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[Intervention Review]

Pharmacotherapy for anxiety and comorbid alcohol use disorders

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ABSTRACT

Background

Anxiety disorders are a potentially disabling group of disorders that frequently co-occur with alcohol use disorders. Comorbid anxiety and alcohol use disorders are associated with poorer outcomes, and are difficult to treat with standard psychosocial interventions. In addition, improved understanding of the biological basis of the conditions has contributed to a growing interest in the use of medications for the treatment of people with both diagnoses.

Objectives

To assess the effects of pharmacotherapy for treating anxiety in people with comorbid alcohol use disorders, specifically: to provide an estimate of the overall effects of medication in improving treatment response and reducing symptom severity in the treatment of anxiety disorders in people with comorbid alcohol use disorders; to determine whether specific medications are more effective and tolerable than other medications in the treatment of particular anxiety disorders; and to identify which factors (clinical, methodological) predict response to pharmacotherapy for anxiety disorders.

Search methods

Review authors searched the specialized registers of The Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDANCTR, to January 2014) and the Cochrane Drugs and Alcohol Group (CDAG, to March 2013) for eligible trials. These registers contain reports of relevant randomized controlled trials (RCT) from: the Cochrane Central Register of Controlled Trials (CENTRAL, all years), MEDLINE (1950 to date), EMBASE (1974 to date) and PsycINFO (1967 to date). Review authors ran complementary searches on EMBASE, PubMed, PsycINFO and the Alcohol and Alcohol Problems Science Database (ETOH) (to August 2013). We located unpublished trials through the National Institutes of Health (NIH) RePORTER service and the World Health Organization (WHO) International Clinical Trials Registry Platform (to August 2013). We screened reference lists of retrieved articles for additional studies.

Selection criteria

All true RCTs of pharmacotherapy for treating anxiety disorders with comorbid alcohol use disorders. Trials assessing drugs administered for the treatment of drinking behaviour, such as naltrexone, disulfiram and acamprosate were not eligible for inclusion in this systematic review.

Data collection and analysis

A systematic review is a standardised evaluation of all research studies that address a particular clinical issue.

Two review authors independently assessed RCTs for inclusion in the review, collated trial data and assessed trial quality. We contacted investigators to obtain missing data. We calculated categorical and continuous treatment effect estimates and their 95% confidence intervals (CI) for treatment using a random-effects model with effect-size variability expressed using Chi² and I² heterogeneity statistics.

Main results

We included five placebo-controlled pharmacotherapy RCTs (with 290 participants) in the review. Most of the trials provided little information on how randomization was performed or on whether both participants and study personnel were blinded to the intervention. Two of the three trials reporting superiority of medication compared with placebo on anxiety symptom outcomes were industry funded. We regarded one trial as being at high risk of bias due to selective reporting.

Study participants had Diagnostic and Statistical Manual (DSM) III- and DSM IV-diagnosed alcohol use disorders and post-traumatic stress disorder (two studies), social anxiety disorder (SAD; two studies) or generalized anxiety disorder (GAD; one study). Four trials assessed the efficacy of the selective serotonin re-uptake inhibitors (SSRIs: sertraline, paroxetine); one RCT investigated the efficacy of buspirone, a 5-hydroxytryptamine (5-HT) partial agonist. Treatment duration lasted between eight and 24 weeks. Overall, 70% of participants included in the review were male.

There was very low quality evidence for an effect of paroxetine on global clinical response to treatment, as assessed by the Clinical Global Impressions - Improvement scale (CGI-I). Global clinical response was observed in more than twice as many participants with paroxetine than with placebo (57.7% with paroxetine versus 25.8% with placebo; risk ratio (RR) 2.23, 95% CI 1.13 to 4.41; 2 trials, 57 participants). However, there was substantial uncertainty regarding the size of the effect of paroxetine due to the small number of studies providing data on clinically diverse patient samples. The second primary outcome measure was reduction of anxiety symptom severity. Although study investigators reported that buspirone (one trial) was superior to placebo in reducing the severity of anxiety symptoms over 12 weeks, no evidence of efficacy was observed for paroxetine (mean difference (MD) -14.70, 95% CI -33.00 to 3.60, 2 trials, 44 participants) and sertraline (one trial). Paroxetine appeared to be equally effective in reducing the severity of post-traumatic stress disorder (PTSD) symptoms as the tricyclic antidepressant desipramine in one RCT. The maximal reduction in anxiety disorder symptom severity was achieved after six weeks with paroxetine (two RCTs) and 12 weeks with buspirone (one RCT), with maintenance of medication efficacy extending to 16 weeks with paroxetine and 24 weeks with buspirone. There was no evidence of an effect for any of the medications tested on abstinence from alcohol use or depression symptoms. There was very low quality evidence that paroxetine was well tolerated, based on drop-out due to treatment-emergent adverse effects. Nevertheless, levels of treatment discontinuation were high, with 43.1% of the participants in the studies withdrawing from medication treatment. Certain adverse effects, such as sexual problems, were commonly reported after treatment with paroxetine and sertraline.

Authors' conclusions

The evidence-base for the effectiveness of medication in treating anxiety disorders and comorbid alcohol use disorders is currently inconclusive. There was a small amount of evidence for the efficacy of medication, but this was limited and of very low quality. The majority of the data for the efficacy and tolerability of medication were for SSRIs; there were insufficient data to establish differences in treatment efficacy between medication classes or patient subgroups. There was a small amount of very low quality evidence that medication was well tolerated. There was no evidence that alcohol use was responsive to medication.

Large, rigorously conducted RCTs would help supplement the small evidence-base for the efficacy and tolerability of pharmacotherapy for anxiety and comorbid alcohol use disorders. Further research on patient subgroups who may benefit from pharmacological treatment, as well as novel pharmacological interventions, is warranted.

PLAIN LANGUAGE SUMMARY

Medication for treating anxiety disorders in people with alcohol use problems

Who may be interested in this review?

People with anxiety disorders and alcohol use problems, as well as their healthcare providers.

Why is this review important?

People with anxiety disorders often also abuse alcohol or have alcohol dependence. All anxiety disorders involve long-lasting and excessive fear, and can be classified according to the cause of the fear: generalized anxiety disorder (everyday situations), obsessive-compulsive disorder (repetitive thoughts and behaviours), panic disorder (panic attacks), post-traumatic stress disorder (previous traumatic events), social anxiety disorder (negative judgements by others) and specific phobia (specific objects or situations). When people with anxiety disorders abuse or are dependent on alcohol, they may be more disabled and difficult to treat than when they have either condition on its own. Psychotherapy is most often used in treating anxiety disorders in people with alcohol use problems. In psychotherapy people are encouraged to explore their feelings, moods, behaviours, thoughts and reactions to the cause of their anxiety. Psychotherapy does not always work though, so it is important to test whether medications are an effective treatment option.

What questions does this review aim to answer?

We wanted to find out whether medication is effective in treating people with both anxiety disorders and alcohol use problems. For this reason, we systematically searched for randomized controlled trials (RCTs) of medication in treating people with both disorders. RCTs

provide a more accurate measure of the effectiveness of medication by making sure that people in the study have an equal chance of being treated with medication or placebo.

Which studies were included in the review?

This review found five RCTs in 290 adults (average age 37.4 years) with anxiety and alcohol use disorders. The evidence is current up to January 2014. Two trials looked at social anxiety disorder, two looked at post-traumatic stress disorder and one trial looked at generalized anxiety disorder. All of the included trials took place in the USA. Most of the study participants were male (70%), and were classified as having alcohol dependence (79%).

What does the evidence from the review tell us?

It was not possible to tell whether medication was effective in treating people with anxiety and alcohol use disorders. Although more than twice as many people (57.7%) with social anxiety disorder who were treated with paroxetine in two trials showed signs of clinical improvement compared with people receiving placebo (25.8%), the quality of the evidence was very low. One study reported that buspirone reduced anxiety disorder symptoms after 12 weeks of treatment. None of the other studies found reductions in symptoms. Treatment with medication appeared to be acceptable to participants, but again the quality of the evidence showing this was very low. Certain medication side effects, such as sexual problems, were commonly reported after treatment with paroxetine and sertraline. There was no evidence that treatment had an effect on alcohol use.

It was difficult to interpret the findings reported by the studies included in this review. Many participants (43.1% altogether) dropped out of the studies before treatment ended. In addition, outcomes that were reported were either not precise, or appeared to be based on the selective reporting of measures that showed an effect of medication. Funding of two of the studies by drug companies may also have led to reporting of results that favoured the medication.

SUMMARY OF FINDINGS

Summary of findings 1. Paroxetine compared with placebo for anxiety and comorbid alcohol use disorders

Paroxetine compared with placebo for anxiety and comorbid alcohol use disorders

Patient or population: people with anxiety and comorbid alcohol use disorders
Settings: Drug and alcohol treatment and community settings in South Carolina, USA
Intervention: paroxetine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Paroxetine				
Treatment response CGI-I	Study population		RR 2.23 (1.13 to 4.41)	57 (2 studies)	⊕⊕⊕⊕ very low 1,2,3	-
	258 per 1000	575 per 1000 (292 to 1000)				
	Moderate					
	248 per 1000	553 per 1000 (280 to 1000)				
Symptom severity reduction LSAS	-	The mean symptom severity reduction in the intervention groups was 14.7 lower (33 lower to 3.6 higher)	-	44 (2 studies)	⊕⊕⊕⊕ very low 1,2,3	-
Treatment acceptability	Study population		RR 3.29 (0.14 to 76.33)	57 (2 studies)	⊕⊕⊕⊕ very low 1,2,3,4,5	-
	0 per 1000	0 per 1000 (0 to 0)				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				
Proportion heavy drinking days	Study population		Not estimable	0 (0)	See comment	No data

	See comment	See comment				
Moderate						
	-	-				
Proportion of days abstinent	-	The mean proportion of days abstinent in the intervention groups was 0.08 higher (0.26 lower to 0.43 higher)	-	54 (2 studies)	⊕⊕⊕⊕ very low 1,2,3,6	-
Drinks per drinking day	-	The mean drinks per drinking day in the intervention groups was 2.42 lower (4.97 lower to 0.14 higher)	-	54 (2 studies)	⊕⊕⊕⊕ very low 1,2,3	-
Depression symptom reduction	-	The mean depression symptom reduction in the intervention groups was 2.3 lower (7.51 lower to 2.91 higher)	-	15 (1 study)	⊕⊕⊕⊕ very low 2	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

CGI: Clinical Global Impressions scale; **CI:** confidence interval; **LSAS:** Liebowitz Social Anxiety Scale; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 [Book 2008](#) restricted participation to people who drank to cope with their social anxiety symptoms and who were not seeking treatment for alcohol disorders. In addition, the authors acknowledged that the low levels of drinking observed in their sample may have biased their results with respect to people with social anxiety disorder seeking treatment for alcohol abuse/dependence. Therefore, their findings may not generalize to all people with social anxiety disorder and comorbid alcohol use disorders.

2 The 95% confidence interval around the effect estimate for the outcome was very wide.

3 Too few trials to reliably assess publication bias.

4 Inconsistency or statistical heterogeneity could not be calculated, due to too few events.

5 Drop-outs due to adverse events only provided a surrogate measure of treatment acceptability.

6 Measure of heterogeneity and consistency (I^2 statistic) indicated that variability between effect estimates from individual trials exceeded what would be expected by chance.

BACKGROUND

Description of the condition

Anxiety disorders are highly prevalent and are associated with high social, personal and economic costs. According to traditional Diagnostic and Statistical Manual (DSM) IV-TR criteria (APA 2000), this class of disorders includes generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD) and specific phobia (SP). Though differing in specific symptom profiles, the anxiety disorders are characterized by a state of chronic physiological hyperarousal to fear-inducing contexts (such as those involving social interaction in the case of SAD).

Alcohol use disorders include alcohol dependence and abuse. Anxiety disorders frequently co-occur with alcohol dependence, defined in the DSM-IV-TR as the presence of three of the following criteria any time over a 12-month period: evidence of tolerance to alcohol; symptoms of withdrawal following termination of alcohol use; consumption of increasing alcoholic beverages in larger amounts or over a longer time span than anticipated; unsuccessful attempts to reduce alcohol intake; the spending of large amounts of time acquiring alcohol; reduction or quitting of social, occupational or recreational activities due to drinking; and continued drinking despite knowledge that this leads to persistent or recurrent physical or psychological problems (APA 2000). Comorbid alcohol abuse is less commonly observed, can only be diagnosed in the absence of alcohol dependence, and is defined as a clinically significant occurrence within a 12-month timeframe of at least one of the following criteria: a recurrent pattern of alcohol use that: interferes with obligations at work, school or home; places a person in physically hazardous situations; results in legal problems; or causes or exacerbates persistent or recurrent social or interpersonal problems (APA 2000).

