2.1](#); [Analysis 2.2](#).

Two studies contributed 64 participants to end-of-treatment analyses (eight weeks/16 weeks), and one study ([Johnson 2012](#)) with 38 participants assessed three-month post-treatment effects. The common outcome measure used in both studies was the clinician-rated Hamilton Rating Scale for Depression (HDRS) (17-item and 24-item scales were used). The end of treatment results, showed no important heterogeneity (I² = 0%; P = 0.54), and suggested participants receiving IPT-D had lower depressive symptoms at post-treatment than other treatment (Brief Supportive Psychotherapy/Psychoeducation; standardised mean difference (SMD) -0.54, 95% CI -1.04 to -0.04; I = 0%; 2 studies, 64 participants; [Figure 6](#)); however, there was no evidence that this effect was maintained at follow-up (IPT-D versus Psychoeducation; MD 3.80, 95% CI -3.83 to 11.43; 1 study, 38 participants).

Figure 6. Comparison 2 Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions, Outcome: Depression at end of treatment.



Substance use

See: [Analysis 2.3](#); [Analysis 2.4](#).

Although both studies used the Timeline Follow-Back (TLFB) ([Sobell 1992](#); [Sobell 1980](#)), the method of reporting this substance use outcome differed between studies, with one study examining percentage of days abstinent in the month prior to the end of treatment ([Markowitz 2008](#)), and the other examining relapse at three months post-treatment (defined as heavy drinking (4+ drinks) or drug use on at least 10% of non-incarcerated days or positive urine test). Due to this heterogeneity, substance use outcomes were examined separately for each study. There was no significant difference in the percentage of days abstinent in the month prior to the end of treatment when comparing IPT-D to Brief Supportive

Psychotherapy (MD -2.70, 95% CI -28.74 to 23.34; 26 participants), and no significant difference in relapse at three months post-treatment when comparing IPT-D to Psychoeducation (RR 0.67, 95% CI 0.30 to 1.50; 38 participants).

Treatment retention

See: [Analysis 2.5](#).

For the meta-analysis comparing IPT-D with other treatment (Brief supportive psychotherapy/psychoeducation), there was no significant difference between the groups in treatment retention (RR 1.00, 95% CI 0.81 to 1.23; I² = 0%; 2 studies 64 participants).

3. Integrated Functional Family Therapy (FFT) and Coping With Depression (CWD) versus sequenced FFT-CWD; Integrated FFT and CWD versus sequenced CWD-FFT

One study with 170 adolescents compared integrated FFT and CWD to sequential FFT followed by CWD, or CWD followed by FFT (Rohde 2014). Adolescents were aged 13 to 18 years, were predominately white (61%) males (88%) experiencing a depressive disorder (54% major depression) and comorbid substance use disorder, which was predominately a cannabis use disorder (94%), comorbid with alcohol use disorder (65%). For ease of comparison the combined treatment was compared with the sequential treatment on primary outcomes. The first row in each analysis compares integrated FFT and CWD versus sequenced FFT-CWD; and the second row compares integrated FFT and CWD versus sequenced CWD-FFT. Assessments were completed at post-treatment (20 weeks) and six and 12 months later.

Depression

See: [Analysis 3.1](#); [Analysis 3.2](#).

The Children's Depression Rating Scale-Revised (CDRS-R), a clinician-rated depression tool for adolescents, adapted from the HDRS, was used for all comparisons (Poznanski 1995). The analyses reported in the article were separated based on whether or not an adolescent experienced Major Depressive Disorder. The authors were contacted, and scores were obtained and are reported for the total sample. There was no difference in depression scores between the integrated treatment and either of the sequential treatments (CWD-FFT or FFT-CWD) immediately post-treatment (MD -3.60, 95% CI -8.76 to 1.56; MD -3.49, 95% CI -8.08 to 1.10) or at 12-month follow-up (MD -1.44, 95% CI -7.98 to 5.10; MD 0.13, 95% CI -6.72 to 6.98).

Substance use

See: [Analysis 3.3](#); [Analysis 3.4](#).

The TLFB interview was used (Miller 1994), with the square root of the percentage of past 90-day daily use reported at all assessment points. The integrated group had higher daily substance use at post-treatment when compared with the FFT-CWD (MD 1.30, 95% CI 0.01 to 2.59) but not the CWD-FFT (MD 0.60, 95% CI -0.69 to 1.89). At 12-month follow-up the integrated treatment had higher daily substance use than both the FFT-CWD (MD 1.32, 95% CI 0.00 to 2.64) and the CWD-FFT (MD 1.32, 95% CI 0.02 to 2.62) sequential groups.

Treatment retention

See: [Analysis 3.5](#); [Analysis 3.6](#).

Treatment adherence was assessed through premature termination (attending < 2 sessions) and mean total session attendance (maximum sessions 24). There was no difference between integrated or sequential treatment for treatment retention (RR 0.47, 95% CI 0.15 to 1.43; RR 0.66, 95% CI 0.20 to 2.12); however, integrated treatment had higher mean treatment attendance than CWD-FFT (MD 4.10, 95% CI 0.98 to 7.22) but not FFT-CWD (MD 1.40, 95% CI -1.58 to 4.38).

4. Behavioral Therapy for Depression in Drug Dependence (BTDD) versus Relaxation Intervention (REL)

One study with 38 participants on methadone maintenance therapy for opiate dependence, who met criteria for a DSM-IV

depressive disorder, compared BTDD with REL (Carpenter 2008). Participants were predominately white (58%) males (82%) with a mean age of 40.1 years (SD = 10.7). Assessments were completed immediately post-treatment (24 weeks).

Depression

See: [Analysis 4.1](#); [Analysis 4.2](#).

The HDRS clinician interview and Beck Depression Inventory (BDI-II) self-report measure (Beck 1996) were used to assess post-treatment depression outcomes. Evidence suggested no difference in depression scores for participants receiving BTDD compared with REL, for either the clinician-rated HDRS (MD 2.10, 95% CI -6.03 to 10.23; 24 participants) or the self-reported BDI-II (MD 6.60, 95% CI -4.94 to 18.14; 24 participants).

Substance use

See: [Analysis 4.3](#); [Analysis 4.4](#); [Analysis 4.5](#).

The Substance Use Weekly Inventory (SUI), a modification of the TLFB (Sobell 1980), was used at the beginning of each treatment session to assess the past week number of substance-using days, with substance use confirmed through a urine test. In the study results, proportion of weeks substances were used was only reported for opiates, cocaine and benzodiazepines. There were no significant differences in the proportion of weeks opiates (MD 0.11, 95% CI -0.09 to 0.31; 24 participants), cocaine (MD 0.10, 95% CI -0.13 to 0.33; 24 participants), and benzodiazepines (MD 0.02, 95% CI -0.21 to 0.25; 24 participants) were used throughout treatment.

Treatment retention

See: [Analysis 4.6](#)

Treatment adherence was examined through the average total session attendance (maximum sessions 24), with no significant difference between the two groups in treatment attendance (MD -3.70, 95% CI -7.83 to 0.43; 38 participants).

5. Cognitive Therapy (CT) versus Narrative Therapy (NT) versus Prescriptive Therapy (PT)

One study with 40 patients experiencing comorbid DSM-IV depression disorder and stimulant (cocaine or methamphetamine) dependence, compared CT, NT and PT (Beutler 2003). Participants were predominately white (75%) males (57%) with a mean age of 33.1 years (SD = 1.83). Assessments were completed immediately post-treatment (20 weeks) and six months post-treatment. Given the very small sample size, and the multiple comparisons that would be required to be conducted between treatment conditions, a narrative review of findings is presented below.

Depression

Depression scores were assessed through the Beck Depression Inventory (BDI; Beck 1961) and the HDRS. No differences between treatments were reported on either of these measures.

Substance use

A modified TLFB (Sobell 1992) was used to assess past 30-day mean days per week of reported substance use, the Addiction Severity Index (ASI; McLellan 1980) was used to create alcohol and drug index scores and urine samples were also conducted

to determine abstinence of participants. There was no reported difference between treatment conditions for clean urine samples or reported abstinence, or on the TLFB or ASI.

Treatment retention

Dropout was assessed as failure to attend three consecutive appointments. The study reported that the NT condition had lower dropout rates than with PT or CT, but no other information was provided.

DISCUSSION

Summary of main results

This review assessed the efficacy of psychological interventions alone or in combination with pharmacotherapy for comorbid depression and substance use disorders. Seven RCTs with a total of 608 participants were included. All studies compared different types of psychological interventions; no studies combining psychological interventions with pharmacotherapy; or comparing psychological interventions with no treatment, treatment as usual or delayed treatment control conditions were found.

Two studies compared Integrated Cognitive Behavioural Therapy (ICBT) with Twelve Step Facilitation (TSF), another two studies compared Interpersonal Psychotherapy for Depression (IPT-D) with other treatment (Brief Supportive Therapy or Psychoeducation), a fifth study compared the integrated delivery of Functional Family Therapy (FFT) and Coping With Depression (CWD) with two sequenced methods (CWD then FFT; FFT then CWD), a sixth study compared Behavioral Therapy for Depression in Drug Dependence (BTDD) with a relaxation intervention, and the final study compared cognitive therapy (CT), narrative therapy (NT) and prescriptive therapy (PT).

Due to heterogeneity in outcomes only two meta-analyses were conducted. The first meta-analysis focused on the two studies comparing ICBT versus TSF (see [Summary of findings for the main comparison](#)). Very low-quality evidence indicated there was no difference in depression symptoms, treatment attendance or retention outcomes at post-treatment or follow-up, but a significant improvement in substance use outcomes in favour of the ICBT was found at six- to 12-month follow-up.

The second meta-analysis, conducted with two studies, compared IPT-D with other treatment (Brief Supportive Psychotherapy/Psychoeducation) (see [Summary of findings 2](#)), and found very low-quality evidence that IPT-D resulted in lower depressive symptoms at post-treatment than other treatment, but this effect was not maintained at three-month follow-up. No significant differences between the groups in treatment retention were found. Substance use was examined separately in each study due to heterogeneity in outcomes. No significant differences in these outcomes (percentage of days abstinent, risk of relapse) were found.

The two other studies, which compared different cognitive behavioural therapy (CBT) interventions (BTDD; CT) with other psychological treatments (Relaxation; NT or PT) found no significant differences on depression, substance use or treatment retention outcomes. The seventh study found integrated FFT and CWD had higher treatment attendance rates than the sequenced treatments but worse substance use outcomes but than the CWD-

FFT group at post-treatment and both the CWD-FFT and FFT-CWD groups at 12-month follow-up.

Overall completeness and applicability of evidence

The seven studies identified are insufficient to address the objectives of this review. All included studies were conducted in the USA, which limits their applicability to other contexts. Moreover, the studies that were included in the meta-analyses were from quite specific populations (i.e. veterans, incarcerated females), with a lack of variation in country source (i.e. all from the USA) or participant demographics (i.e. predominately Caucasian), which also questions the wider application of the findings.

It was difficult to compare the results of studies, as even though five studies compared CBT and two compared IPT-D with other psychological interventions, there was wide variability in the type of CBT (e.g. cognitive therapy, behaviour therapy) and other psychological treatments compared, as well as the treatment target (depression, substance use, depression and substance use), content, intensity/length and mode of delivery (e.g. group, individual, family). There was also wide variability in the definitions and measures of depression, substance use outcomes use and treatment dropout/retention used across the seven studies. The treatment population also varied considerably ranging from veterans and female prisoners to community adults and adolescents potentially limiting the applicability of results to these particular populations. While requiring all study participants to have comorbid depression and substance use disorders strengthened the internal validity of the review, clinicians in real-world settings treat only individuals with substance use and depression problems of varying severity, not only people with fully established disorders. Clinicians are also likely to treat individuals with other comorbid presentations (e.g. substance use, depression and anxiety problems). This limits the external validity of the review.

Quality of the evidence

All seven studies were at high risk of performance bias. Two of six studies were at high risk of selection bias due to inadequate random sequence generation ([Brown 2006](#); [Lydecker 2010](#)). Two studies were at high risk for detection bias due to the use of non-blinded interview raters ([Carpenter 2008](#); [Lydecker 2010](#)). All four studies that reported self-report outcomes were at unclear risk of detection bias ([Beutler 2003](#); [Carpenter 2008](#); [Markowitz 2008](#); [Rohde 2014](#)) and four of the seven studies were at high risk of attrition bias ([Beutler 2003](#); [Brown 2006](#); [Carpenter 2008](#); [Markowitz 2008](#)). Risk of selective reporting was unclear in all seven studies, as none had published research protocols. Due to heterogeneity in outcomes only two meta-analyses were performed, each comprised of two studies.