The diagnosis of alcohol dependence is approximately two to four times more likely for individuals diagnosed with a range of anxiety disorders (Regier 1990; Kessler 1997; Hasin 2007), while alcohol abuse may be under-represented relative to individuals without anxiety disorders (Kessler 1997; Boschloo 2013). One nationally representative survey in the US found lifetime prevalence rates of co-occurring alcohol dependence and anxiety disorders to be as high as 35.8% for men and 60.7% for women (Kessler 1997). In contrast, the European Study of the Epidemiology of Mental Disorders reported a prevalence rate of only 0.1% for comorbidity of these diagnoses over a 12-month period across six European countries (Alonso 2004). Nevertheless, the co-occurrence of these disorders has been associated with more severe symptoms, higher rates of relapse and a corresponding increase in the utilization of mental health services (Kessler 1996). There is also some epidemiological evidence of a poorer prognosis and increased rates of relapse for people with anxiety disorders in alcoholism treatment programmes (Driessen 2001; Kushner 2005).

Several theoretical models have articulated the nature of the relationship between alcohol dependence/abuse and anxiety disorders. Those that assign primacy to the anxiety disorders typically ascribe to the notion that alcohol is abused to help cope with anxiety-provoking situations. Such models include the Tension Reduction Theory (TRT) (Kushner 1990), and the Self-Medication Hypothesis (SMH) (Khantzian 1985), and may be particularly relevant for anxiety disorders that typically precede

onset of dependence, such as SAD and agoraphobia (Kushner 1990; Brady 1993). Indeed, evidence of a causal interaction between anxiety disorder symptoms and alcohol use disorders includes a possible dose-response relationship between the severity of social phobia symptoms and degree of abusive drinking (Morris 2005), as well as the finding that early treatment of anxiety disorder symptoms reduced subsequent alcohol abuse (Kendall 2004).

Description of the intervention

Certain forms of psychotherapy, such as cognitive behaviour therapy (CBT), have been recommended in clinical practice guidelines as first-line treatments for anxiety disorders (NICE 2005; CPA 2006). Although a Cochrane review is currently underway to assess the efficacy of psychotherapy for comorbid PTSD and substance use disorders (Roberts 2012), there is reason to believe that the effectiveness of CBT for treating anxiety disorders might be limited by comorbid alcohol dependency. Alcohol consumption likely to impair desensitisation to stressors and modification of maladaptive cognitions, core components of CBT (Morris 2005). In contrast, behavioural programmes designed for treating alcohol dependence may not be effective in reducing anxiety disorder symptoms, as evident in one controlled trial of CBT for comorbid alcoholism and PD (Bowen 2000). As predicted by SMH, increasing rates of relapse following the application of stress-inducing treatment modalities, such as exposure therapy, might offer one explanation for the failure to detect reduced relapse rates in a number of randomized controlled trials (RCTs) of alcoholism treatment interventions that have incorporated CBT for anxiety disorders (Bowen 2000; Randall 2001a; Schädé 2005a).

The possible limitations of psychotherapy for people with anxiety disorder with comorbid alcohol dependence, and the increasing elucidation of the biological substrates of alcohol dependency and abuse suggest that pharmacotherapy should be considered as a treatment option (Bühler 2011). The selective serotonin re-uptake inhibitors (SSRIs) are regarded as first-line medications in treating anxiety disorders (BAP 2014). The evidence for the efficacy of SSRIs in reducing alcohol consumption is less clear, with some evidence that SSRIs may produce favourable outcomes when treating people with less severe alcohol dependence (Pettinati 2000), but may actually worsen drinking outcomes when administered concurrently with CBT for severe alcohol dependence (Kranzler 2006). Conversely, naltrexone, an opioid receptor antagonist with US Food and Drug Administration (FDA) approval for relapse prevention in alcohol dependence, has shown promise in reducing the severity of PTSD symptoms in several open-label trials (Bills 1993; Lubin 2002). Nevertheless, one large 12-week RCT of naltrexone and the acetaldehyde dehydrogenase inhibitor, disulfiram, in a treatment-seeking veteran sample, did not demonstrate that these medications were significantly more effective in reducing PTSD symptoms compared with placebo (Pettrakis 2006).

The possibility that alcoholism and anxiety disorders may reinforce one another following onset suggests that treatment strategies that target both forms of psychopathology might be effective. Although this is consistent with the expert consensus view (Stewart 2008; Smith 2012), empirical support for the potential usefulness of combining medication with psychotherapy in the simultaneous treatment of both disorders is mixed (Back 2006; Ciraulo 2013). Reported reductions in social anxiety symptoms in people receiving mirtazapine, specific serotonergic and noradrenergic

re-uptake inhibitor (SNRI) antidepressant, as part of a CBT alcohol detoxification protocol, suggest that medications that target neurotransmitter systems implicated in both anxiety and alcohol use disorders may be beneficial in treating this comorbid patient population (Liappas 2003; Liappas 2005). Support for this conclusion is weakened somewhat by difficulty in disentangling these treatment effects from reductions in withdrawal-induced anxiety symptoms, and failure to detect similar effects in controlled studies that combine CBT with venlafaxine, another SNRI (Liappas 2005; Ciraulo 2013).

How the intervention might work

Low levels of extracellular serotonin have been documented in human brains after chronic exposure to alcohol (see Mukherjee 2008 for a review). Medications that increase the availability of serotonin in the synapses, either through inhibiting the re-uptake of serotonin into the pre-synaptic terminal (as in SSRIs) or through other mechanisms (as in buspirone) would be expected to normalize brain function with associated improvements in anxiety symptoms. In addition, alterations in the functioning of the gamma-aminobutyric acid (GABA) neurotransmitter system have been identified as fundamental to alcohol response, dependency, vulnerability to alcohol use disorders and pharmacotherapy of these disorders (Krystal 2006). The activation of GABA receptors and inhibition of the sympathetic system (with corresponding inhibition of the noradrenergic pathway) have been implicated in the stress-reducing effects observed following alcohol consumption. Notably, alcohol dependence and withdrawal is associated with a subsequent reduction in GABA activity (Krystal 2006), potentially explaining how the initial anxiolytic effects of imbibing alcohol gives way to increasing levels of anxiety with alcohol dependence (Kushner 1990). GABAergic medications that have demonstrated some efficacy in treating anxiety disorders, such as the benzodiazepines, and the anticonvulsant pregabalin (Feltner 2003; Pande 2004; Pohl 2005; Rickels 2005), might be expected to be effective in people with comorbid alcohol disorders. However, benzodiazepines are generally not recommended given the risk of dependency, and the finding of prolonged withdrawal symptoms and increased alcohol use following a randomized controlled detoxification treatment with lorazepam (Malcolm 2002).

Why it is important to do this review

There are a number of shortcomings in the literature on the treatment of anxiety disorders in populations diagnosed with comorbid alcohol dependence. A general paucity of evidence exists for recommendations for treating affective or anxiety disorders that are comorbid with substance use disorders (Watkins 2005). Clinical trials of medication for treating anxiety disorders also frequently exclude people with comorbid alcohol dependency, limiting the generalisability of their findings (Hoertel 2012). The small samples employed by dual-diagnosis medication trials may also have prevented the detection of significant differences in the efficacy of treatments for anxiety disorders. A systematic review and meta-analysis, employing the methodology of The Cochrane Collaboration, would help to quantify the extent of these shortcomings, and would extend the narrative reviews conducted to date in this patient population (Schadé 2003; Berenz 2012; Lev-Ran 2012). Moreover, through the quantitative synthesis of trial data, such a review would help address other questions of interest in the treatment of anxiety disorders with comorbid

alcohol dependence or abuse, including the relative efficacy of different drugs in treating particular anxiety disorders; the clinical effectiveness of these same drugs across anxiety disorders; and whether patient characteristics, such as gender, predict response to treatment.

OBJECTIVES

To assess the effects of pharmacotherapy for treating anxiety in people with comorbid alcohol use disorders, specifically: to provide an estimate of the overall effects of medication in improving treatment response and reducing symptom severity in the treatment of anxiety disorders in people with comorbid alcohol use disorders; to determine whether particular medications are more effective and tolerable than other medications in the treatment of particular anxiety disorders; to identify which factors (clinical, methodological) predict response to pharmacotherapy for anxiety disorders.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs of pharmacotherapy for treating anxiety disorders with comorbid alcohol use disorders. We only included group-based treatments if they employed a cluster randomization design. We excluded trials in which the allocation sequence was generated via a quasi-random procedure (such as determining group allocation by day of the week or alternation). We applied no language restrictions.

We included both trials targeting relapse prevention as well as the treatment of ongoing alcohol dependence or abuse in the review. Alcohol withdrawal may result in a short-term increase in anxiety symptoms, with evidence that these symptoms stabilize within four to eight weeks of the onset of abstinence (Schuckit 1988; Driessen 2001). Therefore, we did not include relapse prevention studies that diagnosed anxiety disorders with a symptom profile similar to that observed during withdrawal (i.e. GAD, PD) within four weeks after the discontinuation of alcohol consumption in the review.

Types of participants

Age

We imposed no age restrictions.

Diagnosis

We included people diagnosed with alcohol dependence or abuse and an anxiety disorder according to DSM-III (APA 1980), DSM-IV (APA 1994), or DSM-IV-TR (APA 2000) criteria.

Comorbidities

We used the diagnosis of additional comorbid psychiatric diagnoses (excluding other secondary anxiety disorders) as an exclusion criteria. We revised the original protocol to include participants with major depressive disorder (MDD), given the frequent co-occurrence of MDD in this comorbid population (see [Differences between protocol and review](#)).

The presence of physical disabilities did not qualify as an exclusion criteria, with the exception of traumatic brain injury in RCTs of PTSD

(due to difficulties in distinguishing between the symptoms of PTSD and traumatic brain injury).

Setting

We applied no restrictions with regards to country in which the trial took place, the number of centres involved or whether trials were conducted in outpatient or inpatient settings.

Types of interventions

Experimental interventions

All medication interventions in which the drug was administered to treat anxiety disorders were eligible for inclusion in this review. However, we did not include trials in which people were receiving concurrent psychotropic medications or that were limited to the comparison of drugs administered with the purpose of affecting drinking behaviour, such as naltrexone, disulfiram and acamprostate.

As we anticipated that most treatment studies targeting anxiety disorders in people with comorbid alcohol use disorders would employ concurrent behavioural modification programmes to treat alcohol dependence/abuse, the presence of such strategies did not serve as an exclusion criteria.

Control interventions

Control interventions included placebo, standard treatment and other medications.

Types of outcome measures

Primary outcomes

- Clinical treatment response. The number of responders versus non-responders was determined from the Clinical Global Impressions scale - Improvement item (CGI-I) (or closely related measure), a widely used global outcome measure (Guy 1976). Responders are defined on the CGI-I as those with a score of 1 = 'very much' or 2 = 'much' improved.
- Reduction of symptom severity determined from a variety of validated continuous outcome measures, such as the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz 1987), the Clinician Administered PTSD Scale (CAPS) (Blake 1990), the Hamilton Anxiety scale (HAM-A) (Hamilton 1959), and the Panic Disorder Severity Scale (PDSS) (Shear 1997).
- Acceptability of medication determined by the total proportion of participants who withdrew from RCTs due to treatment-emergent adverse events, which is a surrogate measure used in the absence of other more direct indicators of acceptability. This quantitative measure of the acceptability of medication was supplemented with a narrative review of the most common drug-related adverse events for both the included and excluded studies (defined as those occurring in at least 10% of the participants given medication), as well as significant differences in the rate of occurrence of drug-related adverse events between medication and control groups.

Secondary outcomes

Scores on rating scales for disorders other than the primary anxiety disorder, including:

- abstinence and reduction of alcohol use assessed using the component subscales of standardized instruments such as the Timeline Followback scale (TLFB) (Sobell 1992). In trials that did not use such an instrument, we assessed these outcomes in terms of the operational definitions employed by study authors;
- reduction of comorbid symptoms of depression assessed using scales such as the Beck Depression Inventory (BDI) (Beck 1961), the Hamilton Depression scale (HAM-D) (Hamilton 1969), and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979).

The effectiveness of medication for treating anxiety disorders was assessed with measures of:

- quality of life, such as the 36-item Sort Form (SF-36) Health Survey (Ware 1992);
- functional disability, such as the Sheehan Disability Scale (SDS), which includes subscales to assess work-, social- and family-related impairment (Sheehan 1996).

Timing of outcome assessment

Where studies assessed outcomes at multiple time points, we collated data from the assessments that occurred up until 12 weeks after initiation of treatment for the assessment of the short-term effectiveness of the medication. Where available, we combined data from assessments made after three months as part of an analysis of long-term medication effectiveness.

Selection among multiple measures for the same outcome

Where multiple instruments were employed to assess anxiety disorder symptom severity, we gave preference to gold-standard clinician-rated instruments, including the LSAS for Social Anxiety Disorder, CAPS for PTSD, HAM-A for GAD, and PDSS for PD. Where these were not employed, we used self rating versions of these scales, such as the self rating version of the LSAS (Oakman 2003). Finally, we would have considered other self rating instruments, based on an evaluation of their published psychometric properties. With regards to comorbid depression, a variety of established instruments is currently employed, including the BDI, HAM-D and MADRS. In this instance, we determined which outcome to include in the meta-analysis by maximizing the proportion of data from the same scale across trials.

Search methods for identification of studies

Electronic searches

We conducted searches for published studies on the following databases:

The specialized registers of The Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDANCTR, to January 2014) (Appendix 1) and the Cochrane Drugs and Alcohol Group (CDAG, to March 2013) (Appendix 2). These registers contain reports of relevant RCTs from the Cochrane Central Register of Controlled Trials (CENTRAL, all years), MEDLINE (1950 to date), EMBASE (1974 to date) and PsycINFO (1967 to date).

The review authors conducted additional searches (to August 2013) on PubMed (Appendix 3), using the highly sensitive search strategy developed by Robinson and Dickersin (Robinson 2002), as well as EMBASE (Ovid) (Appendix 4), PsycINFO (Ovid) (Appendix

5) and the Alcohol and Alcohol Problems Science Database (etoh.niaaa.nih.gov) (Appendix 6).

We located ongoing trials using the National Institutes of Health (NIH) RePORTER service (August 2013). We accessed additional trials via the search portal of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/) (August 2013). The WHO database includes the ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry and ISRCTN databases.

We conducted searches in line with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards for the conduct and reporting of new Cochrane reviews of interventions (www.editorial-unit.cochrane.org/mecir).

Searching other resources

Reference lists

We scanned the bibliographies of all identified trials for additional studies.

Correspondence

We obtained published and unpublished trials from key researchers, as identified by the frequency with which they were cited in the bibliographies of RCTs and open-label studies.

Data collection and analysis

Selection of studies

One review author (JI) initially screened the abstracts of RCTs that were potentially eligible for inclusion. Two review authors (DW and TA) independently assessed potential RCTs, based on information included in the main body of the trial report, or its abstract, in cases in which the article was not accessible.

We listed studies for which additional information was required in order to determine eligibility under [Studies awaiting classification](#), pending the availability of this information. We resolved any disagreements in the independent trial assessment and data collation procedures by discussion with a third review author (JI).

Data extraction and management

We designed spreadsheet forms for recording descriptive information, summary statistics of the outcome measures, the quality scale ratings and associated commentary. We subsequently exported data to Review Manager 5 software ([RevMan 2012](#)). Where information was missing, the review authors contacted investigators by email in an attempt to obtain this information. Where this was not successful, we retrieved the data from figures included in the paper, using a data extraction utility (3gdata; www.frantz.fi/software/g3data.php).

Two review authors (DW, TA) independently collated the following information from each trial that satisfied the inclusion criteria.

- Description of the trials, including the primary researcher, year of publication and source of funding.
- Characteristics of the interventions, including the number of participants randomized to the treatment and control groups, number of total drop-outs per group as well as the number that dropped out due to adverse effects, dose of medication

and period over which it was administered, and drugs used for treating the anxiety disorder and alcohol dependence. We recorded details of any concurrent psychotherapy.

- Characteristics of trial methodology, including the diagnostic (e.g. DSM-IV; [APA 1994](#)) and exclusionary criteria employed, the screening instrument used (e.g. Structured Clinical Interview for DSM-IV (SCID; [Spitzer 1996](#)) for both the primary and comorbid diagnoses, presence of comorbid MDD, use of a placebo run-in, whether a minimal severity criterion was employed, number of centres involved, and period of abstinence in relapse-prevention trials.
- Characteristics of participants, including gender distribution and mean and range of ages, mean length of time since diagnosis of the anxiety disorder and alcohol abuse/dependence, number of participants in the sample with MDD, and baseline severity of the anxiety disorder and alcohol abuse/dependence, as assessed by the trial's primary outcome measure or another commonly employed scale.
- Outcome measures employed (primary and secondary), and summary continuous (means and standard deviations (SD)) and dichotomous (number of responders) data. Additional information was also included, such as whether data reflected the intention-to-treat (ITT) with last observation carried forward (LOCF) or completer/observed cases (OC) sample, and the minimal period required for inclusion of participants in the LOCF analyses. We also recorded other methods of estimating the outcome for participants who dropped out of the study, such as mixed effects (ME) modelling.

Main planned comparisons

We compared the following interventions:

- medication versus placebo;
- medication versus standard treatment;
- medication versus other medications;
- combination of medication and concurrent psychotherapy versus pharmacotherapy alone.

We grouped specific pharmacological interventions according to medication class, according to a pragmatic schema based on mechanism of action and year of introduction recommended by The Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) review group for this purpose. These included:

- 5-HT (serotonin) partial agonists;
- anticonvulsants;
- antipsychotics;
- benzodiazepines;
- beta-blockers;
- monoamine oxidase inhibitors (MAOIs);
- noradrenaline re-uptake inhibitors (NARIs);
- noradrenergic and specific serotonergic antidepressants (NaSSAs);
- reversible inhibitors of monoamine oxidase A (RIMAs);
- serotonin antagonist and re-uptake inhibitors (SARIs);
- serotonin and noradrenaline re-uptake inhibitors (SNRIs);
- selective serotonin re-uptake inhibitors (SSRIs);
- tricyclic antidepressants (TCAs);
- other medications.

Assessment of risk of bias in included studies

Two review authors (DW, TA) independently assessed the methodological quality of the trials using the 'Risk of bias' instrument recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). This tool addresses six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues. We listed a description of pertinent information from the study for each domain, and made a judgement relating to the risk of bias assigned (low risk, unclear risk and high risk). We resolved any disagreements about methodological quality by consultation with a third review author (JI).

Measures of treatment effect

Dichotomous data

We calculated risk ratios (RR) and their 95% confidence intervals (CI) and number needed to treat for an additional beneficial outcome (NNTB) for the dichotomous primary outcome of interest (CGI-I or related measure). We used RR instead of odds ratio (OR), as ORs are more difficult to interpret than RRs, and when confused with RRs they tend to overestimate the size of the treatment effect. This is especially the case when the occurrence of the outcome of interest is common (as anticipated in this review, with an expected response greater than 20%) (Deeks 2011). We defined NNTB as the inverse of the absolute risk difference due to the active intervention. In this review, it was used to indicate the number of participants who required treatment with medication, relative to control participants, before a single additional participant in the medication group responded to treatment. We calculated the number of people who relapsed in relapse-prevention studies for categorical measures of treatment response for both the anxiety disorder and alcohol use.

Continuous data

We had planned to calculate mean difference (MD) or standardized mean difference (SMD) estimates and their 95% CIs for continuous summary data.

Unit of analysis issues

Trials with multiple treatment groups

Unit-of-analysis bias may be introduced from trials testing the efficacy of medication through comparing the summary statistics for multiple groups against the same control group (Deeks 2011). This is a particular issue for trials comparing different dosages of medication or multiple intervention arms versus a common control group. We found no eligible trials employing these designs for inclusion in the current version of the review. We will minimize potential bias resulting from inclusion of dose comparison studies in future versions of this review by pooling the means and SDs across all of the treatment arms as a function of the number of participants in each arm. We will restrict the pooling of outcome data to those arms that employ at least the minimum dose recommended by clinical guidelines. We will circumvent unit-of-analysis bias resulting from the simultaneous comparison of multiple arms from the same trial in future updates of this review by means of a multiple-treatments meta-analysis (MTM) (Lumley 2002). An MTM allows the assessment of treatment efficacy through the combination of both direct and indirect comparisons of all

interventions on a specific outcome. Potential unit-of-analysis bias can be subsequently assessed in a sensitivity analysis in which the results obtained are compared with those from a meta-analysis restricted to data from direct comparisons of interventions.

Cross-over trials

We found no RCTs employing cross-over study designs for inclusion in this review. Please refer to the [Differences between protocol and review](#) section for details of how cross-over trials will be analysed for future versions of this review.

Cluster-randomized trials

In cluster-randomized trials, groups of individuals rather than individuals are randomized to different interventions. Cluster-randomized trials face potential issues because participants within any one cluster often tend to respond in a similar manner, and thus their data can no longer be assumed to be independent of one another. Cluster-randomized trials also face risk of bias issues including recruitment bias, baseline imbalance, loss of clusters, incorrect analyses and comparability with individually randomized trials. We found no cluster-randomized trials that were eligible for inclusion in this review. To prevent unit-of-analysis errors in future updates of this review, we will divide the effective sample size of each comparison group in trials that did not adjust for clustering by the design effect metric (Higgins 2011b), with the intraclass correlation coefficient (ICC) that is incorporated within the design effect set equivalent to the median ICC from published cluster-randomized pharmacotherapy RCTs for anxiety disorders.

Dealing with missing data

All analyses of dichotomous data were ITT. We used the total number of participants randomized to the different comparison groups as the denominator in comparisons of treatment response. We included only data from trials that provided information on the original group size (prior to drop-outs) in the analyses of treatment response. We gave preference within studies to the inclusion of summary statistics for continuous outcome measures derived from ME models, followed by LOCF and OC summary statistics (in that order). This is in line with evidence that ME methods are more robust to bias than LOCF analyses (Verbeke 2000).

Assessment of heterogeneity

We assessed heterogeneity of treatment response and symptom severity visually from the forest plot of RR, to determine whether the differences between the results of trials were greater than would be expected by chance alone. We also assessed heterogeneity by means of the Chi² test of heterogeneity. We interpreted a P value of less than 0.10 in the Chi² test as evidence of heterogeneity, given the low power of the Chi² statistic when the number of trials is small (Deeks 2011).

In addition, we used the I² heterogeneity statistic reported by Review Manager 5 to determine differences in effect size across trials that cannot be explained by chance alone (Higgins 2003; RevMan 2012). We interpreted the magnitude of heterogeneity for the primary outcomes following the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), as follows:

- 0% to 40%: might be important;
- 30% to 60%: moderate;

- 50% to 90%: substantial;
- 75% to 100%: considerable.

In recognition of the possibility of differential effects for different medications, we stratified all of the outcome comparisons by the drug employed.

Assessment of reporting biases

Publication is not necessarily related to study quality and indeed publication may imply certain biases (Dickersin 1992; Song 2000). The review authors planned to inspect a funnel plot of treatment response visually in order to detect small-trial effects, including those resulting from publication bias. However, this was not feasible in the current version of the review, given the small number of included trials. In future updates, we will undertake this if we identify more than 10 studies.

Data synthesis

We obtained dichotomous and continuous treatment effect estimates from a random-effects model and expressed results in terms of a mean effect size for each subgroup, as well as by 95% CIs. We stratified comparisons of global treatment response and reduction of anxiety disorder symptom severity by study design (acute treatment interventions (12 weeks or less) and maintenance studies (more than 12 weeks)). We included data from the assessment point closest to 12 weeks in secondary outcome analyses for each trial. We grouped the comparisons by medication class, as listed in the [Data extraction and management](#) section of the review. We only combined outcome data for drugs within each of these medication classes in the meta-analyses on the proviso that the medications were administered for the treatment of the same anxiety disorder, with separate analyses reported for individual drugs within each class otherwise.

Where there was evidence that data were skewed, we planned to obtain individual patient data (where possible) for normalizing the data by means of log transformation techniques. If this proved unsuccessful, we would have excluded those studies providing skewed data from the analysis. For the purposes of this review, the following constituted evidence of skewness: cases in which the difference between the observed mean and the lowest possible value or highest possible value on the scale was less than twice as large as the SD (Deeks 2011), or where data were reported as skewed by the study authors.