The quality of evidence of the meta-analysis comparing IPT-D studies with other treatment (Brief Supportive Psychotherapy / Psychoeducation) was very low for assessing its impact on depression and for the substance use and treatment retention outcomes. The meta-analysis comparing ICBT to TSF also provided very low-quality evidence for all outcomes. Moreover, other methodological flaws in the seven studies included the use of small sample sizes ([Brown 2006](#); [Carpenter 2008](#); [Johnson 2012](#); [Markowitz 2008](#)), the reporting of only post-treatment outcomes ([Beutler 2003](#); [Carpenter 2008](#); [Markowitz 2008](#)) or short-term

outcomes (Johnson 2012), and the uneven group distribution of adjunctive treatment (both pharmacological and psychosocial). While all studies conducted treatment fidelity ratings, risk of bias was unclear in all but the two studies in which the fidelity ratings were performed by independent raters, and no studies tested for possible contamination effects in the control conditions.

Potential biases in the review process

There was low risk of publication bias, as a comprehensive search of published and unpublished studies without any language restrictions was conducted. Nevertheless, there is a chance some trials were missed during the search including unpublished studies, particularly those with negative results; as well as some studies in non-English languages. A funnel plot to assess publication bias was not constructed due to the small number of studies. The authors of studies that did not report the data required to complete the review were contacted. All responded and provided the relevant data.

Agreements and disagreements with other studies or reviews

The findings of this review are consistent with other meta-analyses and narrative systematic reviews of the literature, which have found insufficient empirical support to inform psychological treatments for comorbid substance use disorders and depression (Babowitch 2016; Baker 2012; Hesse 2009; Hobden 2018; Riper 2014). Previous reviews have focused on adolescent (Babowitch 2016) and adult (Baker 2012; Hesse 2009; Hobden 2018) populations, and on a wide variety of psychological treatments including CBT, FFT, IPT-D and TSF. Most of the previous reviews found CBT to be the most popular therapy investigated, and all four of the reviews included studies with integrated motivational interviewing/CBT treatments, with one study only investigating the efficacy of motivational interviewing/CBT in treating comorbid alcohol use disorders and depression (Riper 2014).

Previous reviews have highlighted the promise of integrated approaches (Hesse 2009), particularly those that integrate motivational interviewing and CBT (Babowitch 2016; Baker 2012; Hobden 2018; Riper 2014). Small but significant effect sizes have been found for integrated motivational interviewing/CBT in both adolescent (Babowitch 2016) and adult (Baker 2012; Riper 2014) populations, with longer interventions shown to have greater improvements in mood and alcohol use outcomes (Baker 2012). Unfortunately, many of these studies only focused on alcohol misuse (Babowitch 2016; Baker 2012), examined comorbid depression and/or anxiety (Baker 2012; Hesse 2009), or included non-randomised controlled trials (Hobden 2018; Riper 2014). No integrated motivational interviewing/CBT studies that meet the strict inclusion criteria of this review (i.e. randomised controlled trial, with diagnostic interviews to confirm presence of a substance use and depression disorder at study entry). Therefore, comments on the efficacy of integrated motivational interviewing/CBT treatments for comorbid substance use and depression disorders could not be made in this review.

AUTHORS' CONCLUSIONS

Implications for practice

The conclusions of this review are limited due to the low number and poor quality of included studies. No conclusions can be made

about the efficacy of psychological interventions (delivered alone or in combination with pharmacotherapy) for the treatment of comorbid depression and substance use disorders, as they are yet to be compared with no treatment, treatment as usual or delayed interventions in this population. All seven studies included in this review compared psychological interventions. However, no conclusions can be made about which psychological treatment is most effective, as although some significant effects were found, the effects were too small and inconsistent, and the evidence too poor quality to be of relevance to practice.

Implications for research

More research on the psychological treatment of comorbid depression and substance use disorders using well-designed randomised controlled trials (RCTs) based on accepted guidelines (CONSORT (Consolidated Standards of Reporting Trials), Cochrane, SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)) are required (Boutron 2008; Chan 2013). This should include RCTs comparing the efficacy of psychological interventions delivered alone or in combination with pharmacotherapy, and comparing them with delayed or no treatment control conditions. A number of studies were excluded from this review because they did not use diagnostic criteria for depression and substance use disorder. Consensus definitions and measures of depression and substance use outcome variables, as well as consistent scale cut-offs to accurately identify individuals with comorbid depression and substance use problems are needed to improve the quality of evidence. Future research needs to clearly specify the qualifications, training and supervision of therapists and ensure fidelity checks are conducted regularly by independent raters to ensure high-quality psychological treatments are delivered in RCTs. However, acknowledgement is also required that this need for qualification, training and supervision, and the higher rigor required for RCTs is expensive, and may preclude the conduct of these high-quality trials, particularly in countries beyond the USA. Hence, consideration of how to adequately fund these trials is also needed. It is imperative that information on the number and length of sessions and the delivered treatment components is recorded and compared with other active and non-active treatments to avoid contamination effects. The treatment dose within and across intervention arms and the impact of this on depression and substance use outcomes also needs to be examined. Larger sample sizes and more ethnically diverse samples would enable subgroup analyses to control for heterogeneity in the inclusion/exclusion criteria used, as well as the length, intensity, target (depression, substance use, depression and substance use), content and modality of treatment provided. The impact of assessments, treatment as usual and regression to the mean among treatment-seeking populations also requires consideration when comparing psychological treatments.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Beutler 2003

Methods	<p><i>Design:</i> randomised controlled trial</p> <p><i>Follow-up:</i> 20 weeks post-treatment and 6 months post-treatment follow-up.</p> <p><i>Setting:</i> outpatients recruited from community and advertising</p> <p><i>Country:</i> USA</p>
Participants	<p><i>Participants:</i> 40 patients with comorbid DSM-IV depression disorder and stimulant (cocaine or methamphetamine) dependence on the Structured Clinical Interview (SCID)</p> <p><i>Mean age (years):</i> 33.06 (SD = 8.67)</p> <p><i>Sex:</i> 57% male</p> <p><i>Ethnicity:</i> 25% minority group</p>
Interventions	<p><i>Description:</i> Cognitive Therapy (CT) for drug abuse (Beck 1993), Narrative Therapy (NT; Scogin 1987) versus Prescriptive Therapy (PT). CT was therapist-guided, symptom-focused and emotionally supportive. NT was patient-led, non-confrontational and insight-focused; outside self-help groups (e.g. AA, NA) were recommended as part of this treatment. PT targeted the patient-treatment fit between four patient qualities (functional impairment, coping style, resistance traits, subjective distress) and four treatment variables (intensity, focus, directiveness, affective regulation).</p> <p><i>Format:</i> individual therapy</p> <p><i>Duration:</i> CT: 14-18 weeks (16-20 sessions); NT: 14-18 weeks (patient-selected frequency; weekly recommended); PT: 14-18 weeks (16-20 sessions).</p> <p><i>Allocation:</i> CT n = 15; NT n = 12; PT n = 13</p>
Outcomes	<p><i>Treatment retention:</i> dropout defined as missing 3 consecutive sessions; recoded as treatment retention for review</p> <p><i>Self-report:</i> BDI mean (SD) total score (past 7 days); TLFB mean days/week (past 30 days; modified self-report version)</p> <p><i>Interviewer-rated:</i> HDRS mean (SD) total score (past 7 days), ASI mean (SD) alcohol and drug index scores (past 30 days)</p> <p><i>Attrition:</i> proportion with missing data at post-treatment and 6-month follow-up HDRS data (overall attrition rate of each treatment group not reported)</p>
Notes	Therapists carefully selected and trained

Beutler 2003 (Continued)

Funding: National Institute of Drug Abuse (NIDA) RO1DA09294 (Beutler)

Conflict of interest: no statement provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote (via author email): "Assignment one of the three groups was accomplished by drawing poker chips representing the three groups from a hat. The drawing for therapists within groups was accomplished by poker chips on which were written a therapist number that had been pre-assigned."</p> <p>Comment: participants were randomly assigned to a treatment group and therapist.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (via author email): "Each participants group assignment was logged into a computer file and stored within a password protected file."</p> <p>Comment: investigators enrolling participants could not foresee assignment because group assignment was concealed in a password-protected file.</p>
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	<p>Quote (via author email): "Participants - We cautioned therapists and staff to avoid telling patients which group to which they were assigned. Groups were referred to by numbers indicating group and therapist (e.g., group #2, therapist #5). At the end of treatment we checked to see if patient's knew which group they had been assigned to."</p> <p>Comment: blinding of study participants was attempted, the success of this was checked, but not reported and blinding could have been broken and influenced outcomes.</p> <p>Three separate sets of therapists were used to deliver each treatment to reduce treatment allegiance/contamination effects.</p> <p>Quote: "Therapist belief in and satisfaction with the treatment model selected was routinely and formally assessed (p. 72); all had high levels of therapist commitment; PT therapists thought it would more acceptable to their peers. Nevertheless, the authors were unable to blind therapists to the psychological treatment they were delivering, which could have influenced outcomes."</p>
Blinding of participants and personnel (performance bias) objective outcomes	High risk	Participant and providers knowledge of group allocation may influence treatment engagement/participation/ attendance
Blinding of outcome assessment (detection bias) self-report	Unclear risk	<p>Blinding of study participants was attempted, but success of blinding was not reported.</p> <p>Comment: The authors judge risk of bias to be unclear. While participants were not blind to treatment allocation and self-report measures may be impacted by self-presentation bias or client insight, it is unlikely that any such risk of bias will vary by treatment condition.</p>
Blinding of outcome assessment (detection bias) interviewer-rated outcomes	Low risk	Quote (via author email): "Blind ratings were made by clinicians who were unfamiliar with the particular patients."
Blinding of outcome assessment (detection bias)	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding

Beutler 2003 (Continued)
treatment retention/at-
tendance

<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>High risk</p>	<p><i>Treatment retention:</i> 48% of participants; Quote: "Treatments differed significantly in rate of drop out ($\text{Chi}^2 = 9.70$; $P < 0.05$), favouring lower dropout in the NT group (p. 77)</p> <p>Comment: low treatment retention rate (< 50%), between group differences in treatment dropout rate</p> <p><i>Outcome assessment:</i> attrition rate in each treatment group using HDRS data</p> <p>Attrition post-treatment: Total 50%; CT 47%; NT 42%; PT 62%</p> <p>Attrition at the 6 month follow-up: Total 53%; CT 47%; NT 58%; PT 54%</p> <p>No reasons for missing data reported.</p> <p>Comment: high level of attrition (> 50%) at post-treatment and 6-month follow-up unlikely to be related to true outcome, even though the attrition rates across the three treatment groups were similar.</p>
<p>Selective reporting (reporting bias)</p>	<p>Unclear risk</p>	<p>Quote: "While the study was constructed as a RCT in which the three groups were compared, the usual methods of analysing RCT designs using end-point or intent-to-treat analysis are inappropriate for detecting multiple contributors to change. (p. 70)The current study afforded the opportunity of comparing the relative yield of traditional intent-to-treat comparisons with the more flexible and inclusive Hierarchical Liner Methods (p. 70)"</p> <p>Comment: risk is unclear as no study protocol is available. All expected outcomes specified in the method are published in the paper, but end-point analysis results are only reported at post-treatment, and not at 6-month follow-up.</p>
<p>Other bias</p>	<p>High risk</p>	<p><i>Fidelity:</i> fidelity ratings of videotapes of early and late sessions conducted by supervisors not independent raters.</p> <p><i>Other treatments:</i> unclear whether participants were able to receive concurrent out-of-study psychotherapy. Reported that antidepressants were prescribed by project psychiatrist; however, the type of medication, dose, and consistency of medication adherence between group conditions is not reported.</p>

Brown 2006

<p>Methods</p>	<p><i>Design:</i> randomised controlled trial</p> <p><i>Follow-up:</i> 12 weeks (mid-treatment), 24 weeks (post-treatment), 3 and 6 months post-treatment follow-up</p> <p><i>Setting:</i> dual diagnosis outpatient clinic</p> <p><i>Country:</i> USA</p>
<p>Participants</p>	<p><i>Participants:</i> 90 veterans with DSM-IV Major Depressive Disorder and co-occurring alcohol, cannabis and/or stimulant dependence on the Comprehensive International Diagnostic Interview (CIDI)</p> <p><i>Mean age (years):</i> 48.8 (SD = 7.9)</p> <p><i>Sex:</i> 92% male</p>

Brown 2006 (Continued)

Ethnicity: 74% Caucasian

Interventions

Description: Integrated manualised Cognitive Behavior Therapy (ICBT) versus Twelve Step Facilitation (TSF).