Subgroup analysis and investigation of heterogeneity

We had planned several subgroup analyses to assess the degree to which clinical (gender, presence of MDD in sample) and methodological differences (single centre or multicentre trials, whether trials were industry funded, order of anxiety/alcohol interventions) between trials might have systematically influenced differences observed in the primary treatment outcomes (see [Differences between protocol and review](#)). However, it was not possible to conduct these subgroup analyses due to an insufficient number of eligible trials.

Sensitivity analysis

We included a series of sensitivity analyses in the original protocol of this review. These included a 'worst-case/best-case' test of the assumptions regarding the outcome of drop-outs, as well as a test of differences resulting from analysing treatment responders rather

than non-responders. We did not conduct these analyses for the reasons provided in the [Differences between protocol and review](#) section.

'Summary of findings' tables

[Summary of findings 1](#) shows the results for the treatment comparisons on the primary and secondary outcomes of this review. We compiled this table using GRADE Pro 3.6 software. 'Summary of findings' tables present the findings of a review in a transparent and simple tabular format, and provide key information concerning the quality of evidence and the magnitude of effect of the interventions examined (Higgins 2011a).

We classified study quality downgrades as 'serious' (downgrading the quality rating by one level) or 'very serious' (downgrading the quality grade by two levels), and based them on five factors:

- limitations in the design and implementation;
- indirectness of evidence;
- unexplained heterogeneity or inconsistency of results;
- imprecision of results;
- high probability of publication bias.

We determined best evidence by the following conclusions:

- high quality: further research is very unlikely to change our confidence in the estimate of effect;
- moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- very low quality: we are very uncertain about the estimate.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#) tables.

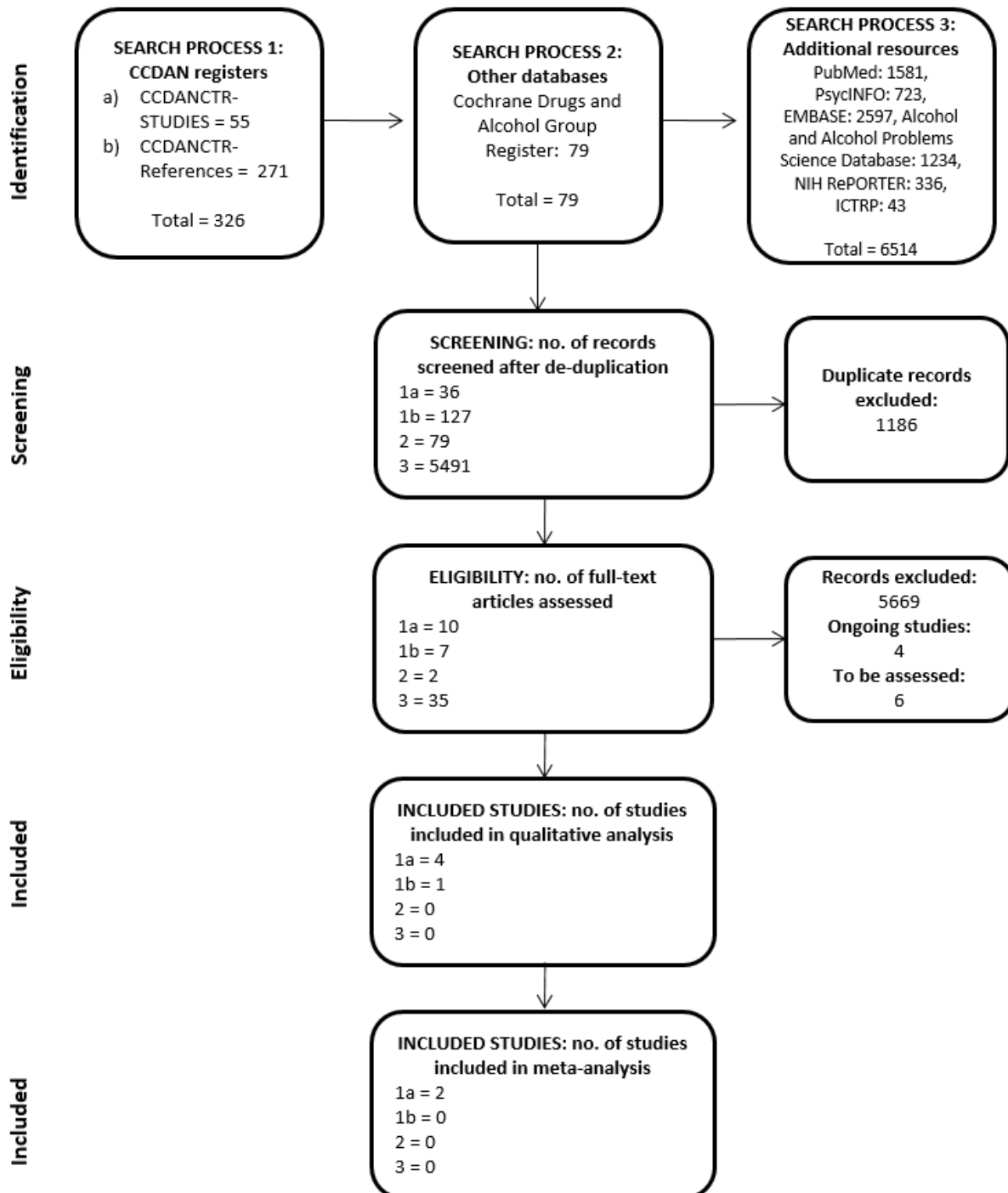
Results of the search

Initial searches of CCDAN's specialized trial register retrieved 307 records: 36 studies (from the CCDANCTR-Studies Register) and an additional 271 untagged/uncoded references (from the CCDANCTR-References Register) (see [Figure 1](#) for the PRISMA trial selection flowchart). A January 2014 update of the CCDANCTR search yielded 19 unique studies. The specialized register for the Cochrane Drug and Alcohol review groups yielded 79 references. A search of the PubMed (1581 references), EMBASE (2597 references), PsycINFO (723 references) and Alcohol and Alcohol Problems Science Database (AAPSD) (1234 references) databases retrieved a cumulative total of 6135 records, of which 5111 were unique. Records from the NIH RePORTER database totalled 336 and WHO ICTRP database totalled 43 unique results. We retained less than 1% (54/5733) of the records following inspection of their titles and abstracts, and kept eight abstracts from unpublished studies for further assessment. Five trials satisfied all inclusion criteria upon inspection of the full-text reports (Tollefson 1992; Randall

2001b; Brady 2005; Book 2008; Petrakis 2012). We contacted the lead investigators of all of the included studies (Drs Sudie Back, Sarah Book, Ismene Petrakis, Carrie Randall and Gary Tollefson) via email for additional information. Authors for two of the five studies

responded to our queries. Six trials are awaiting classification, pending the availability of additional information and four trials are listed as ongoing.

Figure 1. PRISMA flowchart



Included studies

Five RCTs were eligible for inclusion in the review, with a sample size of 290 participants. The [Characteristics of included studies](#) table shows a summary of the trials.

Design

Four included studies employed a parallel-group design in which participants were randomized to monotherapy with either medication or placebo ([Tollefson 1992](#); [Randall 2001b](#); [Brady 2005](#); [Book 2008](#)). [Petrakis 2012](#) randomly allocated participants to one of four interventions, in which antidepressants were supplemented with either naltrexone or placebo.

Sample sizes

Study samples were generally small, ranging in size between 15 and 94 (mean 29, SD 23.9).

Setting

All of the included studies were conducted in the US. [Petrakis 2012](#) was the only trial that took place at more than one centre (two centres).

Participants

The review included two RCTs assessing interventions for PTSD ([Brady 2005](#); [Petrakis 2012](#)), two evaluating pharmacotherapies for generalized SAD ([Randall 2001b](#); [Book 2008](#)), and RCT for GAD ([Tollefson 1992](#)). In the trials that distinguished between alcohol use subtype, the majority of the participants were diagnosed with alcohol dependence (79%), and the remainder with alcohol abuse (21%) ([Randall 2001b](#); [Brady 2005](#); [Book 2008](#); [Petrakis 2012](#)); [Tollefson 1992](#) did not provide information on diagnostic subtype. [Book 2008](#) restricted study participation to individuals who described themselves as drinking to cope with the SAD symptoms. Four of the included studies diagnosed anxiety disorders and alcohol abuse/dependence according to DSM-IV criteria ([Randall 2001b](#); [Brady 2005](#); [Book 2008](#); [Petrakis 2012](#)), while one study employed DSM-III criteria ([Tollefson 1992](#)). The participants across all included trials were 37.4 years old (SD 6.5) on average, with a majority consisting of males (70%). The samples in both [Randall 2001b](#) and [Petrakis 2012](#) consisted of fewer than 20% women.

The interventions for PTSD differed with respect to PTSD subtype and symptom severity; the sample in [Brady 2005](#) was restricted to individuals exposed to civilian traumas with a moderately severe PTSD (CAPS total score 58.9), while the participants in [Petrakis 2012](#) consisted primarily of combat veterans (81/88 participants, 92%) with greater severity of PTSD symptoms (CAPS total score: 70.9). Although both PTSD trials restricted comorbid substance abuse to alcohol dependence, drinking behaviour was more extreme in [Petrakis 2012](#) than [Brady 2005](#) (mean number of drinks on each drinking occasion/day: 23.5 in [Petrakis 2012](#) and six in [Brady 2005](#)).

Diagnoses in the included RCTs of current anxiety disorders in addition to those that formed the focus of the interventions were relatively infrequent. Comorbid anxiety disorders in at least 10% of participants included GAD ([Book 2008](#): 8/42 participants) SAD ([Brady 2005](#): 15/92 participants), SP ([Brady 2005](#): 12/92 participants) and PD ([Brady 2005](#): 15/92 participants; [Randall 2001b](#): 2/15 participants). [Petrakis 2012](#) provided no information regarding comorbid anxiety disorders, although they excluded participants

with serious current psychiatric symptoms from the study. [Brady 2005](#) observed high rates of concurrent major depression only in the PTSD interventions, where MDD was present in 48% of the participants and [Petrakis 2012](#) described MDD as being present in a large subsample of participants (personal communication; 1 August 2012). [Tollefson 1992](#) did not permit concurrent Axis I psychiatric diagnoses.

Interventions

[Brady 2005](#) initiated treatment of civilian PTSD with 50 mg/day of sertraline (49 participants) or placebo (45 participants), increasing doses incrementally by 50 mg to a target of 150 mg/day by the third week of the 12-week intervention. [Petrakis 2012](#) randomly allocated participants diagnosed with PTSD to one of four intervention groups, constructed by combining treatment with the TCA desipramine or the SSRI paroxetine with either naltrexone or placebo. These groups were desipramine/placebo (24 participants), paroxetine/placebo (20 participants), desipramine/naltrexone (22 participants) and paroxetine/naltrexone (22 participants). For the purposes of this review, we compared only the antidepressant and placebo combinations.

[Book 2008](#) and [Randall 2001b](#) randomized people with SAD to treatment with 60 mg/day of paroxetine or placebo. In [Book 2008](#), people with generalized SAD randomized to medication (20 participants) and placebo (22 participants) were started at 10 mg/day in the first week, uptitrated to 20 mg/day in week two, 40 mg/day by week three and then maintained on the full dose of 60 mg/day from the fourth week of the 16-week trial. In [Randall 2001b](#), the dosage was started at 20 mg/day in study participants randomized to medication (six participants) or placebo (nine participants), increased to 40 mg/day by the second week and increased to 60 mg/day, where tolerated, from the third week to the end of the eight-week study.

[Tollefson 1992](#) administered 15 mg/day of the 5-HT partial agonist buspirone (26 participants) or placebo (25 participants) at study onset to people with GAD, uptitrated to at least 30 mg/day by week two, to a maximum of 60 mg/day at week three to four, after which the dose was held constant for the remainder of the 24-week trial.

The interventions included in this review varied in duration from eight to 24 weeks. Two trials included individual CBT targeting alcohol abuse as part of the treatment protocol ([Randall 2001b](#); [Brady 2005](#)). These interventions were based on the MATCH (Matching Alcoholism Treatment to Client Heterogeneity) project protocol ([Project MATCH 1993](#)). In [Randall 2001b](#), participants were provided with an individual session of motivational interviewing, whereas in [Brady 2005](#), participants were administered weekly one-hour sessions of CBT. [Tollefson 1992](#) controlled the number of Alcoholics Anonymous meetings (an alcoholics treatment programme) attended by study participants.