ICBT was based on two empirically-based interventions: Cognitive-Behavioural Depression Treatment (Muñoz 1993) and Cognitive-Behavioural Coping Skills Training of Addiction (Kadden 1994). It included three models (thoughts, activities and people) followed by relapse prevention and focus on core skills learned. TSF consisted of the National Institute on Alcohol Abuse and Alcoholism Project MATCH TSF intervention (Nowinski 1994), covering four core topics (e.g. acceptance, surrender) and six electives (e.g. enabling, and persons, places, or things) to support the goal of abstinence.

Format: group therapy

Duration: 24 weeks (36 sessions); Phase 1 60 minutes biweekly for 12 weeks + Phase 2 60 minutes weekly for 12 weeks + standard pharmacotherapy

Allocation: ICBT n = 48; TSF n = 42

Outcomes

Treatment retention: attended at least 8 of the 36 treatment sessions.

Treatment attendance: mean number of sessions attended

Self-report: not included

Interviewer-rated: HDRS mean (SD) total score (past 7 days); TLFB mean (SD) proportion of days abstinent (past 90 days)

Attrition: treatment dropout (attended < 8 treatment sessions; were excluded from post-treatment, 3- and 6-month follow-up) plus those who missed ≥ 2 follow-up points

Notes

Matched for therapist contact; both groups running at all times with staggered start times (every 2 weeks) to allow rolling admissions; therapists were rotated every 6 months so that at least one therapist per group was changed to avoid therapist effects; ongoing weekly supervision; TSF continued in the community.

Fidelity: all sessions videotaped, a random sample of 25% of both treatments reviewed by supervisors for integrity of implementation, adherence to protocol and avoid contamination.

Funding: Veteran Affairs (VA) Medical Research Merit Review Grant (Brown), VA Associate Investigator Awards (Glasner, Tate).

Conflict of interest: no statement provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Consecutive admissions ..meeting inclusion criteria were sequentially allocated by cohorts into either into TSF group intervention or ICBT (p. 451). No significant difference between treatment completer groups on baseline demographic, depression or substance use variables; but non-treatment completers were excluded from this analysis." Comment: high risk due to non-random component (sequential allocation by cohorts) in the sequence generation process
Allocation concealment (selection bias)	High risk	Quote (via author email): "Therapists were verbally informed of participant assignment to condition by the research assistant 1 to 3 days before initial group participation. Participants were similarly informed by the research assistant of their assignment to condition the week prior to starting group attendance."

Brown 2006 (Continued)

		Comment: investigators enrolling participants could possibly foresee assignments due to use of sequential cohort randomisation
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Participants and personnel were not blind to treatment allocation (same procedures as Lydecker 2010 , p. 456)
Blinding of participants and personnel (performance bias) objective outcomes	High risk	Participant and personnel knowledge of group allocation may influence treatment engagement/participation/ attendance
Blinding of outcome assessment (detection bias) self-report	Low risk	This study did not include self-report measures
Blinding of outcome assessment (detection bias) interviewer-rated outcomes	Low risk	Quote (via author email): "Outcome assessors were blind to treatment allocation"
Blinding of outcome assessment (detection bias) treatment retention/attendance	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	<p><i>Treatment retention:</i> ICBT n = 37, 77%; TSF n = 29, 69% (excluded participants who attended < 8 sessions)</p> <p><i>Treatment attendance:</i> ICBT 17.9 (SD = 11.4); TSF 22.1 (SD = 8.9) (excluded participants who attended < 8 sessions)</p> <p>Comment: Differences in between-group treatment retention/attendance likely</p> <p><i>Outcome assessment:</i></p> <p>Treatment dropout ICBT n = 11; TSF n = 13 plus missed ≥ 2 follow-ups: ICBT n = 9; TSF n = 11; based on HDRS data)</p> <p>Total attrition: ICBT n = 20, 42%; TSF n = 24, 57%</p> <p>No ITT conducted</p> <p>Comment: reason for missing outcome data likely to be related to true outcome, with imbalance in numbers missing data across intervention groups</p>
Selective reporting (reporting bias)	Unclear risk	Risk is unclear as no study protocol is available. An endpoint analysis was reported for the 6-month but not the 3-month follow-up, but the results of all planned analyses using the outcome listed in the methods are reported in the manuscript.
Other bias	High risk	<p><i>Fidelity:</i> assessment of treatment fidelity was conducted but not performed by an independent rater. There was no significant impact of therapists/therapists within treatment groups on primary outcomes.</p> <p><i>Other treatments:</i> an initial medication evaluation was conducted and 30-minute monthly appointments were made available with the treating psychiatrist, with 97% of participants prescribed an antidepressant medication (predominately selective serotonin reuptake inhibitors (SSRIs) or atypical antide-</p>

Brown 2006 (Continued)

pressants). There were no reported groups differences in the proportion of clients receiving antidepressant medication or in attending medication management appointments. The medication dose and medication adherence for each group was not reported. Groups did not partake in other treatment beyond Community 12-step involvement, which was higher for the TSF than ICBT group.

Carpenter 2008

Methods	<p><i>Design:</i> randomised controlled trial</p> <p><i>Follow-up:</i> 24 weeks post-treatment only</p> <p><i>Setting:</i> two university-affiliated, outpatient community-based treatment programs</p> <p><i>Country:</i> USA</p>
Participants	<p><i>Participants:</i> 38 methadone-maintained DSM-IV opiate-dependent patients with major depressive disorder/dysthymia on the Structured Clinical Interview-Substance Abuse Comorbidity (SCID-SAC)</p> <p><i>Mean age (years):</i> BTDD 38.8 (SD = 10.4); REL 41.2 (SD = 10.9)</p> <p><i>Sex:</i> 58% male</p> <p><i>Ethnicity:</i> 82% Caucasian</p>
Interventions	<p><i>Description:</i> Behavioral Therapy for Depression in Drug Dependence (BTDD) versus Structured Relaxation Intervention (REL). BTDD incorporated aspects of three operant-based treatment programs: Changing Reinforcing Events (Lewinsohn 1980), the Community Reinforcement Approach (Meyers 1995), and Treatment Plan Contingency Management (points were earned for participating in the therapy session (3 points) and completing out-of-session assignments (up to 10 points); maximum of 208 points (1 point = 1 dollar) could be earned for 100% attendance (72 points) and completion of out-of-session assignments (136 points). Points were exchangeable for goods and services consistent with the treatment plan (Iguchi 1997). REL was based on a structured manual (Brown 1997) focusing on three relaxation strategies: 1) progressive muscle relaxation, 2) autogenic relaxation exercises, and 3) visual imagery based on idiographic scenarios of relaxation or tranquility.</p> <p><i>Format:</i> group therapy; plus community-based methadone treatment programs</p> <p><i>Duration:</i> 24 weekly sessions</p> <p><i>Allocation:</i> BTDD n = 18 ; REL n = 20</p>
Outcomes	<p><i>Treatment attendance:</i> mean number of sessions attended</p> <p><i>Self-report:</i> BDI mean (SD) total score (past 7 days)</p> <p><i>Interviewer-rated:</i> HDRS (SD) mean total score (past 7 days); Substance Use Weekly Inventory (SUI modification of TLFB) - percentage of weeks cocaine, opiate and benzodiazepine use during treatment (past 30 days; data collected weekly for 24 weeks).</p> <p><i>Attrition:</i> proportion of participants with missing 24 weeks post-treatment data</p>
Notes	<p><i>Fidelity:</i> all therapists completed a BTDD or Relaxation Therapy Checklist following each treatment session. Checklists outlined key components of each respective treatment and provided a means to assess adherence to each therapy condition. Session audiotapes were reviewed by senior therapists to monitor adherence to the treatment structure.</p> <p><i>Funding:</i> NIDA grants R01 DA13118, K02 DA00288, K24 DA021850 (Nunes), K23 DA021850 (Carpenter).</p>

Carpenter 2008 (Continued)

Conflict of interest: no statement provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote (via author email): "The randomisation scheme (blocks) were generated by an independent person (based on a random number process)"</p> <p>Quote: "The treatment groups did not differ significantly on most baseline measures. Although stratification procedures balanced the proportion of participants using illicit substances in the week before treatment between the two treatment groups, the proportion of days that opiates were used in the month prior to treatment was greater among those in BTDD. (p. 647)"</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (via author email): "The randomisation grid was maintained in a private password account held by the independent person."</p> <p>Comment: investigators enrolling participants could not foresee assignment.</p>
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Participants and therapists were not blinded to treatment allocation.
Blinding of participants and personnel (performance bias) objective outcomes	High risk	Participant and personnel knowledge of group allocation may influence treatment engagement/participation/ attendance.
Blinding of outcome assessment (detection bias) self-report	Unclear risk	<p>Quote (via author email): "The self-report assessments were to be given by the research assistant - who may or may not have been blind to therapy condition."</p> <p>Comment: The authors judge risk of bias to be unclear. While participants were not blind to treatment allocation and self-report measures may be impacted by self-presentation bias or client insight, it is unlikely that any such risk of bias will vary by treatment condition. The research assistant administering the self-report measures is unlikely to have influenced the results.</p>
Blinding of outcome assessment (detection bias) interviewer-rated outcomes	High risk	Quote (via author email): "It could not be guaranteed they were blind to condition."
Blinding of outcome assessment (detection bias) treatment retention/attendance	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	<p><i>Treatment attendance:</i> BTDD n = 11.6 (SD=6.1); REL n = 15.3 (SD = 6.9); (P = 0.10)</p> <p>Comment: the number of treatment sessions completed was similar and did not differ significantly between groups</p> <p><i>Outcome assessment:</i> attrition total n = 38, 37%; BTDD n = 9, 50%; REL n = 15, 25%; (P = 0.05)</p> <p>Quote: "No significant differences on baseline measures between those participants completing the study and those who dropped out. (p. 647)."</p>

Carpenter 2008 (Continued)

Comment: BTDD group had double the attrition rate of the REL group; LOCF was used for missing data and ITT was not used for the endpoint analysis.

Selective reporting (reporting bias)	Unclear risk	Risk is unclear as no study protocol is available. The results of all outcomes included in the method section of the paper are reported.
Other bias	Unclear risk	<p><i>Fidelity:</i> therapist completed checklists for each session. Recordings were reviewed by senior therapists but no independent fidelity ratings were conducted.</p> <p><i>Other treatments:</i> all participants were receiving at least 60 mg of methadone, it is unclear whether dosage was consistent between groups. Randomisation was stratified by antidepressant medication, and antidepressant medication was controlled in outcome analyses with a null effect reported for depression outcomes. It is unclear whether participants were able to receive other psychotherapy, in addition to that provided through the study.</p>

Johnson 2012

Methods	<p><i>Design:</i> randomised controlled trial</p> <p><i>Follow-up:</i> 8 weeks post-treatment; 3-months post-treatment follow-up (post release)</p> <p><i>Setting:</i> prison-based substance use treatment program</p> <p><i>Country:</i> USA</p>
Participants	<p><i>Participants:</i> 38 volunteer incarcerated females with a current DSM-IV major depressive disorder (1 month after abstinence + HDRS >17) and substance abuse or dependence disorder (1 month prior to incarceration) diagnosed on the Structured Clinical Interview (SCID); all within 14-28 weeks of release</p> <p><i>Mean age (years):</i> 35.0 (SD = 9.2)</p> <p><i>Sex:</i> 100% female</p> <p><i>Ethnicity:</i> 18% Hispanic; 18% African American</p>
Interventions	<p><i>Description:</i> IPT-D (Wilfey 2000) versus psychoeducation for co-occurring mental health and substance use disorders (PSYCHOED). For the IPT-D group, the interpersonal deficits focus for MDD among female prisoners was adapted to address current problematic relationship patterns (including isolation) that resulted from interpersonal trauma. PSYCHOED focused on the meaning of dual diagnosis, women's experience with dual diagnosis, mood, anxiety, personality, psychotic and eating disorders, as well as self-care. Both groups also received: TAU (16-30 hours per week for SUD and mental health - drug education and coping skills groups + weekly drug counselling) + 6 weekly post-release individual sessions.</p> <p><i>Format:</i> group plus individual therapy; plus prison treatment as usual</p> <p><i>Duration:</i> group 8 weeks (24 sessions) plus 3 individual sessions (pre-, mid- and post-group)</p> <p><i>Allocation:</i> IPT-D: n = 19; PSYCHOED: n = 19</p>
Outcomes	<p><i>Treatment retention:</i> missed < 2 sessions by choice - including sessions missed due to medical or legal appointments or early release from prison</p> <p><i>Treatment attendance:</i> mean number of sessions attended</p> <p><i>Self report:</i> not included</p>

Johnson 2012 (Continued)

Interviewer-rated: HDRS mean total score (7 days); TLFB percentage substance use relapse heavy drinking (4+ standard drinks) or drug use on at least 10% of days or any positive breath test/urine drug screen at follow-up (90 days)

Attrition: percentage that completed each follow-up assessment

Notes

Unequal distribution between groups on ethnicity and comorbidity. One-month abstinence was a requirement at baseline.