Outcomes

Anxiety disorder outcomes

[Brady 2005](#) and [Petrakis 2012](#) assessed PTSD severity using the CAPS. In addition, [Brady 2005](#) employed the Impact of Event Scale (IES) ([Horowitz 1979](#)), and the Civilian Mississippi Scales for PTSD (MISS) ([Keane 1988](#)). [Book 2008](#) and [Randall 2001b](#) assessed SAD symptom severity using a modified version of LSAS, in which participants were instructed to respond to the fear and avoidance

items as if they did not have access to alcohol with which to cope. [Connor 2000](#) used the CGI-I and the Social Phobia Inventory (SPIN) to assess treatment response. [Tollefson 1992](#) assessed the response of GAD symptoms using the HAM-A ([Hamilton 1959](#)), and the CGI-I. We extracted data on the HAM-A from a figure included in [Tollefson 1992](#) (Figure 2).

Drinking outcomes

The TLFB was the most commonly employed measure of the effect of medication on drinking in the studies included in this review ([Randall 2001b](#); [Brady 2005](#)), or a modified version thereof ([Book 2008](#); [Petrakis 2012](#)). The TLFB provides measures of total number of drinks, number of drinks per drinking day, proportion of drinking days and proportion of heavy drinking days. The TLFB was modified in [Book 2008](#) to include items assessing drinking to cope with SAD symptoms. [Petrakis 2012](#) used the Substance Abuse Calendar, a scale derived from the TLFB, to assess drinking behaviour (the mean number of drinks per week, per cent heavy drinking days and drinks per drinking day) as well as other substance use. Another frequently used measure of drinking behaviour included the Addiction Severity Index (ASI; [McLellan 1990](#)), which measures impairment across a number of functional domains (including social, legal, medical and psychiatric). Three of the five RCTs administered the ASI ([Tollefson 1992](#); [Randall 2001b](#); [Brady 2005](#)). The ASI was the only drinking outcome reported in the trial of GAD ([Tollefson 1992](#)).

Excluded studies

The most common reason for excluding studies from the review was that the investigators assessed the effect of pharmacotherapy on anxiety symptoms without diagnosing anxiety disorders according to DSM criteria ([Caponi 1985](#); [Loo 1986](#); [Krupitsky 1993](#); [Kranzler 1994](#); [Guardia 2012](#)). In addition, [Malcolm 1992](#) and [Ciraulo 2013](#) required that participants diagnosed with anxiety disorders including GAD and PD be abstinent from alcohol for fewer than four weeks prior to the start of treatment. We excluded the studies by [Batki 2011](#) and [Oluwadara 2013](#) because they allowed the inclusion of participants receiving concurrent psychotropic medication. See [Characteristics of excluded studies](#) table for more details.

Ongoing studies

We identified four ongoing studies that may be eligible for inclusion in future versions of this review. One RCT is currently recruiting participants to evaluate the efficacy of 12 weeks of treatment with a fixed dose (16 mg) of the alpha-1 adrenergic receptor antagonist prazosin relative to placebo in people with PTSD and alcohol dependence ([NCT00744055](#)). In addition, one 12-week placebo-controlled RCT of 16 mg prazosin (three times daily), in which the interventions will be administered to 150 alcohol-dependent participants evenly split by presence of a concurrent anxiety disorder, was listed as recruiting participants as of April 2013 ([NCT00585780](#)). Dr Batki and colleagues are conducting a second 12-week double-blinded placebo-controlled RCT investigating the efficacy of the anticonvulsant topiramate in people diagnosed with current PTSD and alcohol use disorders who are drinking heavily, in which the maximum dosage of 300 mg/day will be administered

to 150 veterans ([NCT01749215](#)). We excluded the earlier pilot study as 60% of the participants were receiving concurrent psychotropic medication ([Batki 2011](#)). Finally, 50 veterans with PTSD will be randomly assigned in a 3: 1 ratio to 12 weeks of zonisamide or placebo in addition to Enhanced Cognitive Processing Therapy-C (E-CPT-C), with the medication uptitrated to 400 mg/day during the first six weeks and henceforth maintained to the end of the study ([NCT01847469](#)). See [Characteristics of ongoing studies](#) table for further details.

Studies awaiting classification

Six trials are currently awaiting classification (see [Characteristics of studies awaiting classification](#) table). Five of these are unpublished, including a trial in which 180 outpatients meeting DSM-IV criteria for alcohol dependence or abuse and with a comorbid diagnosis of PD, social phobia or GAD were randomized to 12 weeks of treatment (including a one-week initial run-in period and a two-week taper period) with venlafaxine, CBT or placebo medication with relaxation therapy ([NCT00248612](#)), and a small 12-week comparison of the atypical antipsychotic quetiapine (maximum of 300 to 400 mg/day) with placebo in 20 people with alcohol dependence and a comorbid anxiety disorder ([NCT00352469](#)). We have requested additional information from the investigators in one small, 12-week, placebo-controlled paroxetine trial in 20 outpatients with comorbid PTSD and substance dependence ([NCT00330239](#)). We are also waiting clarification on the number of participants receiving concurrent antidepressant medication in one placebo-controlled prazosin trial for alcohol dependence and PTSD ([NCT01518972](#)). Although the manner in which PTSD (total scores of at least 50 on the CAPS) and alcohol use disorders (diagnosis with alcohol abuse or dependence or the consumption of more than 35 standard drinks per week over the previous four weeks) was defined in male veterans appears to preclude an ongoing study of the anticonvulsant topiramate (maximum dose 400 mg/day) from inclusion in this review, we will defer a final decision until additional information regarding the participants is obtained at study completion ([NCT01408641](#)). Finally, data for people who had completed a 21-day alcohol dependence treatment programme, who were diagnosed with an affective or anxiety (or both) disorder (without comorbid antisocial personality disorder), and who subsequently participated in a six-month follow-up RCT of bromocriptine, a dopamine agonist, and nortriptyline, an adrenergic re-uptake inhibitor, may be included in a future version of this review, pending additional information on the criteria employed in diagnosing anxiety disorders in this published study ([Powell 1995](#)).

Risk of bias in included studies

We assessed risk of bias using The Cochrane Collaboration's 'Risk of bias' tool, which assessed bias across multiple domains, including random sequence generation, allocation concealment, blinding (of outcome assessment and participants and personnel), incomplete outcome data, selective reporting and other potential sources of bias (see [Figure 2](#) and [Figure 3](#) for summaries of judgements across studies and domains).

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

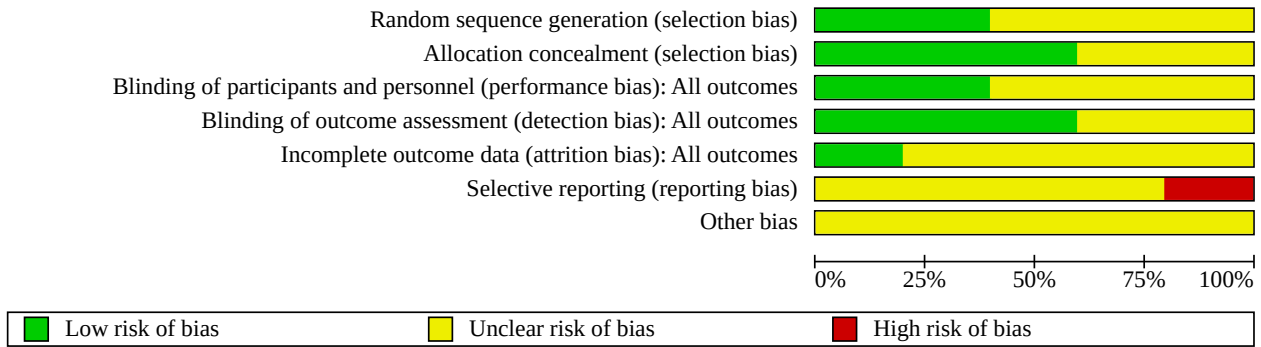


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Book 2008	+	+	+	+	+	?	?
Brady 2005	+	?	?	?	?	?	?
Petrakis 2012	?	+	?	?	?	?	?
Randall 2001b	?	+	+	+	?	?	?
Tollefson 1992	?	?	?	+	?	-	?

Allocation

Random sequence generation

Three of the five included trials provided insufficient information to determine whether they employed adequate randomization procedures (Tollefson 1992; Randall 2001b; Petrakis 2012). The two remaining RCTs employed urn randomization (Brady 2005; Book 2008). Book 2008 grouped random sequences by gender, social anxiety severity and diagnosis with MDD and Brady 2005 grouped random sequences by sex, depressive disorder, trauma type and age of index trauma.

Allocation concealment

Institutional research pharmacists maintained the treatment allocation in both Book 2008 and Randall 2001b. Neither Brady 2005 nor Tollefson 1992 provided information on how allocation was concealed.

Blinding

Blinding of outcome assessment

The extent to which the assessment of study outcomes was blinded was unclear in two of the trials, in which the study design was merely described as "double-blinded" (Brady 2005; Petrakis 2012). Randall 2001b assessed outcomes separately from side effect evaluation and medication administration, while Book 2008 and Tollefson 1992 described assessors involved in evaluation of outcomes as blinded (in Tollefson 1992, blinding was only described for the primary efficacy outcome).

Blinding of participants and personnel

Both Book 2008 and Randall 2001b used matching capsules for medication and placebo to ensure the blinding of study personnel and participants. Petrakis 2012 described dispensing medication in blister packs that were packaged in separate bottles, labelled as antidepressants in the one container and naltrexone in the other. Email correspondence with the investigators confirmed that this procedure was employed to blind participants to whether they were receiving desipramine or paroxetine (labelled antidepressant) and naltrexone or placebo (labelled naltrexone). Tollefson 1992 and Brady 2005 provided insufficient information to determine whether both parties were blinded.

Incomplete outcome data

A large proportion of participants withdrew prematurely from the trials (mean 43.1%; see [Effects of interventions](#)), although attrition rates were relatively low in Book 2008. Drop-out rates were significantly higher in the paroxetine (55%) than the desipramine (35%) groups in Petrakis 2012, although potential bias resulting from differential attrition in this trial may have been ameliorated somewhat by employing a mixed-effects regression approach to model missing data. Likewise, a substantially larger proportion of study withdrawals in the placebo (84%) than buspirone (61.5%) treatment arms after 24 weeks in Tollefson 1992 may have introduced bias into the outcomes reported for this trial. None of the studies compared study drop-outs with those who remained in the study, making it difficult to determine the extent to which attrition bias may have affected the study results.

Selective reporting

Evidence of incomplete reporting of study outcomes was evident for Tollefson 1992, in which it appears as if they only report those outcomes amongst the many that were assessed that yielded statistically significant group differences. Protocols were not available for most of the included studies (Brady 2005; Randall 2001b; Tollefson 1992), making determination of reporting bias difficult.

Other potential sources of bias

A greater proportion of participants in Tollefson 1992 had previously been exposed to benzodiazepines in the buspirone than the placebo arms. Although the authors asserted that this may have blunted the response to buspirone, they based this conclusion on post-hoc findings from one small controlled trial (Schweizer 1986), and it was not sufficient to mask the observation of a significant medication effect in reducing the severity of GAD symptoms.

Effects of interventions

See: [Summary of findings 1 Paroxetine compared with placebo for anxiety and comorbid alcohol use disorders](#)

It was not possible to conduct all planned comparisons, as, with exception of the comparison of desipramine and paroxetine (Petrakis 2012), the RCTs included in this review only provided data on the efficacy and acceptability of medication compared with placebo.

Comparison 1: medication versus placebo

One RCT compared the 5-HT partial agonist buspirone versus placebo (51 participants diagnosed with GAD) (Tollefson 1992). Three studies provided data on outcomes for the comparison of SSRIs versus placebo (Randall 2001b; Brady 2005; Book 2008). Two trials compared paroxetine versus placebo (57 participants; [Summary of findings 1](#)) and one trial compared sertraline versus placebo (94 participants).

Comparison 1.1: 5-HT partial agonists versus placebo

1.1.1: buspirone versus placebo

1.1.1.1: anxiety disorder treatment response

There were no data on treatment responders on the CGI-I (Tollefson 1992).

1.1.1.2: reduction of anxiety disorder symptom severity

The trial investigators reported that treatment with buspirone resulted in an advantage for medication at the 12-week assessment on the HAM-A ($t = -2.6$, degrees of freedom (df) = 40, P value < 0.01). Extraction of data from a bar chart in Tollefson 1992 depicting treatment response on the HAM-A (Figure 2 in Tollefson 1992) revealed that buspirone reduced the score on the HAM-A in 42 people with GAD by a mean of 5 points at week 12 relative to placebo. A significant divergence between the buspirone and placebo arms in the response of GAD symptoms to treatment emerged at the 12-week assessment, with the size of the effect remaining stable for the following 12 weeks of the study.