Funding: United States National Institute of Drug Abuse (NIDA; K23DA021159, Johnson).

Conflicts of interest: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent individual generated the randomisation sequence and concealed the assignment of each wave before the study started. (p. 1176). The study used wave randomisation with at least an 8 week hiatus between then end of one group and the beginning of the next group to avoid contamination. (p. 1176)" Quote (via author email): "Random number generator (used to generate randomisation)" No significant between-group differences on baseline demographic, depression or substance use variables (Table 1, p. 1179).
Allocation concealment (selection bias)	Low risk	Quote (via author email): "Group allocation concealed via sealed envelopes labelled with stratification variables and order until each group started."
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Participants and therapists not blind to treatment allocation
Blinding of participants and personnel (performance bias) objective outcomes	High risk	Participant and therapists knowledge of group allocation may influence treatment engagement/participation/ attendance.
Blinding of outcome assessment (detection bias) self-report	Low risk	This study did not include self-report measures
Blinding of outcome assessment (detection bias) interviewer-rated outcomes	Low risk	Quote: "RAs, who conducted follow-up assessments (after the in-prison portion of the treatment and at 3 months after prison release), were kept blind to condition assignment. At study completion, blinded study RAs matched participants to conditions with chance (50%) accuracy. (p. 1176)."
Blinding of outcome assessment (detection bias) treatment retention/attendance	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	<i>Treatment retention/attendance:</i> IPT 98%; PSYCHOED 89% <i>Treatment attendance:</i> IPT 16 sessions; PSYCHOED 18 sessions

Johnson 2012 (Continued)

Comment: the number of treatment sessions completed across groups was similar

Outcome assessment: 100% follow-up at post-treatment and 3-month follow-up; ITT performed

Selective reporting (reporting bias)	Unclear risk	Risk is unclear as no study protocol is available. The results of all outcomes included in the method section of the paper are reported.
Other bias	High risk	<p><i>Fidelity</i> (via author email): both IPT and PSYCHOED adherence, competence and contamination were independently rated; Quote: "the two conditions were actually clearly different - much more than for most therapy trials; Therapists trained in and ran both groups but allegiance effects were not assessed."</p> <p><i>Other treatments:</i> the majority of participants were taking antidepressants, with many taking multiple anti-depressants (average 2.1; e.g. lithium, aripiprazole, or quetiapine). There were differences between the treatment groups in proportion taking antidepressants (79% PSYCHOED versus 47% IPT). Clients were also able to receive non-study prison mental health treatment, with uneven distribution of treatment received between groups (PSYCHOED: 63% versus 21% IPT).</p> <p>Comment: high risk due to the differences in other treatment received between PSYCHOED and IPT</p>

Lydecker 2010

Methods	<p><i>Design:</i> randomised controlled trial</p> <p><i>Follow-up:</i> 12-weeks (mid-treatment), 24-weeks (post-treatment), 3-, 6-, 9- and 12-months post-treatment follow-up</p> <p><i>Setting:</i> Dual diagnosis outpatient clinic</p> <p><i>Country:</i> USA</p>
Participants	<p><i>Participants:</i> 206 Veterans with DSM-IV Major Depressive Disorder and co-occurring alcohol, cannabis and/or stimulant dependence on Comprehensive Diagnostic Interview (CIDI) + HDRS > 20 and recent substance use (past 90 days);</p> <p><i>Mean age</i> (years): 48.2 (SD = 7.7)</p> <p><i>Sex:</i> 92% male</p> <p><i>Ethnicity:</i></p> <p>71% Caucasian</p>
Interventions	<p><i>Description:</i> Identical to Brown 2006 above.</p> <p><i>Format:</i> group therapy</p> <p><i>Duration:</i> 24 weeks (36 sessions); Phase 1: 60 minutes biweekly for 12-weeks + Phase 2: 60-minutes weekly for 12-weeks + standard pharmacotherapy</p> <p><i>Allocation:</i> ICBT: n = 107; TSF: n = 99</p>
Outcomes	<p><i>Treatment completion:</i> mean number of sessions completed</p> <p><i>Self-report:</i> not included</p>

Lydecker 2010 (Continued)

Interviewer-rated: HDRS mean (SD) total score (past 7 days); TLFB mean percentage days abstinent (past 90 days).

Attrition: proportion not completed research follow-up assessment

Notes

Abstinence was a requirement at baseline

Each therapy session was videotaped, and a random sample (25%) of sessions were reviewed by a condition-specific clinical supervisor to ensure fidelity to the manual and avoid contamination

Funding: Veteran Affairs (VA) Medical Research Merit Review Grant (Brown), VA Merit Review Entry Program Grant (Tate).

Conflict of interest: No statement provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Consecutive admissions to the study were sequentially allocated by cohorts into ICBT or TSF. Participants were sequentially assigned to the group with the next entry date. (p. 456) No significant differences between treatment groups on baseline demographic, depression or substance use variables." Comment: high risk due to non-random component in the sequence generation process
Allocation concealment (selection bias)	High risk	Allocation not concealed because participants were consecutively assigned into cohorts Comment: Investigators enrolling participants could possibly foresee assignments
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Quote: "Given the nature of this study in a clinical context, participants, administrators, and interviewers were not blinded to patients' treatment assignment." (p. 456)
Blinding of participants and personnel (performance bias) objective outcomes	High risk	Participant and personnel knowledge of group allocation may influence treatment engagement/participation/ attendance.
Blinding of outcome assessment (detection bias) self-report	Low risk	This study did not include self-report measures
Blinding of outcome assessment (detection bias) interviewer-rated outcomes	High risk	Quote: "Given the nature of this study in a clinical context, participants, administrators, and interviewers were not blinded to patients' treatment assignment." (p. 456)
Blinding of outcome assessment (detection bias) treatment retention/attendance	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	<i>Treatment attendance:</i> ICBT: 20.2 (SD = 9.5); TSF: 19.4 (SD = 10.5)

Lydecker 2010 (Continued)

All outcomes

Comment: the number of treatment sessions completed across groups was similar

Outcome assessment:

Attrition mid post 3 month, 6 month, 9 month, 12 month

TSF 17% 25% 26% 30% 31% 33%

ICBT 14% 19% 22% 22% 28% 36%

Comments: the two groups had similar attrition rates; statistical analyses used were robust to missing data; ITT analyses performed

Selective reporting (reporting bias)

Unclear risk

Risk is unclear as no study protocol is available. Trajectory analyses and not endpoint analyses at 3- and 9-month follow-up were performed, but the results of all planned analyses using the outcome listed in the methods are reported in the manuscript.

Other bias

High risk

Fidelity: treatment fidelity assessed but not performed by independent rater; groups had entry times every 4 weeks, unclear if group contamination effects were controlled for.

Other treatments: an initial medication evaluation was conducted and 30-minute monthly appointments were made available with the treating psychiatrist, with 2.7% of participants were prescribed a substance use medication and between 92% and 98% prescribed an antidepressant medication. Differences between the groups were reported for antidepressant prescription (higher for TSF than ICBT) at follow-up. Reported that participants agreed not to partake in other psychotherapy beyond involvement in community 12-Step addiction meetings. The TSF group reported greater involvement in 12-Step community meetings.

Markowitz 2008

Methods

Design: randomised controlled trial

Follow-up: 16-week (post-treatment)

Setting: outpatients at Cornell University Medical College

Country: USA

Participants

Participants: 26 adults with DSM-IV dysthymia and secondary alcohol abuse or dependence diagnosed on the Structured Clinical Interview for DSM-IV; HDRS > 13

Mean age (years): 38.4 (SD = 10.5)

Sex: 69% male

Ethnicity: 69% White

Interventions

Description: Interpersonal Psychotherapy Treatment for Depression (IPT-D) versus Brief Supportive Therapy (BST). IPT-D employs a medical model of illness that excuses the patient from blame, and focuses on their emotional responses to and coping strategies to resolve life crises. IPT-D encourages patients to change their life situations so as to improve their mood disorder. BST employs elicitation of affect and reflective listening but provides no explicit theoretical formulation to the patient and does not focus as directly on exploring pragmatic options for changing the environment.

Participants in both conditions were encouraged to attend AA meetings.

Markowitz 2008 (Continued)

Format: individual therapy

Duration: 16-18 sessions over 16 weeks

Allocation: IPT-D = 14 , BST = 12

Outcomes	<p><i>Treatment retention:</i> failed to complete treatment but re-coded into treatment completion for this review</p> <p><i>Self-report:</i> BDI mean total score (7 days)</p> <p>Interviewer-rated: HDRS mean (SD) total score (past 7 days), TLFB mean (SD) percentage of days abstinent (past 30 days)</p> <p><i>Attrition:</i> proportion not completed research follow-up assessment</p>
Notes	<p>A relatively high percentage of participants who met study entry criteria also reported alcohol abstinence in the month before treatment.</p> <p><i>Funding:</i> National Institute of Mental Health (NIHM; MH- 49635), the Weill Cornell Department of Psychiatry, MINT: Mental Health Initiative.</p> <p><i>Conflict of interest:</i> no statement provided.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Eligible subjects signed separate informed consent for study entry and were assigned to IPT-Dor BSP in a 1:1 distribution using a computer-generated random number program. (p. 469)."</p> <p>Quote (via author email): "The study statistician, otherwise not involved in the clinical procedure of the trial, computer-generated a random number sequence. computer-generated a random number sequence."</p> <p>Quote: " The 2 treatment groups did not differ on demographic or clinical variables." (p. 470)</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (via author email): "Patient assignments were sealed in numbered, otherwise blank, opaque, sealed envelopes, which I as Principal Investigator opened in the patient's presence after the patient had signed informed consent."</p>
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	<p>Participants, therapists and the principal investigator was not blinded to treatment allocation.</p>
Blinding of participants and personnel (performance bias) objective outcomes	High risk	<p>Participant and therapist knowledge of group allocation may influence treatment engagement/participation/ attendance.</p>
Blinding of outcome assessment (detection bias) self-report	Unclear risk	<p>Comment: The authors judge risk of bias to be unclear. While participants were not blind to treatment allocation and self-report measures may be impacted by self-presentation bias or client insight, it is unlikely that any such risk of bias will vary by treatment condition.</p>
Blinding of outcome assessment (detection bias)	Low risk	<p>Quote: " Independent evaluators blinded to clinical assignment rated subjects." (p. 470)</p>

Markowitz 2008 (Continued)

interviewer-rated outcomes

Blinding of outcome assessment (detection bias) treatment retention/attendance	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p><i>Treatment retention:</i> IPT-D = 57%; BST = 58%</p> <p>Comment: the number of treatment completers was similar</p> <p><i>Outcome assessment:</i> IPT-D=42.9% , BST=16.7%; LOCF and ITT was used</p> <p>Comment: The IPT-D group had double the attrition rate of the BST group; LOCF was used for missing data</p>
Selective reporting (reporting bias)	Unclear risk	Risk is unclear as no study protocol is available, but the results of all planned analyses using the outcome listed in the methods are reported in the manuscript.
Other bias	Low risk	<p><i>Fidelity:</i> all sessions audio-taped and random sessions rated by an independent rater. Separate therapists delivered the two treatments to avoid therapist allegiance/contamination effects but the success of this was not formally assessed.</p> <p><i>Other treatments:</i> concurrent pharmacotherapy or psychotherapy was an exclusion criteria</p>

Rohde 2014

Methods	<p><i>Design:</i> randomised controlled trial;</p> <p><i>Follow-up:</i> 20-weeks (post-treatment), 6- and 12-months follow-up</p> <p><i>Setting:</i> outpatient substance use treatment services in Portland, Oregon, Albuquerque, New Mexico</p> <p><i>Country:</i> USA</p>
Participants	<p><i>Participants:</i> 170 adolescents with a current DSM-IV depression disorder (MDD, dysthymia, adjustment disorder with depressed mood; depression NOS) and non-nicotine substance use disorder on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL); Drug use within the last 90 days (TLFB)</p> <p><i>Mean age (years):</i> 13-18 years</p> <p><i>Sex:</i> > 25% female</p> <p><i>Ethnicity:</i> 61% non-Hispanic white</p>
Interventions	<p><i>Description:</i> (i) Functional Family Therapy (FFT) followed by modified adolescent Coping With Depression course (CWD) (FFT/CWD): CWD provided cognitive and behavioral strategies to address adolescent depression (Clarke 1990). The communication and problem-solving skills were included in FFT and a points system was added to reward participation. FFT is a behaviourally-based model of family therapy (Alexander 1982) that targets addictive behaviours by altering family systems using five treatment phases (engagement, motivation, relational assessment, behaviour change, generalisation).</p> <p>(ii) CWD followed by FFT (CWD/FFT)</p>

Rohde 2014 (Continued)

(iii) Integrated FFT & CWD treatment (CWD+FFT): Family sessions followed FFT. Group treatment consisted of CWD augmented to provide skills aimed at reducing substance use (Waldron 2004).