1.1.1.3: acceptability of treatment

There were insufficient data on the number of people who withdrew due to treatment-emergent adverse effects for meta-

analysis (Analysis 1.3). Three participants being treated with 24 weeks of buspirone withdrew from treatment compared with one person receiving placebo (reasons for withdrawal not provided) (Tollefson 1992). The most frequently occurring drug-related adverse event in response to 24 weeks of buspirone was dizziness, reported by 9/26 (35%) participants receiving medication compared with 4/25 (16%) participants receiving placebo (Tollefson 1992).

1.1.1.4: abstinence and reduction of alcohol use

There were no data on drinking outcomes for the single trial of buspirone (Tollefson 1992).

1.1.1.5: reduction of comorbid symptoms of depression

Tollefson 1992 reported a reduction in symptoms of depression (as assessed on the HAM-D) only at the week 12 assessment of the 24-week treatment intervention ($t = -2.08$, $df = 40$, P value = 0.05).

1.1.1.6: quality of life

We found no data to determine the effects of buspirone on quality of life.

1.1.1.7: functional disability

We found no data to determine the effects of buspirone on functional disability associated with the anxiety disorder. Buspirone had a greater adverse effect than placebo on clinician rating of "functioning" assessed using the ASI, though this was not regarded by the investigators as problematic.

Comparison 1.2: selective serotonin re-uptake inhibitors versus placebo

1.2.1: paroxetine versus placebo

1.2.1.1: anxiety disorder treatment response

There was very low quality evidence for an effect of paroxetine on treatment response in people diagnosed with SAD, as assessed on the CGI-I (RR 2.23, 95% CI 1.13 to 4.41, 2 trials, 57 participants; Analysis 1.1) (Randall 2001b; Book 2008). Low variability was observed for effect estimates across trials and is of unclear clinical importance (heterogeneity: $I^2 = 0\%$, $Chi^2 = 0.25$, $df = 1$, P value = 0.62). More than twice as many participants responded to short-term treatment with paroxetine than placebo (57.7% with paroxetine versus 25.8% with placebo). This translates to an NNTB of 4, indicating that four participants would have to be treated with paroxetine for one additional treatment responder, relative to the control condition.

1.2.1.2: reduction of anxiety disorder symptom severity

There was a lack of evidence for the efficacy of 12 weeks of treatment with paroxetine in decreasing the severity of SAD symptoms (MD -14.70, 95% CI -33.00 to 3.60, 2 trials, 44 participants; Analysis 1.2). The quality of the evidence on this outcome was very low and between-trial heterogeneity on this outcome of unclear clinical importance ($I^2 = 0$, $Chi^2 = 0.03$, P value = 0.87). Longer-term treatment over 16 weeks was reported in Book 2008 as resulting in a mean reduction in total LSAS scores of 53% (SD = 29.52%) in the paroxetine group versus 32% (SD = 29.08%) in the placebo group ($t = 2.34$, $df = 40$, P value < 0.05). Separating the treatment effects into an early (six weeks or less) and later phase (seven to 16 weeks), the investigators observed the largest reduction in symptoms with

administration of a maximum of 60 mg/day of paroxetine by six weeks of treatment, with a levelling off of the treatment effect for the remaining 10 weeks of the trial. Using a similar 20 to 60 mg/day flexible dosing regimen, Randall 2001b also reported a maximal medication effect after six weeks of the intervention, after which treatment response stabilized for the remainder of the study. The mean reduction at study endpoint in the total LSAS score reported by Randall 2001b was 44% for paroxetine and 14% for placebo.

1.2.1.3: acceptability of treatment

There was very low quality evidence of differences in the acceptability of paroxetine and placebo interventions based on drop-out rates due to adverse events (RR 3.29, 95% CI 0.14 to 76.33, 2 trials, 57 participants; Analysis 1.3). Two of the six participants who were administered with paroxetine for eight weeks experienced fatigue, with somnolence, nausea, abnormal ejaculation, headache and dry mouth reported by one person each (Randall 2001b). Sixteen weeks of treatment with paroxetine was associated with a greater frequency of adverse events in Book 2008 for three of 32 items from an adverse effects checklist; 11/20 (55%) participants on paroxetine experienced anorgasmia/delayed ejaculation compared with 4/22 (18%) participants on placebo (P value = 0.01). The equivalent figures for tremor were 45% with paroxetine versus 14% with placebo (P value = 0.03) and 35% with paroxetine versus 5% with control for myoclonus (P value = 0.01).

1.2.1.4: abstinence and reduction of alcohol use

Evidence that data for the proportion of heavy drinking days was not normally distributed in either Book 2008 or Randall 2001b mitigated against conducting a meta-analysis of this outcome; for instance, the SD of patient data on this outcome was almost twice as large as the mean in the medication intervention in Randall 2001b (mean 0.214, SD 0.391). Very low quality evidence for the proportion of days during the trial in which participants were abstinent was inconclusive with respect to the efficacy of short-term treatment with paroxetine relative to placebo (MD 0.08, 95% CI -0.26 to 0.43, 2 trials, 54 participants; Analysis 1.4). There was substantial variability for effect estimates ($I^2 = 68\%$; $Chi^2 = 3.11$, P value = 0.08), although statistically significant reductions on medication were not observed for either Book 2008 or Randall 2001b. Although the number of drinks consumed on a drinking day was numerically smaller in the paroxetine and placebo groups (4.73 with paroxetine versus 7.36 with placebo), and was observed to a similar extent in both trials providing data on this outcome ($I^2 = 0\%$, $Chi^2 = 0.52$, P value = 0.47), there was no evidence that paroxetine reduced the number of drinks consumed (MD -2.42, 95% CI -4.97 to 0.14, 2 trials, 64 participants; Analysis 1.5). In Book 2008, treatment with paroxetine was associated with a reduction in the proportion of drinking events motivated by the need to cope with social anxiety relative to placebo by the 16-week assessment. This was evident for modified TLFB measures of the proportion of participants who reported avoiding social situations if they could not drink during or prior to the event (25% with paroxetine versus 45% with placebo, P value = 0.006), as well as the percentage of people who reported drinking before social events to feel more comfortable (35% with paroxetine versus 68% with placebo, P value = 0.014) (Thomas 2008).

1.2.1.5: reduction of comorbid symptoms of depression

There were insufficient data on the effect of acute treatment with paroxetine on depression for meta-analysis.

1.2.1.6: quality of life

There were no data to determine the effects of paroxetine on quality of life.

1.2.1.7: functional disability

There were no data to determine the effects of paroxetine on functional disability.

1.2.2: sertraline versus placebo

1.2.2.1: anxiety disorder treatment response

There were no data from the trial of sertraline included in this review to determine the effects of this sertraline on treatment response (Brady 2005).

1.2.2.2: reduction of anxiety disorder symptom severity

Brady 2005 reported marginal superiority of sertraline to placebo in reducing the severity of PTSD symptoms on the CAPS total score, though this effect was not statistically significant ($F = 2.68$, $df = 2,68$, P value = 0.08).

1.2.2.3: acceptability of treatment

The trial reported no drop-outs due to adverse events for either the sertraline or placebo groups. Sexual dysfunction, headache, dizziness, insomnia, nervousness and drowsiness were reported as the most commonly occurring adverse events in the sertraline arm, though exact frequencies were not provided (Brady 2005).

1.2.2.4: abstinence and reduction of alcohol use

There were no differences over the course of the treatment for sertraline versus placebo on percentage of drinking days (23.0% with sertraline versus 20.4% with placebo), number of drinks consumed per day (mean (SD): 2.0 (2.9) with sertraline versus 1.4 (1.9) with placebo), number of drinks consumed per drinking day (mean (SD): 6.8 (6.5) with sertraline versus 6.3 (7.8) with placebo) and number of heavy drinking days (mean (SD): 10.4 (2.3) with sertraline versus 8.9 (2.5) with placebo) (Brady 2005).

1.2.2.5: reduction of comorbid symptoms of depression

Brady 2005 reported no evidence for the reduction of depression symptoms, as assessed by the BDI, after 12 weeks of treatment with sertraline.

1.2.2.6: quality of life

We found no data to determine the effects of sertraline on quality of life.

1.2.2.7: functional disability

We found no data to determine the effects of sertraline on functional disability.

Comparison 2: medication versus standard treatment

We found no RCTs comparing treatment of anxiety and comorbid alcohol use disorders with treatment 'as usual'.

Comparison 3: medication versus other medications

We found one study that compared paroxetine plus placebo with desipramine plus placebo (Petrakis 2012).

3.1: paroxetine plus placebo versus desipramine plus placebo

3.1.1: anxiety disorder treatment response

We found no data on treatment responders on the CGI-I for the trial comparing paroxetine plus placebo with desipramine plus placebo (Petrakis 2012).

3.1.2: reduction of anxiety disorder symptom severity

An analysis across all four arms of Petrakis 2012 revealed no difference between paroxetine and desipramine on reductions in the CAPS total score over time, as reported in the trial report ($F = 1.25$, $df = 6108.8$, P value > 0.05; Analysis 2.1).

3.1.3: acceptability of treatment

We found insufficient data on the acceptability of treatment with paroxetine and desipramine (in combination with placebo) for 12 weeks for meta-analysis (Analysis 2.2). In the paroxetine plus placebo arm, 1/20 participants discontinued treatment after having a seizure and 1/20 participants was hospitalized due to severe anxiety (Petrakis 2012). Petrakis 2012 reported that significantly more participants treated with desipramine reported gastrointestinal symptoms than participants treated with paroxetine (with concurrent placebo or 50 mg/day of naltrexone). The ability of this study to detect group differences in drug-related adverse effects may have been compromised by the investigators' decision to only report events that were significantly more common at a Bonferroni corrected statistical threshold of $\alpha = 0.007$ (to control for comparisons for seven adverse effect symptom groups; gastrointestinal, emotional, cold and flu symptoms, skin, sexual, neurological and cardiac).

3.1.4: abstinence and reduction of alcohol use

Fifty-one per cent of participants in Petrakis 2012 remained abstinent throughout the study. Comparison of the paroxetine plus placebo and desipramine plus placebo arms revealed greater reductions on drinking outcomes for the desipramine plus placebo group, including endpoint assessments for mean number of drinking days (Analysis 2.3), drinks per drinking day (Analysis 2.4) and proportion of heavy drinking days (Analysis 2.5). This is consistent with the finding that the administration of desipramine with either placebo or naltrexone resulted in greater reductions in the proportion of heavy drinking days ($F = 7.22$, $df = 1,84$, P value < 0.01) and the mean number of drinks per drinking day ($F = 5.04$, $df = 1,84$, P value < 0.05) than the equivalent comparison groups for paroxetine.

3.1.5: reduction of comorbid symptoms of depression

There were insufficient data on the effects of paroxetine and desipramine (in combination with placebo) on symptoms of depression for meta-analysis (Analysis 2.6).

3.1.6: quality of life

We found no data to determine the effects of medication versus other medications on quality of life.

3.1.7: functional disability

We found no data to determine the effects of medication versus other medication on functional disability.

Comparison 4: combination of medication plus concurrent psychotherapy versus pharmacotherapy alone

We identified no eligible RCTs that compared treatment of anxiety and comorbid alcohol use disorders with medication plus concurrent psychotherapy versus pharmacotherapy alone.

Subgroup analyses

It was not possible to conduct any of the planned subgroup analyses (see [Differences between protocol and review](#)), due to the small number of trials included in this review.

Sensitivity analyses

It was not possible to conduct any of the planned sensitivity analyses (see [Differences between protocol and review](#)), due to the small number of trials included in this review.

Reporting bias

We planned to inspect a funnel plot of treatment response in order to detect small-trial effects, including those resulting from publication bias. However, this was not feasible in the current version of the review, given the small number of included trials.

DISCUSSION

Summary of main results

Evidence collated as part of this review to determine the efficacy of medication in treating anxiety disorder symptoms in people with comorbid alcohol use disorders was inconclusive. Although the majority of data on treatment efficacy in this review were from serotonergic drugs, we rated evidence on this outcome as being of very low quality. This was primarily due to the small number of studies providing data on a clinically diverse population. Despite imprecise estimates of the effect of the SSRI paroxetine, the quantitative synthesis of data from RCTs included in this review provided preliminary support for the efficacy of this medication in improving clinical response in people with SAD (see [Summary of findings 1](#)). More than twice as many people with SAD responded to paroxetine (57.7%) than placebo (25.8%) after a mean of 12 weeks of treatment. This difference in treatment response was equivalent to an additional four people who would have to be treated with medication for one additional treatment responder, relative to the control condition and corresponding imprecise estimates of effect.