Format: group and family therapy

Duration: FFT/CWD: 12 x 90min group sessions in 10 weeks + 12 family sessions in 10 weeks (24 sessions in 20 weeks); CWD/FFT: 12 family sessions in 10 weeks + 12 x 90min group sessions in 10 weeks (24 sessions in 20 weeks); CWD+FFT: 4 family sessions prior to 10 group sessions over 10 weeks + 2 additional sessions (24 sessions over 20 weeks)

Allocation: FFT/CWD = 61; CWD/FFT = 56; CWD+FFT = 53

Outcomes	<p><i>Treatment attendance:</i> number of sessions completed</p> <p><i>Self-report:</i> CDRS-R mean (SD) total score (past 7 days)</p> <p><i>Interviewer-rated:</i> TLFB mean (SD) percentage of days of all drug use (past 90 days)</p> <p><i>Attrition:</i> proportion not completed research follow-up assessment</p>
Notes	<p>No nesting effects for cohorts or therapists; site effects non-significant</p> <p><i>Funding:</i> National Institute on Drug Abuse Research Grant (DA21357).</p> <p><i>Conflict of interest:</i> no statement provided.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote (via author email). "Adolescents were recruited until a cohort could be formed composed of 4-9 families. Each cohort (total = 27) was randomly assigned to one of the three sequences. Assignment of cohorts to conditions occurred in blocks of three at each site so that all conditions were completed before any was repeated. We adopted the cohort strategy so that we could coordinate the formation of group CWD sessions across all three treatment sequences. Once cohorts had been randomised, caseload and scheduling factors were used to assign therapists (i.e., therapists were not randomly assigned)."</p> <p>Quote (via author email): "The analyst used a computer-based randomisation procedure"</p> <p>No baseline differences between treatments groups except for age (CWD+FFT younger; $P < 0.05$)</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (via author email) "The randomisation sequence was known by the project coordinator in Eugene, Oregon (a separate site) and she told the therapists at each site which condition would be provided next – we needed to do this so that FFT and CWD-A therapists could be available to provide treatment when it would occur. Therapists did not do the assessments (they were conducted by separate research assistants who remained masked to condition throughout assessments). Once enough families had enrolled and been found to be eligible, they were told which condition they would receive."</p>
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Participants and personnel were not blind to treatment allocation.
Blinding of participants and personnel (performance bias)	High risk	Participant and personnel knowledge of group allocation may influence treatment engagement/participation/ attendance

Rohde 2014 (Continued)
 objective outcomes

Blinding of outcome assessment (detection bias) self-report	Unclear risk	Comment: The authors judge risk of bias to be unclear. While participants were not blind to treatment allocation and self-report measures may be impacted by self-presentation bias or client insight, it is unlikely that any such risk of bias will vary by treatment condition.
Blinding of outcome assessment (detection bias) interviewer-rated outcomes	Low risk	Quote (via author email): "Follow up assessors were blind to treatment allocation. The interview data were collected by trained research assistants who were not the treating clinician."
Blinding of outcome assessment (detection bias) treatment retention/attendance	Low risk	Blinding unclear, but outcome measure is unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p><i>Treatment attendance:</i> FFT/CWD = 15.4, CWD/FFT = 12.7, CWD+FFT = 16.8; Significantly lower in CWD/FFT than CWD+FFT ($P < 0.03$), neither differed from FFT/CWD.</p> <p>Comment: the number of treatment sessions completed was similar, one significant difference found</p> <p><i>Outcome assessment:</i></p> <p>Attrition post-treatment: FFT/CWD 21%; CWD/FFT 25%; CWD+FFT 17%</p> <p>Attrition 6-month: FFT/CWD 39%; CWD/FFT 27%; CWD+FFT 25%</p> <p>Attrition 12-month: FFT/CWD 26%; CWD/FFT 16%; CWD+FFT 9%</p> <p>Comment: similar attrition across groups missing data imputed (10 imputed data sets to run analyses); ITT analysis performed</p>
Selective reporting (reporting bias)	Unclear risk	Risk is unclear as no study protocol is available, but the results of all planned analyses using the outcome listed in the methods are reported in the manuscript.
Other bias	High risk	<p><i>Fidelity:</i> weekly supervision; videotaped sessions rated for adherence but unclear if rater was independent. Therapists adhered to the treatments with no differences across treatment sequences.</p> <p><i>Other treatment:</i> participants were able to attend adjunctive treatment or use anxiety/depression medication. A difference between treatment groups is reported for concurrent adjunctive therapy during therapy (FFT/CWD = 16%; CWD/FFT = 49%; CT = 20%), but not at follow-up. No difference in medication use is reported. Receiving adjunctive therapy was found to positively impact outcome results.</p>

AA: Alcoholics Anonymous; ASI: Addiction Severity Index; AUD: alcohol use disorder; BDI: Beck Depression Inventory; BTDD: Behavioral Therapy for Depression in Drug Dependence; CT: cognitive therapy; DSM 1V: Diagnostic and Statistical Manual 4th edition; HDRS: Hamilton Rating Scale for Depression; ICBT: Integrated Cognitive Behavioural Therapy; IPT-D: Interpersonal Psychotherapy for Depression; ITT: intention-to-treat; LOCF: last observation carried forward; MDD: major depressive disorder; NT: narrative therapy; pt: prescriptive therapy; SD: standard deviation; SUD: substance use disorder; TAU: treatment as usual; TLFB: Timeline Follow Back

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aghataher 2014	Depression criteria not met
Agyapong 2012a	Psychotherapy criteria not met - text messaging - not specified psychotherapy
Agyapong 2012b	Psychotherapy criteria not met - text messaging - not specified psychotherapy
Agyapong 2013	Psychotherapy criteria not met - text messaging - not specified psychotherapy
Allsop 2014	Depression criteria not met
Arian 2008	Depression criteria not met
Aschbrenner 2015	Depression and SUD criteria not met
Baker 2010	SUD criteria not met
Baker 2013	SUD criteria not met
Baker 2014	SUD criteria not met
Banducci 2015	Depression criteria not met
Barlow 2015	Depression and SUD criteria not met
Battersby 2013	Depression criteria not met
Becker 2015	Depression criteria not met
Bellack 2006	Depression criteria not met
Berman 2015	Depression criteria not met
Bernard 2015	Depression criteria not met
Bluth 2016	Depression and SUD criteria not met
Bolton 2014	SUD criteria not met
Bowman 1996	Depression criteria not met
Bricker 2007	SUD criteria not met
Briere 2014	Depression criteria not met
Brody 2012	Depression and SUD criteria not met
Brown 1997	Depression criteria not met
Brown 2007	Depression criteria not met
Capron 2014	Depression criteria not met
Carroll 1995	Depression criteria not met
Clair-Michaud 2016	Depression criteria not met

Study	Reason for exclusion
Collins 2015	Depression and SUD criteria not met
Cornelius 2011	Not RCT
Cucciare 2013	Depression criteria not met
Delgadillo 2015	SUD criteria not met
Detweiler 2015	Depression criteria not met
Duffy 2006	Depression and SUD criteria not met
Essex 2014	Depression and SUD criteria not met
Forray 2014	Depression criteria not met
Garcia-Fernandez 2013	Depression criteria not met
Gardner 2016	Depression and SUD criteria not met
Geisner 2015	Depression criteria not met
Giovancarli 2016	Depression criteria not met
Glasner 2012	Depression criteria not met
Gonzalez-Menendez 2014	Depression criteria not met
Gottheil 2002	Depression criteria not met
Grothues 2008	Depression criteria not met
Grothues 2008a	Depression criteria not met
Guo 2014	Depression criteria not met
Hall 1994	Depression criteria not met
Hall 1996	Depression criteria not met
Hall 2006	SUD criteria not met
Haller 2016	Depression criteria not met - specifically targeting PTSD and trauma
Hallgren 2014	Depression criteria not met
Hickman 2015	Depression and SUD criteria not met
Hides 2010	SUD criteria not met
Hides 2011	Depression criteria not met
Horigian 2013	Depression criteria not met
Hosseinzadeh 2014	SUD criteria not met

Study	Reason for exclusion
Johnson 2017	Depression criteria not met
Jones 2015	Depression and SUD criteria not met
Kahler 2002	Depression criteria not met
Kahler 2015	Depression criteria not met
Kalapatapu 2014	SUD criteria not met
Kapson 2010	Depression criteria not met
Katz 2008	Depression and SUD criteria not met
Kavanagh 2006	Depression criteria not met
Kay-Lambkin 2009	SUD criteria not met
Kay-Lambkin 2011a	SUD criteria not met
Kay-Lambkin 2011b	Depression criteria not met
Kay-Lambkin 2017	SUD criteria not met
Lanza 2014	Depression criteria not met
Lehman 1993	Depression criteria not met
McClanahan 2001	Depression criteria not met
McDevitt-Murphy 2014	Depression criteria not met
McDonnell 2013	Depression criteria not met
McHugh 2010	Depression criteria not met
McKay 2002	Depression criteria not met
Menchetti 2014	SUD criteria not met
Milby 2015	Depression criteria not met
Montag 2015	Depression and SUD criteria not met
Morley 2016	Depression and SUD criteria not met
Mujika 2014	Depression and SUD criteria not met
Muller 2015	SUD criteria not met
Myers 2016	Depression criteria not met
Neumann 2016	Depression criteria not met
Oesterle 2015	Depression and SUD criteria not met

Study	Reason for exclusion
Oslin 2003	Depression and SUD criteria not met
Oslin 2004	Depression criteria not met
Ostergaard 2018	Depression criteria not met
Pachankis 2015	SUD criteria not met
Palfai 2014	Depression criteria not met
Patten 1998	Depression criteria not met
Patten 2002	Depression criteria not met
Peck 2005	Depression criteria not met
Peckham 2015	Depression criteria not met
Pedrelli 2015	Depression and SUD criteria not met
Petersen 2009	Depression criteria not met
Polcin 2015	Depression criteria not met
Ponizovsky 2015	Depression criteria not met
Rawson 2015	Depression criteria not met
Reid 2016	Depression criteria not met
Rohde 2014a	Depression and SUD criteria not met
Rose 2015	Depression and SUD criteria not met
Ruscio 2016	Depression criteria not met
Ryb 2011	Depression criteria not met
Saedy 2015	Depression criteria not met
Safren 2012	Depression criteria not met
Satre 2013	SUD criteria not met
Satre 2016	Depression and SUD criteria not met
Seghatoleslam 2014	SUD criteria not met
Seitz-Brown 2015	Depression and SUD criteria not met
Shoptaw 2006	Depression criteria not met
Singla 2019	Depression criteria not met
Stein 2011	SUD criteria not met

Study	Reason for exclusion
Stockings 2014	Depression and SUD criteria not met
Sun 2007	Depression criteria not met
Tapert 2003	Depression criteria not met
Tempersta 1998	Psychotherapy criteria not met - pharmacological treatment within a therapeutic context - not randomised to psychotherapy, only to pharmacological treatment
Tempesta 2000	Psychotherapy criteria not met - pharmacological treatment within a therapeutic context - not randomised to psychotherapy, only to pharmacological treatment
Tiburcio 2016	Depression criteria not met
Vinci 2014	Depression criteria not met
Wilks 2018	Depression criteria not met
Wilson 2014	Depression criteria not met
Womack 2004	Not RCT
Wusthoff 2014	Depression criteria not met
Zemestani 2016	Depression criteria not met