With the exception of one trial of buspirone ([Tollefson 1992](#)), there was no evidence that the severity of anxiety disorder symptoms were reduced after acute (12 weeks or less) treatment with medication. Moreover, caution should be exercised in interpreting the finding from [Tollefson 1992](#) of a significant reduction of GAD symptoms following 12 weeks of treatment with buspirone, given concerns regarding possible reporting bias (see [Quality of the evidence](#)). A narrative review of changes in SAD symptom severity on treatment over time suggested that paroxetine may have to be administered for at least six weeks in doses of up to 60 mg/day to achieve maximal reductions in SAD symptoms.

We found few effects of pharmacotherapy on drinking outcomes in this review. Lack of evidence for the effectiveness of the SSRIs in reducing drinking was consistent with the observation that the majority of rigorously designed studies of the efficacy of SSRIs in treating alcohol abuse without comorbidities has been negative

([Torrens 2005](#)). Instead, there were preliminary indications from [Petrakis 2012](#) that TCAs may be more effective for this purpose, while potentially possessing similar efficacy in treating anxiety disorder symptoms.

Despite a high overall rate of attrition in the included studies, we found no evidence of an increased number of treatment withdrawals due to drug-related adverse events. This suggests that pharmacotherapy and interventions with serotonergic drugs in particular may be an acceptable treatment option for anxiety and comorbid alcohol use disorders. Although this finding was based on very low quality evidence with respect to paroxetine, the only medication for which sufficient data were available for meta-analysis for this outcome, this was in agreement with previous reports that SSRIs are well tolerated in the treatment of the major anxiety disorders ([Koen 2011](#)). Reports of high frequencies of sexual dysfunction in response to treatment with paroxetine and sertraline is also consistent with the adverse effects profile for the SSRIs ([Brady 2005](#); [Book 2008](#)).

Overall completeness and applicability of evidence

There was a paucity of evidence regarding the clinical effectiveness of medication. The trials included in this review were restricted to the SSRIs paroxetine and sertraline, the TCA desipramine, and the partial serotonin agonist buspirone. Furthermore, we identified no rigorously conducted trials of medication treatment for comorbid alcohol misuse and PD or OCD for this review.

The SSRIs have generally been recommended as first-line drugs in meta-analyses and systematic reviews of pharmacotherapy for anxiety disorders ([Stein 2009](#)). Although this review provided some evidence that these drugs may also be effective in people with concurrent alcohol dependence or abuse, there were few direct comparisons of the efficacy of different drugs in this population. The observation in [Petrakis 2012](#) that the TCA desipramine and SSRI paroxetine were of equivalent efficacy in reducing PTSD symptom severity after 12 weeks should be considered preliminary, given the potential bias introduced through the substantially higher drop-out rate for the paroxetine (55%) than desipramine (35%) treatment arm in this study. In addition, the lack of a placebo-only arm in this RCT leaves open the possibility that the effects on anxiety symptoms attributed to medication reflect general effects of study participation.

It is not clear to what extent the results of this review are applicable to patients typically seen in the clinic. The majority of the studies included in this review reported restricting inclusion to people without other substance use disorders ([Tollefson 1992](#); [Randall 2001b](#); [Brady 2005](#); [Book 2008](#)), despite evidence for a high degree of comorbidity between alcohol and drug use disorders in community samples ([Hasin 2007](#)), and that concurrent drug use problems increase the utilisation of mental health services ([Cohen 2007](#)). [Book 2008](#) restricted participation in a 16-week trial of paroxetine to people who drank to cope with their social anxiety symptoms and who were not seeking treatment for alcohol disorders. Therefore, reported reductions in drinking to cope with social anxiety symptoms in this trial may not generalize to all participants receiving medication for comorbid SAD and alcohol use disorders. Finally, close to three-quarters of the participants from the RCTs included in this review were male, despite large-scale, nationally representative community surveys in the USA reporting a greater 12-month and lifetime prevalence of anxiety

disorders in women than men (Vesga-López 2008; McLean 2011). The preponderance of men in this review may reflect the nature of recruitment sources utilized (veterans in Petrakis 2012), the possibility of a stronger association of anxiety disorders with alcohol use disorders in men (Vesga-López 2008; Dawson 2012), and evidence that men with alcohol use disorders may more readily receive specialized mental health/substance use treatment than women (Booth 2000; Dawson 2012; Alvanzo 2014). The observation that men and women metabolize alcohol differently (Kwo 1998), that anxiety disorders precede alcohol dependence significantly more frequently in women than men (Kessler 1997), and that men have different expectancies regarding the effects of alcohol than women (Morris 2005), further limits the strength of the conclusions of this review with regards to the efficacy of medication in treating anxiety disorders in women with concurrent alcohol use disorders.

All of the trials included in this review applied either DSM-III or DSM-IV diagnostic criteria in screening participants to determine study eligibility. It is not yet apparent how findings from these trials apply to people diagnosed using DSM-V criteria. Post-hoc observations in Brady 2005 and Pettinati 2000 suggested that sertraline may also be associated in less severe late-onset alcoholism with greater reductions in drinking following pharmacotherapy, while this medication may result in heavier drinking in more severe early-onset alcoholics. Therefore, the treatment implications of the observation that lack of convergence between diagnoses made using DSM-IV and DSM-V criteria are most evident at the less severe end of the alcohol use disorder spectrum may need to be considered (Dawson 2013).

We were unable to retrieve sufficient data to address the majority of the outcomes of interest in this review, despite a comprehensive search of the literature. None of the included studies assessed the effect of medication on quality of life and functional disability, despite documented impairments in these domains for both alcoholism and anxiety disorders (Ugochukwu 2013; Baxter 2014), and evidence that pharmacotherapy may improve quality of life in placebo-controlled trials of anxiety disorder (Hofmann 2013). Moreover, failure to detect effects of medication on alcohol use in people with comorbid anxiety disorders in this review may reflect the fact that the effects of medication on alcohol use are likely to be complex and multifactorial, and that current measures of drinking do not adequately capture this complexity.

The trials included in this review were restricted to a few drugs with relatively circumscribed, primarily serotonergic, mechanisms of action. RCTs of other drugs that target multiple neurotransmitter systems and for which there is some evidence from controlled trials for effectiveness in treating anxiety disorders did not meet the inclusion criteria for this review (e.g. mirtazapine, Liappas 2003; venlafaxine, Ciraulo 2013). Although the TCA desipramine demonstrated equivalent efficacy in treating PTSD than the SSRI paroxetine in Petrakis 2012, and was actually more effective in reducing the severity of drinking behaviour, the overdose potential of TCAs suggest it should not be prescribed as a first-line drug in people with a history of substance misuse (Shah 2001). In contrast, preliminary evidence from case studies of a possible association between treatment with SSRIs and heavier drinking in certain people (Brookwell 2014), and increases in drinking in early-onset alcohol-dependent people treated with 12 weeks of sertraline relative to controls (Kranzler 2012), highlights the importance of

identifying drugs with extra-serotonergic mechanisms of action that are effective in treating this comorbid population of people.

Emerging drugs that target the GABA and glutaminergic systems, such as the N-methyl-D-aspartate (NMDA) antagonists memantine and ketamine, as well as the anticonvulsant topiramate, hold promise in treating comorbid anxiety and alcohol use disorders (Sofuoglu 2014). GABA dysregulation has been documented in alcoholism (Krystal 2006), and initial findings from one RCT of PTSD suggest it plays a role in anxiety disorders as well (Tucker 2007). Indeed, RCTs of topiramate for the treatment of PTSD and alcohol dependence or abuse are currently underway (NCT01408641; NCT01749215). Although the GABA analogue pregabalin has demonstrated some success in RCTs of anxiety disorders, including GAD (Feltner 2003; Pohl 2005; Rickels 2005), and SAD (Pande 2004), case reports of abuse of pregabalin among people with a history of substance abuse indicates that additional characterization of its safety profile in people with comorbid anxiety and alcohol use disorders is warranted (Schwan 2010; Gahr 2013; Papazisis 2013). Other extra-serotonergic agents being trialed in this population include the alpha-adrenergic blocker prazosin (NCT00585780; NCT00744055), and the sulphonamide anticonvulsant zonisamide (NCT01847469). It is of some concern that we were unable to identify ongoing RCTs in other anxiety disorders besides PTSD, despite the scarcity of rigorous trials evaluating the efficacy and tolerability of medication for these conditions in people with alcohol use disorders.

Quality of the evidence

Considerable uncertainty regarding estimates of the effects of medication over the short-term is reflected in the rating of evidence for all outcomes in this review as being of very low quality. Although RCTs represent the gold-standard study design for clinical trials, we downgraded ratings of quality for particular outcomes for a variety of reasons, including the imprecision of effect estimates (see Summary of findings 1). In the absence of published study protocols, selective reporting of outcomes may also have biased conclusions regarding treatment efficacy for some of the included RCTs. For instance, one of the two trials assessing the effect of medication in participants treated for longer than 12 weeks may have been susceptible to this form of bias (Tollefson 1992), undermining the finding that medication is effective over the long term in treating comorbid anxiety and alcohol use disorders.

High attrition rates represent a general cause for concern in this review, with 43.1% of participants across all eligible studies withdrawing prior to study endpoint. Apart from the difficulty of ruling out the possibility that reasons for drop-out vary as a function of the intervention, and hence may lead to biased outcomes, sample attrition would have further compromised the ability of the small studies included in this review to detect effects of medication on alcohol use and anxiety disorder symptoms. Failure to detect an effect of medication on any of the drinking outcomes employed in this review may reflect the low power of these studies, even when we combined their data in a meta-analysis. For instance, the small sample employed in Randall 2001b (15 participants) may partially account for the lack of evidence of group differences in drinking outcomes in this trial, despite moderate effect sizes (ranging from 0.54 to 0.66), as well as a statistically significant treatment response for drinking on the CGI-I after eight weeks ($\text{Chi}^2 = 2.78$, $\text{df} = 1$, P value = 0.05).

Treatment withdrawal rates were particularly large in [Petrakis 2012](#) and [Tollefson 1992](#). The greater efficacy of desipramine compared with paroxetine after 12 weeks in treating alcohol dependence in [Petrakis 2012](#) could explain the higher drop-out rate in the paroxetine (55%) than the desipramine (35%) group, particularly given the relatively severe alcohol dependence presented at baseline in this trial. This is consistent with the notion that the likelihood of retention in intervention programmes for anxiety disorders depends to a large extent on successful treatment of comorbid alcohol use disorders. This interpretation is supported by the observation that the drop-out rate in the paroxetine arm of [Petrakis 2012](#) was almost a third larger than the mean drop-out rate (39%) for three RCTs of paroxetine in largely civilian PTSD samples ([Marshall 2001](#); [Tucker 2001](#); [Marshall 2007](#)), and that it was comparable with withdrawal rates observed in other pharmacotherapy trials for male alcoholics with comorbid psychiatric disorders ([Powell 1995](#)). The large overall withdrawal rate after 24 weeks of treatment with buspirone in [Tollefson 1992](#) (16/26 (61.5%) participants) raises questions regarding the suitability of this medication for maintenance treatment, particularly given the possibility that people in this study may have been aware that they were receiving the active drug. Although the adequacy of study blinding is a general concern in this study, as none of the included studies assessed the degree to which participants were able to guess which arm they had been assigned to at study endpoint, [Kranzler](#) and colleagues reported that between two-thirds and three-quarters of the alcohol-dependent participants in a placebo-controlled double-blind study of buspirone were able to guess their group assignment at the end of the study ([Kranzler 1994](#)).

Potential biases in the review process

One complication of the limited number of studies included in this review was that the presence of possible sources of bias could not be tested formally, by means of planned subgroup analyses. This may have been particularly problematic with regard to the decision to not exclude studies containing participants diagnosed with MDD (see [Differences between protocol and review](#)). Although this change to the protocol was regarded as warranted by the observation that MDD is frequently comorbid with both anxiety disorders and substance use disorders, the classification of all of the drugs assessed in this review as antidepressants suggests that any evidence of their efficacy in treating anxiety and comorbid alcohol use disorders may have arisen from their effectiveness in treating symptoms of depression. This concern is somewhat ameliorated by the null findings of the majority of studies that tested the intervention on depression symptoms ([Randall 2001b](#) [Brady 2005](#); [Petrakis 2012](#)). The only exception was the finding of a significant reduction in depression symptoms on the HAM-D at 12 weeks in the only trial to exclude people with a DSM-III diagnosis of MDD ([Tollefson 1992](#)).