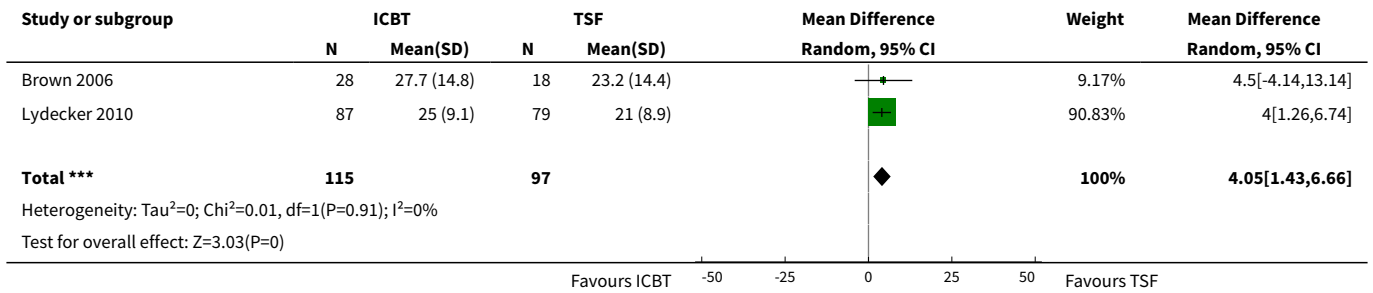
PTSD: post-traumatic stress disorder; RCT: randomised controlled trial; SUD: substance use disorder

DATA AND ANALYSES

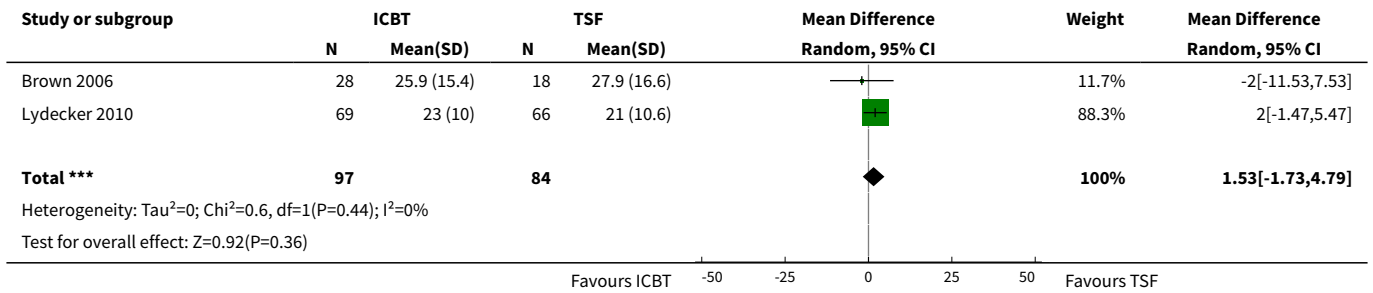
Comparison 1. Integrated CBT vs Twelve Step Facilitation - Post Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression - HDRS: end of treatment	2	212	Mean Difference (IV, Random, 95% CI)	4.05 [-1.43, 6.66]
2 Depression - HDRS: 6- to 12-month follow-up	2	181	Mean Difference (IV, Random, 95% CI)	1.53 [-1.73, 4.79]
3 Substance use - PDA: end of treatment	2	220	Mean Difference (IV, Random, 95% CI)	-2.84 [-8.04, 2.35]
4 Substance use - PDA: 6- to 12-month follow-up	2	189	Mean Difference (IV, Random, 95% CI)	10.76 [3.10, 18.42]
5 Treatment retention	2	296	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.25]
6 Treatment attendance	2	270	Mean Difference (IV, Random, 95% CI)	-1.27 [-6.10, 3.56]

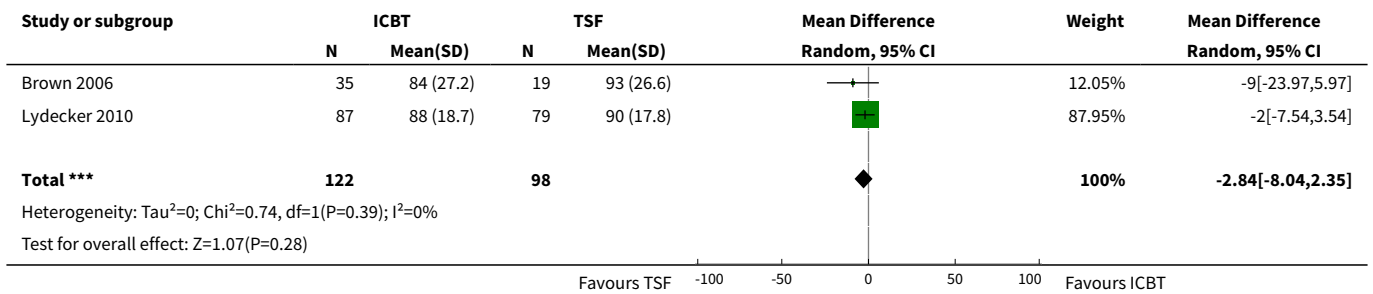
Analysis 1.1. Comparison 1 Integrated CBT vs Twelve Step Facilitation - Post Treatment, Outcome 1 Depression - HDRS: end of treatment.



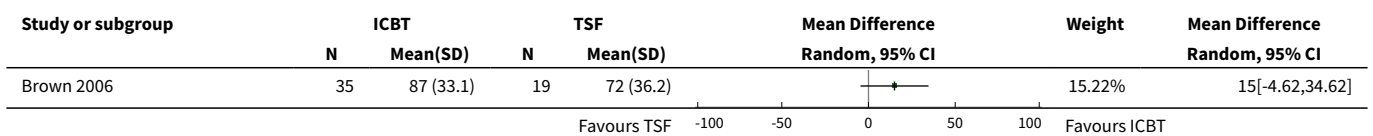
Analysis 1.2. Comparison 1 Integrated CBT vs Twelve Step Facilitation - Post Treatment, Outcome 2 Depression - HDRS: 6- to 12-month follow-up.

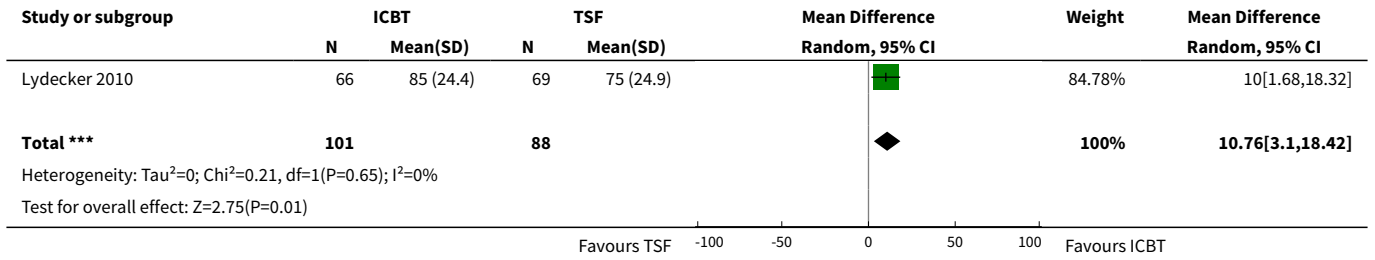


Analysis 1.3. Comparison 1 Integrated CBT vs Twelve Step Facilitation - Post Treatment, Outcome 3 Substance use - PDA: end of treatment.

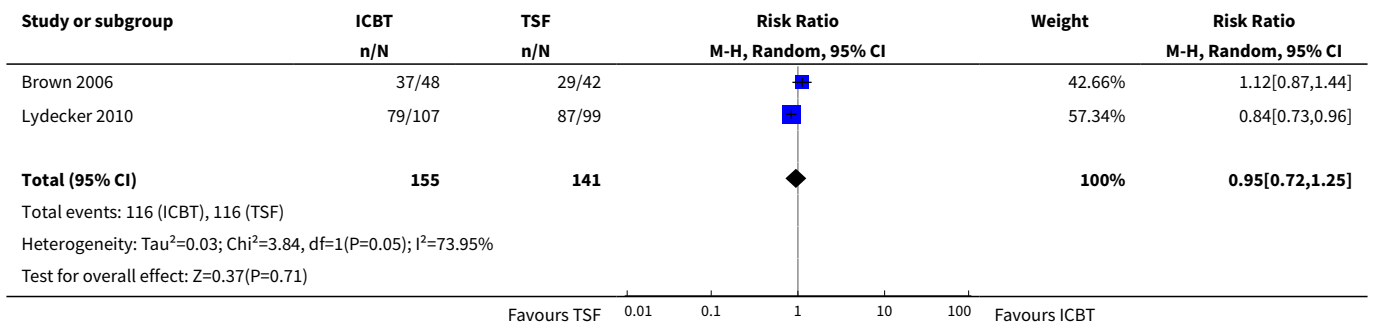


Analysis 1.4. Comparison 1 Integrated CBT vs Twelve Step Facilitation - Post Treatment, Outcome 4 Substance use - PDA: 6- to 12-month follow-up.

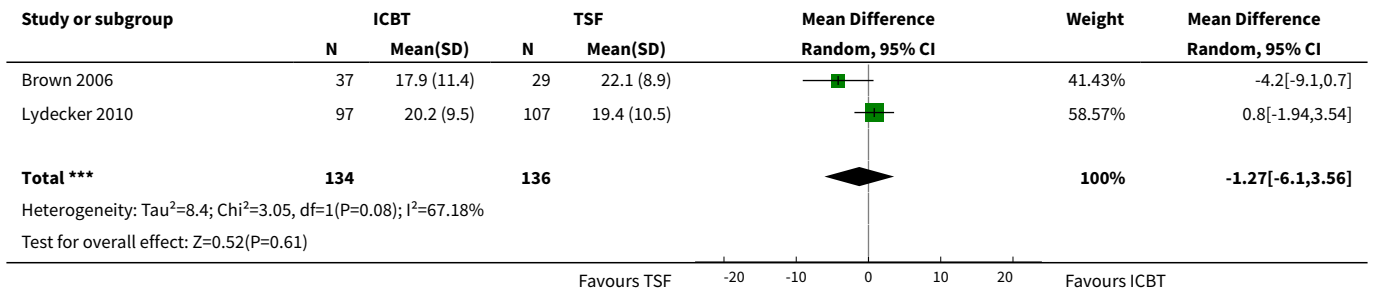




Analysis 1.5. Comparison 1 Integrated CBT vs Twelve Step Facilitation - Post Treatment, Outcome 5 Treatment retention.



Analysis 1.6. Comparison 1 Integrated CBT vs Twelve Step Facilitation - Post Treatment, Outcome 6 Treatment attendance.

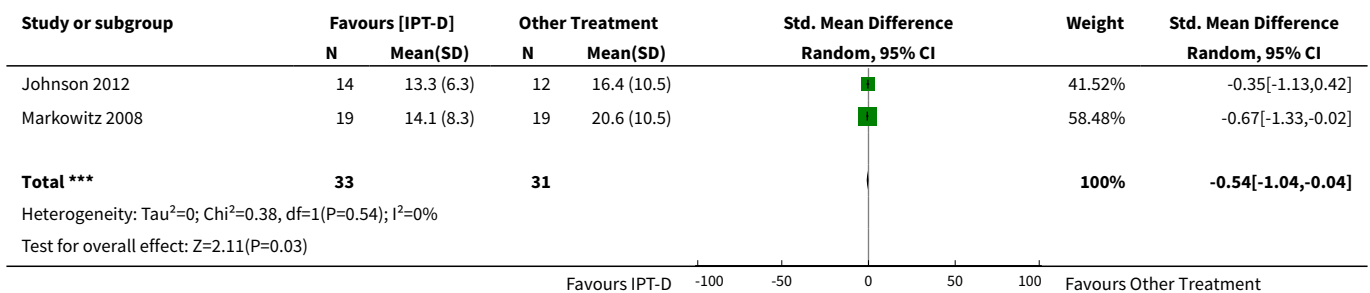


Comparison 2. Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions

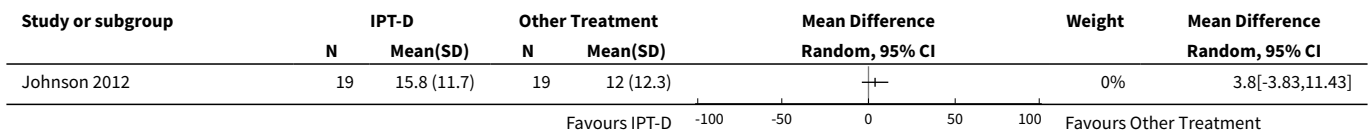
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression - HDRS: end of treatment	2	64	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.04, -0.04]
2 Depression - HDRS - 3-month follow-up (IPT-D vs Psychoed)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Substance use - PDA: end of treatment (IPT vs BST)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Substance use - Relapse: 3-month follow-up (IPT vs Psychoed)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Treatment retention	2	64	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.23]

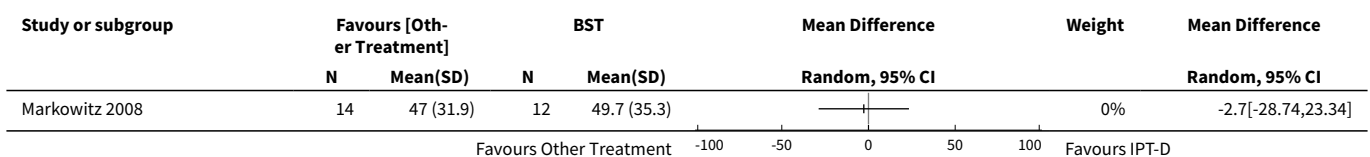
Analysis 2.1. Comparison 2 Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions, Outcome 1 Depression - HDRS: end of treatment.



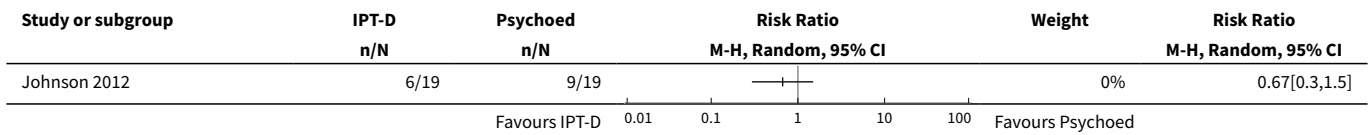
Analysis 2.2. Comparison 2 Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions, Outcome 2 Depression - HDRS - 3-month follow-up (IPT-D vs Psychoed).



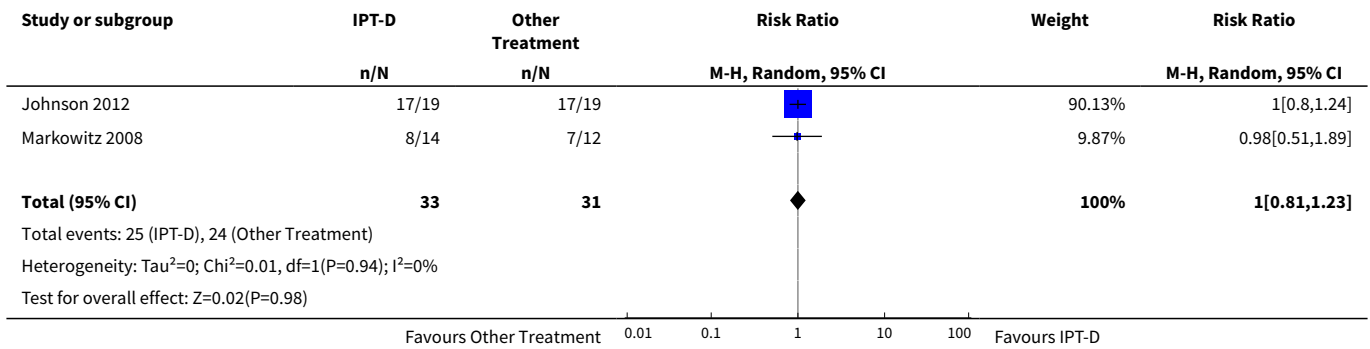
Analysis 2.3. Comparison 2 Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions, Outcome 3 Substance use - PDA: end of treatment (IPT vs BST).



Analysis 2.4. Comparison 2 Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions, Outcome 4 Substance use - Relapse: 3-month follow-up (IPT vs Psychoed).



Analysis 2.5. Comparison 2 Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapeutic Interventions, Outcome 5 Treatment retention.



Comparison 3. Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression - CDRS-R: end of treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Depression - CDRS-R: 12-month follow-up	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Substance use - square root % daily use: end of treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Substance use - square root % daily use: 12-month follow-up	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Premature termination	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Treatment attendance	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3 Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT, Outcome 1 Depression - CDRS-R: end of treatment.

Study or subgroup	Combined		Sequential		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Rohde 2014	42	28.5 (10.2)	41	32.1 (13.5)	+	0%	-3.6[-8.76,1.56]
Rohde 2014	42	28.5 (10.2)	48	31.9 (12)	+	0%	-3.49[-8.08,1.1]

Favours Combined -100 -50 0 50 100 Favours Sequenced

Analysis 3.2. Comparison 3 Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT, Outcome 2 Depression - CDRS-R: 12-month follow-up.

Study or subgroup	Combined		Sequential		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Rohde 2014	39	30.6 (12.7)	35	30.4 (16.8)	+	0%	0.13[-6.72,6.98]
Rohde 2014	39	30.6 (12.7)	34	32 (15.5)	+	0%	-1.44[-7.98,5.1]

Favours Combined -100 -50 0 50 100 Favours Sequential

Analysis 3.3. Comparison 3 Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT, Outcome 3 Substance use - square root % daily use: end of treatment.

Study or subgroup	Combined		Sequential		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Rohde 2014	44	6.4 (3)	42	5.8 (3.1)	+	0%	0.6[-0.69,1.89]
Rohde 2014	44	6.4 (3)	48	5.1 (3.3)	+	0%	1.3[0.01,2.59]

Favours Combined -10 -5 0 5 10 Favours Sequential

Analysis 3.4. Comparison 3 Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT, Outcome 4 Substance use - square root % daily use: 12-month follow-up.

Study or subgroup	Combined		Sequential		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Rohde 2014	48	7.1 (3.1)	47	5.7 (3.4)	+	0%	1.32[0.02,2.62]
Rohde 2014	48	7.1 (3.1)	45	5.7 (3.4)	+	0%	1.32[0,2.64]

Favours Combined -10 -5 0 5 10 Favours Sequential

Analysis 3.5. Comparison 3 Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT, Outcome 5 Premature termination.

Study or subgroup	Combined		Sequential		Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
	n/N	n/N	n/N	n/N			
Rohde 2014	4/53	7/61	7/61	7/61	+	0%	0.66[0.2,2.12]
Rohde 2014	4/53	9/56	9/56	9/56	+	0%	0.47[0.15,1.43]

Favours Combined 0.01 0.1 1 10 100 Favours Sequential

Analysis 3.6. Comparison 3 Combined FFT & CWD vs sequential FFT-CWD; Combined FFT & CSD vs sequential CWD-FFT, Outcome 6 Treatment attendance.

Study or subgroup	Combined		Sequential		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Rohde 2014	53	16.8 (8.1)	61	15.4 (8.1)		0%	1.4[-1.58,4.38]
Rohde 2014	53	16.8 (8.1)	56	12.7 (8.5)		0%	4.1[0.98,7.22]

Favours Sequential -20 -10 0 10 20 Favours Combined

Comparison 4. Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression - HDRS: end of treatment	1	24	Mean Difference (IV, Random, 95% CI)	2.10 [-6.03, 10.23]
2 Depression - BDI-II: end of treatment	1	24	Mean Difference (IV, Random, 95% CI)	6.60 [-4.94, 18.14]
3 Substance use - Opiates: end of treatment	1	24	Mean Difference (IV, Random, 95% CI)	0.11 [-0.09, 0.31]
4 Substance use - Cocaine: end of treatment	1	24	Mean Difference (IV, Random, 95% CI)	0.1 [-0.13, 0.33]
5 Substance use - Benzodiazepines: end of treatment	1	24	Mean Difference (IV, Random, 95% CI)	0.02 [-0.21, 0.25]
6 Treatment attendance	1	38	Mean Difference (IV, Random, 95% CI)	-3.70 [-7.83, 0.43]

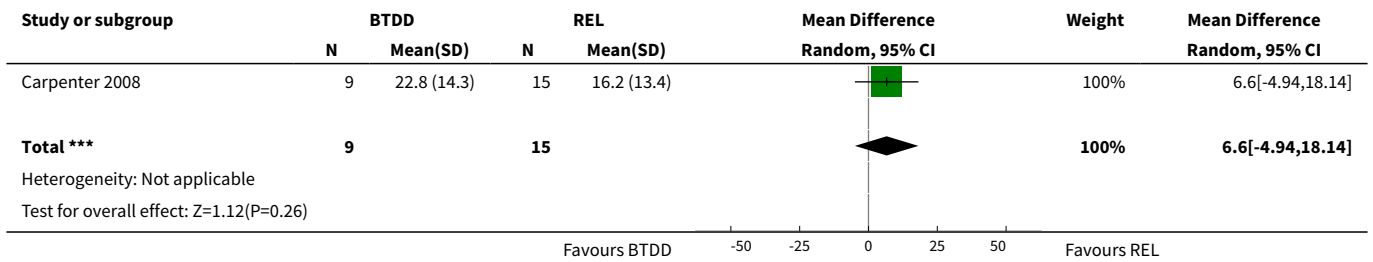
Analysis 4.1. Comparison 4 Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention, Outcome 1 Depression - HDRS: end of treatment.

Study or subgroup	BTDD		REL		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Carpenter 2008	9	14.8 (9.8)	15	12.7 (9.9)		100%	2.1[-6.03,10.23]
Total ***	9		15			100%	2.1[-6.03,10.23]

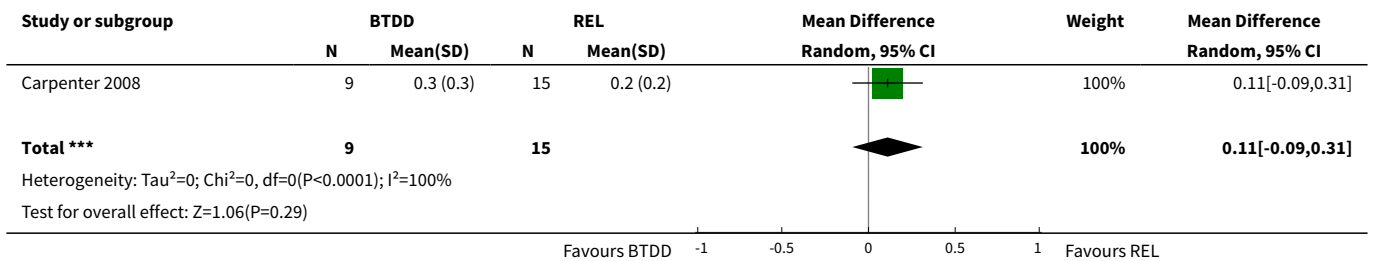
Heterogeneity: Not applicable
Test for overall effect: Z=0.51(P=0.61)

Favours BTDD -50 -25 0 25 50 Favours REL

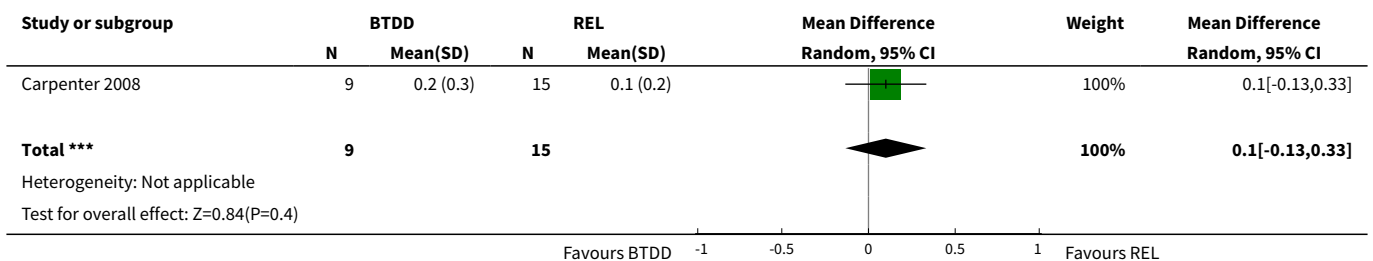
Analysis 4.2. Comparison 4 Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention, Outcome 2 Depression - BDI-II: end of treatment.



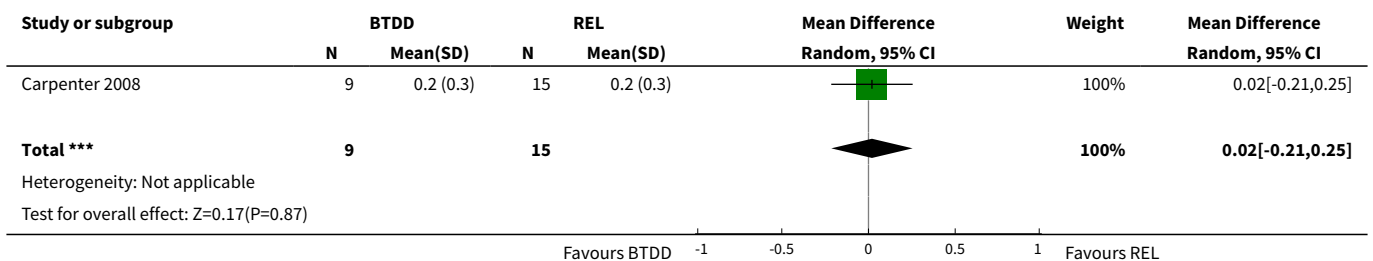
Analysis 4.3. Comparison 4 Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention, Outcome 3 Substance use - Opiates: end of treatment.



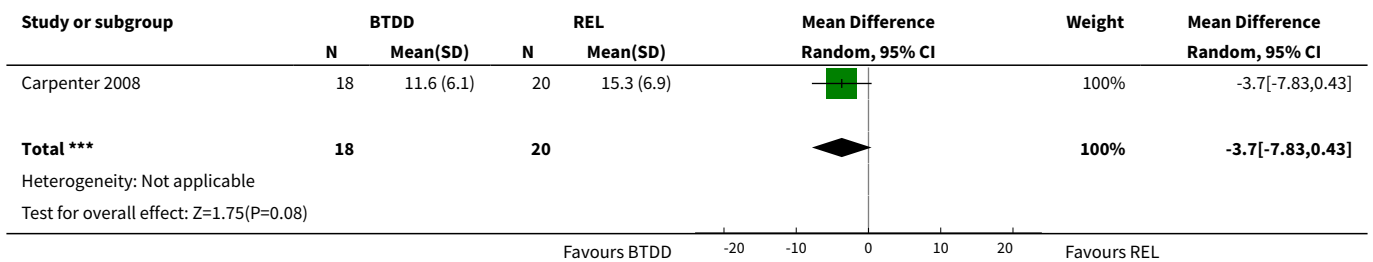
Analysis 4.4. Comparison 4 Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention, Outcome 4 Substance use - Cocaine: end of treatment.



Analysis 4.5. Comparison 4 Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention, Outcome 5 Substance use - Benzodiazepines: end of treatment.



Analysis 4.6. Comparison 4 Behavioral Therapy for Depression in Drug Dependence vs Relaxation intervention, Outcome 6 Treatment attendance.



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Mood Disorders] explode all trees

#2 affective or depression or "depressive disorder" or "mood disorder" or anxiety or dysthymic:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Substance-Related Disorders] explode all trees

#5 drug or substance or alcohol or marijuana or cannabis or meth-amphetamine or dextro- or amphetamine or MDMA or heroin or narcotic or opiate or opioid or opium or ecstasy or methadone or cocaine or psychostimulant* or inhalant* or solvent*:ti,ab,kw and abus* or use* or misus* or usin* or utilis* or depend* or addict* or illegal* or illicit* or habit* or withdraw* or behavi* or abstinence* or abstain* or intoxica* or addict * or disorder*:ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 MeSH descriptor: [Psychotherapy] explode all trees

#8 psychotherapy or counselling or behavior* or contigenc* or supportive or reinforcement or motivation* or incentive or "cognitive therapy" (Word variations have been searched)

#9 #7 or #8

#10 #3 and #6 and #9

Appendix 2. PubMed search strategy

1. mood disorders [mh]
2. affective[tw] OR depression[tw] OR "depressive disorder" [tw] OR "mood disorder"[tw] OR anxiety[tw] OR dysthymic[tw]
3. #1 OR #2
4. Substance-related disorders [mh]
5. ((drug OR substance OR alcohol OR marijuana OR cannabis OR meth/dextro-amphetamine OR amphetamine OR MDMA OR heroin OR narcotic OR opiate OR opioid or opium OR ecstasy OR methadone OR cocaine or psychostimulant* or inhalant* OR solvent*) AND (abus* OR use* OR misus* OR usin* OR utilis* OR depend* OR addict* OR illegal* OR illicit* OR habit* OR withdraw* OR behavi* OR abstinence* OR abstain* OR intoxica* OR addict * or disorder*))
6. #5 OR #6
7. Psychotherapy [mh]
8. psychotherapy[tw] OR counselling[tw] OR behavior*[tw] OR contigenc*[tw] OR supportive[tw] OR reinforcement[tw] OR motivation*[tw] OR incentive[tw] OR "cognitive therapy"[tw]
9. #7 OR #8

- 10.randomized controlled trial [pt]
- 11.controlled clinical trial [pt]
- 12.randomized [tw]
- 13.placebo [tw]
- 14.clinical trials as topic [mesh: noexp]
- 15.randomly [tw]
- 16.trial [tw]
- 17.#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
- 18.animals [mh] NOT humans [mh]
- 19.#17 NOT #18
- 20.#3 AND #6 AND #9 AND #19

[pt] denotes a Publication Type term;

[tiab] denotes a word in the title or abstract;

[sh] denotes a subheading;

[mh] denotes a Medical Subject Heading (MeSH) term ('exploded');

[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (not 'exploded');

[ti] denotes a word in the title;

[tw] denote text words across the record included in the title, abstract, MeSH, Publication Types or Substance Names

Appendix 3. Embase search strategy

Single syntax:

'mood disorders'/exp/mj OR affective OR depression OR 'depressive disorder' OR 'mood disorder' OR anxiety OR dysthymic AND 'substance-related disorders'/exp/mj OR 'drug':ab,ti OR 'substance':ab,ti OR 'alcohol':ab,ti OR 'marijuana':ab,ti OR 'cannabis':ab,ti OR 'meth-amphetamine':ab,ti OR 'dextro':ab,ti OR 'amphetamine':ab,ti OR 'mdma':ab,ti OR 'heroin':ab,ti OR 'narcotic':ab,ti OR 'opiate':ab,ti OR 'opioid':ab,ti OR 'opium':ab,ti OR 'ecstasy':ab,ti OR 'methadone':ab,ti OR 'cocaine':ab,ti OR 'psychostimulant*':ab,ti OR 'inhalant*':ab,ti OR 'solvent*':ab,ti AND ('abus*':ab,ti OR 'use*':ab,ti OR 'misus*':ab,ti OR 'usin*':ab,ti OR 'utilis*':ab,ti OR 'depend*':ab,ti OR 'illegal*':ab,ti OR 'illicit*':ab,ti OR 'habit*':ab,ti OR 'withdraw*':ab,ti OR 'behavi*':ab,ti OR 'abstinence*':ab,ti OR 'abstain*':ab,ti OR 'intoxica*':ab,ti OR 'addict*':ab,ti OR 'disorder*':ab,ti) AND 'psychotherapy'/exp/mj OR psychotherapy OR counselling OR behavior* OR contigenc* OR supportive OR reinforcement OR motivation* OR incentive OR 'cognitive therapy' AND randomized OR placebo OR randomly OR trial NOT animals NOT human AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)

Appendix 4. CINAHL Search Strategy

S20	S3 AND S6 AND S9 AND S19
S19	S17 NOT S18
S18	TX animal* NOT TX human*
S17	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16	TX trial
S15	TX randomly
S14	SU clinical trial
S13	TX placebo

(Continued)

S12	TX randomized
S11	PT clinical trial
S10	PT randomized controlled trial
S9	(TX psychotherapy OR counselling OR behavior* OR contigenc* OR supportive OR reinforcement OR motivation* OR incentive OR "cognitive therapy") AND (S7 OR S8)
S8	TX psychotherapy OR counselling OR behavior* OR contigenc* OR supportive OR reinforcement OR motivation* OR incentive OR "cognitive therapy"
S7	(MH "Psychotherapy+") OR (MH "Psychotherapy, Brief") OR (MH "Psychotherapy, Psychodynamic") OR (MH "Psychotherapy, Group+") OR (MH "Cognitive Therapy+") OR (MH "Equine-Assisted Therapy")
S6	(TX (drug OR substance OR alcohol OR marijuana OR cannabis OR meth/dextro-amphetamine OR amphetamine OR MDMA OR heroin OR narcotic OR opiate OR opioid or opium OR ecstasy OR methadone OR cocaine or psychostimulant* or inhalant* OR solvent*) AND TX (abus* OR use* OR misus* OR usin* OR utilis* OR depend* OR addict* OR illegal* OR illicit* OR habit* OR withdraw* OR behavi* OR abstinence* OR abstain* OR intoxica* OR addict* or disorder*)) AND (S4 OR S5)
S5	TX (drug OR substance OR alcohol OR marijuana OR cannabis OR meth/dextro-amphetamine OR amphetamine OR MDMA OR heroin OR narcotic OR opiate OR opioid or opium OR ecstasy OR methadone OR cocaine or psychostimulant* or inhalant* OR solvent*) AND TX (abus* OR use* OR misus* OR usin* OR utilis* OR depend* OR addict* OR illegal* OR illicit* OR habit* OR withdraw* OR behavi* OR abstinence* OR abstain* OR intoxica* OR addict* or disorder*)
S4	(MH "Substance Use Disorders+") OR (MH "Organic Mental Disorders, Substance-Induced+") OR (MH "Alcohol-Related Disorders+")
S3	(TX affective OR depression OR "depressive disorder" OR "mood disorder" OR anxiety OR dysthymic) AND (S1 OR S2)
S2	TX affective OR depression OR "depressive disorder" OR "mood disorder" OR anxiety OR dysthymic
S1	(MH "Affective Disorders+")

Appendix 5. Criteria for 'Risk of bias' assessment

Item	Judgment	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.

(Continued)

2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	high risk	Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias) Objective outcomes	low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers ensured and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding

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	Unclear risk	Insufficient information to permit judgement of low or high risk.
6. Blinding of outcome assessor (detection bias)	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Subjective outcomes	high risk	<p>No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding.</p> <p>Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.</p>
	Unclear risk	Insufficient information to permit judgement of low or high risk.
7. Incomplete outcome data (attrition bias)	Low risk	<p>No missing outcome data.</p> <p>Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).</p> <p>Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.</p> <p>For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.</p> <p>Missing data have been imputed using appropriate methods.</p> <p>All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat).</p>
For all outcomes except retention in treatment or drop out	High risk	<p>Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.</p> <p>For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.</p> <p>'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.</p>
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group).
8. Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

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		The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk	<p>Not all of the study's pre-specified primary outcomes have been reported.</p> <p>One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.</p> <p>One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).</p> <p>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.</p> <p>The study report fails to include results for a key outcome that would be expected to have been reported for such a study.</p>
	Unclear risk	Insufficient information to permit judgement of low or high risk.
9. Other bias (treatment fidelity, completeness and contamination adequately addressed)	Low risk	<p>The number of sessions and treatment components delivered were reported; Treatment fidelity was assessed by an independent rater; The content of separate treatments was compared for cross-contamination effects.</p> <p>Separate therapists delivered different treatments to avoid cross-contamination.</p>
	High risk	Treatment completeness, fidelity and contamination not assessed.
	Unclear risk	Insufficient information to permit judgement. This is usually the case if treatment fidelity was assessed by non-independent raters or if treatment completeness, fidelity and contamination were assessed but not described or not described in sufficient detail to allow a definite judgement.

CONTRIBUTIONS OF AUTHORS

LH wrote the protocol and the initial version of the review. LH, CQ and SS undertook the searches and screening, LH and CQ extracted the data and appraised the quality of papers. AB and DK provided advice on the screening, quality appraisal and assisted with the interpretation of data. All authors assisted with the writing and editing of the review.

DECLARATIONS OF INTEREST

No authors have any conflict of interests to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The inclusion criteria in the protocol stated all studies including individuals with a current depressive disorder with comorbid substance use problem according to DSM-IV, ICD-10 criteria applied by a clinician, via structured clinical interview or via clinical cut-offs on a psychometric measure of substance misuse would be included. This criteria was revised to only include studies which included individuals with a current comorbid DSM/ICD depression and substance use disorder derived using structured clinical interviews, due to the considerable heterogeneity in the cut-offs used on psychometric instruments to identify individuals with depression and substance use. This change resulted in the exclusion of four studies that used screening tools to identify individuals with depression and/or substance use disorders ([Brown 1997](#); [Johnson 2017](#); [Geisner 2015](#); [Kalapatapu 2014](#)) and seven studies that used various definitions of hazardous or harmful substance use as an inclusion criteria for substance use ([Baker 2010](#); [Baker 2013](#); [Baker 2014](#); [Kay-Lambkin 2009](#); [Kay-Lambkin 2011a](#); [Satre 2013](#); [Satre 2016](#)).

Planned subgroup and sensitivity analyses could not be conducted due to the small number of included studies and their clinical heterogeneity limiting the possibility to pool data.