Insufficient data for conducting planned tests of publication bias, in which studies that reported positive results for the active intervention were more likely to be published, represented another potential source of bias in this review ([Hopewell 2009](#)). Moreover, both RCTs that were funded by pharmaceutical companies reported efficacy of medication in treating anxiety disorders ([Tollefson 1992](#); [Randall 2001b](#)). Reports that pharmacotherapy trials that reported positive effects for medication were more likely to be industry funded ([Als-Nielsen 2003](#); [Baker 2003](#)) raises

the possibility that these trials may have been biased, further complicating the interpretation of data supporting the efficacy of medication in industry-funded trials in this review.

In addition, the decision to include studies in which participants were diagnosed with alcohol abuse rather than dependence may potentially have reduced the effect of treatment, given the relatively poor reliability of the diagnosis of alcohol abuse compared with dependence ([Hasin 2003](#)), and a stronger association between dependence and anxiety disorders ([Kessler 1997](#)). The effect of this decision was again likely to have been minimal, though, as people diagnosed with alcohol abuse formed a small proportion of the total sample in two of the three studies that did not restrict trial participation to alcohol-dependent participants (21% in [Book 2008](#) and 7% in [Randall 2001b](#), with no data available for [Tollefson 1992](#)).

Additional potential sources of bias in this review included the assessment of the effect of medication on alcohol use using the TLFB, a subject-rated measure of alcohol use that may be susceptible to multiple forms of bias, such as recall and social desirability bias. Bias may also have been introduced through pre-screening of the electronic database search results by a single review author (JI) as part of the trial identification process, prior to the independent application of the full set of inclusion criteria. Finally, the decision to classify the medications by medication class in a post-hoc fashion, while in keeping with the recommended grouping, based on mechanism of action, of these drugs by the CCDAN review group, could potentially have introduced bias in interpretation of these results.

Agreements and disagreements with other studies or reviews

This review identified few rigorously designed RCTs assessing the effectiveness of medication in people with comorbid anxiety and alcohol use disorders, despite employing a systematic and comprehensive search of the literature. Therefore, we concur with the authors of qualitative reviews that there is an urgent need for additional controlled pharmacotherapy trials in this population ([Schadé 2003](#); [Berenz 2012](#); [Lev-Ran 2012](#)). Moreover, we were able to confirm that RCTs do not demonstrate robust effects of serotonergic medications on the frequency and quantity of drinking in the eligible RCTs.

Preliminary evidence presented in this review for the efficacy of serotonergic agents in treating anxiety disorders may underestimate the effect of these drugs for interventions that target subgroups based on drinking history and individual differences in the metabolism of serotonin. For instance, one randomized double-blind trial of 12 weeks of sertraline treatment (200 mg/day) for alcohol dependence reported beneficial effects that persisted over a three-month follow-up period only for late-onset alcoholics with the 'LL' variant of the *5HTTLPR* serotonin transporter gene ([Kranzler 2012](#)). Furthermore, findings from one placebo-controlled RCT of the serotonin-3 antagonist ondansetron suggested that serotonergic drugs might be more effective at reducing mood symptoms (including anxiety) in early-onset rather than late-onset alcoholism ([Johnson 2003](#)). Taken together, these findings imply that serotonergic medications such as the SSRIs and buspirone may be most effective in treating both anxiety and alcohol use disorders in people with less severe early-onset alcohol

dependence, and that efficacy of this treatment may be influenced by genetic factors.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence-base for the effectiveness of medication in treating anxiety disorders and comorbid alcohol use disorders is currently inconclusive. Evidence for a response to pharmacotherapy (namely selective serotonin re-uptake inhibitors (SSRIs)) was limited by the paucity of rigorous studies, contributing to very low quality estimates of outcome. There was also very low quality evidence that medication in these comorbid participants was well tolerated, with equivalent proportions of participants withdrawing prior to study endpoint in the medication and comparison groups. High overall rates of attrition were observed in some of the randomized controlled trials (RCTs) included in the review. Accordingly, although there was little evidence that medication has an impact on alcohol use (with the possible exception of the tricyclic antidepressant (TCA) desipramine), successful retention in treatment may be facilitated by targeting alcohol use as part of combined interventions.

Implications for research

Controlled studies of the efficacy and tolerability of pharmacotherapy for anxiety disorders and comorbid alcohol use disorders are remarkably sparse, given the recognition that anxiety disorders may play a major role in the pathogenesis, early onset and continuation of alcohol dependence. Future multicentre RCTs could help identify patient subgroups that respond preferentially to treatment with serotonergic drugs, based on clinical and demographics factors (moderate versus severe alcoholics, men

versus women), as well as genetic factors; isolate promising pharmacological interventions with novel mechanisms of action; and assess the efficacy of candidate drugs with established anxiolytic potential, such as pregabalin, topiramate, trazodone and venlafaxine in treating this patient population. The relative timing of the onset of anxiety disorders and alcohol dependence may have treatment implications and would also warrant additional investigation. Finally, studies targeting the predictors of treatment withdrawal, including the influence of alcohol use on attrition and the response of alcohol use to treatment, would be valuable in attempts to improve adherence in this difficult-to-treat population.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Book 2008

Study characteristics

Methods	<p>DESIGN Description: randomized, placebo-controlled flexible-dose study with end-of-study taper. 1 optional individual motivational enhancement therapy session provided</p> <p>BLINDING Participants: yes Assessors: yes Administrators: yes</p> <p>ALLOCATION CONCEALMENT Method: group assignment maintained by investigational pharmacist</p> <p>RANDOMIZATION Method: urn randomization by gender, SAD severity and presence of comorbid MDD</p>
Participants	<p>SAMPLE Description: 42 DSM-IV SAD and alcohol dependence (79%) or abuse (21%), 48% female, mean age: 29 years, baseline severity on LSAS: 90. Mean of 6 drinks on each drinking occasion in past month, with at least 15 standard drinks in last 30 days. Comorbid psychopathology over 10%: GAD (8/42)</p> <p>SCREENING Primary diagnosis: SCID Comorbidity: SCID</p>
Interventions	<p>Interventions: paroxetine 60 mg/day (10 mg/day week 1, 20 mg/day week 2, 40 mg/day week 3, 60 mg/day week 4) versus placebo x 16 weeks</p>
Outcomes	<p>Primary outcomes: LSAS-SR (modified), TLFB (drinks per drinking day, days abstinent, drinks per week, proportion heavy drinking days), modified to include items assessing drinking to cope with SAD Secondary outcomes: LSAS subscales, CGI-I for SAD, SPIN, Drinking to Cope survey Data estimation: mixed-effects modelling for primary outcomes. LOCF for SPIN and LSAS subscales</p>
Notes	<p>INDUSTRY SUPPORT Industry funded: no Medication provided by industry: yes Any of the authors work for industry: no</p> <p>ADDITIONAL INFORMATION Drop-out rates: 7/20 (35%) participants in paroxetine and 8/22 (36.5%) in placebo groups stopped taking medications by study endpoint</p>

Book 2008 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomized to either paroxetine or matching capsule placebo, using a computerized urn randomization program" ... "Urn randomization variables were gender, social anxiety severity (baseline LSAS total score ≤ 76 vs. > 76), and the presence of co-occurring major depressive disorder as determined by the SCID"
Allocation concealment (selection bias)	Low risk	Quote: "group assignment was maintained by an investigational pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paroxetine and placebo were provided in matching capsules Quote: "All individuals involved in direct care or evaluation of study subjects, or who were involved in study supervision, were blind to group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All individuals involved in direct care or evaluation of study subjects...were blind to group assignment." "Data analyses were conducted maintaining coded group assignment (group A vs. group B), and the blind was broken when analyses were completed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates were statistically equivalent at different timepoints, and statistical analyses of primary outcomes employed all available data Quote: "All but four participants provided week 16 (end of trial) data, for a 90% research data completion rate" The proportion of dropouts or those that continued on treatment till study endpoint was not statistically different between groups
Selective reporting (reporting bias)	Unclear risk	It was not possible to determine whether all outcomes were reported, as the protocol for the study (clinicaltrials.gov/ct2/show/record/NCT00246441) did not contain information on specific outcomes
Other bias	Unclear risk	Insufficient information to determine whether additional source of bias exists

Brady 2005
Study characteristics

Methods	DESIGN Description: randomized, placebo-controlled double-blind, parallel-group fixed-dose design with 1-week placebo run-in and end-of-study 4-day medication taper. Participants received 1 hour weekly of individual CBT targeted at alcohol dependence and based on the Project MATCH treatment protocol BLINDING Participants: unclear Assessors: unclear Administrators: unclear ALLOCATION CONCEALMENT Method: unclear RANDOMIZATION Method: urn randomization by sex, depressive disorder status, trauma type, age at index trauma
Participants	SAMPLE

Brady 2005 (Continued)

Description: 94 DSM-IV civilian PTSD and alcohol dependence, 45.7% female, mean age: 36.6 years, baseline PTSD severity on CAPS: 58.9, mean drinks per day at baseline (prior 90 days): 12.9; 48/94 with additional depression/dysthymia
 SCREENING
 Primary diagnosis: SCID, CAPS
 Comorbidity: SCID

Interventions Description: sertraline 150 mg/day (50 mg/day for first 2 days, 100 mg/day for next 2 days, 150 mg/day from day 5, in 50 mg tablets) versus placebo x 12 weeks

Outcomes Outcomes: CAPS, IES, MISS, TLFB (% drinking days, % heavy drinking days, mean number of drinks per day, mean number of drinks per drinking day), ASI, HAM-D, OCDS
 Data estimation: mixed-effects ANOVA or ANCOVA modelling for continuous variables, Chi² analysis for categorical outcomes

Notes INDUSTRY SUPPORT
 Industry funded: no
 Medication provided by industry: yes
 Any of the authors work for industry: no
 ADDITIONAL INFORMATION
 Drop-out rates: 18/49 (36.7%) participants in sertraline and 15/45 (31.1%) participants in placebo groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "urn randomization was used to ensure equal representation in each group by sex, depressive disorder, trauma type, and age of index trauma"
Allocation concealment (selection bias)	Unclear risk	No information on allocation was provided in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial described as "double-blinded". It is unclear from the report who exactly was blinded Quote: "each week, participants received a 10-day supply of medications, included blinded study medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessment provided in report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information on differences at baseline between drop-outs and treatment completers not provided
Selective reporting (reporting bias)	Unclear risk	It was not possible to determine whether all outcomes were reported, as no protocol for the study was available
Other bias	Unclear risk	Quote: "that assessments of alcohol use was based on self report and thus may be biased"

Petrakis 2012

Study characteristics

Petrakis 2012 (Continued)

Methods	DESIGN Description: randomized, double-blind, parallel-group fixed-dose design, 2-week titration for antidepressants. All participants also received clinical management Enhancement therapy BLINDING Participants: unclear Assessors: unclear Administrators: unclear ALLOCATION CONCEALMENT Method: unclear RANDOMIZATION Method: unclear
Participants	SAMPLE Description: 88 DSM-IV PTSD and alcohol dependence, mean age: 47.1 years, 8.9% female, 75% Caucasian, mean number of standard drinks on drinking day: 23.5, abstinent ≥ 2 days and ≤ 29 days before treatment SCREENING Primary diagnosis: SCID
Interventions	Description: 4 interventions: desipramine 200 mg/day (attained after 2 weeks, starting at 25 mg/day), paroxetine 40 mg/day (starting at 10 mg/day), naltrexone 50 mg/day (25 mg/day on first day) and placebo, administered in the following combinations: desipramine plus placebo, paroxetine plus placebo, desipramine plus naltrexone, paroxetine plus naltrexone x 12 weeks
Outcomes	Primary outcomes: CAPS, SAC (mean number of drinks per week, % heavy drinking days, drinks per drinking day) Secondary outcomes: OCDS, Systematic Assessment of Treatment Emergent Events Data estimation: mixed-effects modelling
Notes	INDUSTRY SUPPORT Industry funded: no Medication provided by industry: unclear Any of the authors work for industry: no ADDITIONAL INFORMATION Drop-out rates: 16/46 (35%) participants in desipramine and 23/42 (55%) in paroxetine groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Authors responded to email request for additional information by stating that this procedure was followed as "We wanted to make sure that one bottle contained one of two antidepressants (desipramine or paroxetine), and the other bottle contained either naltrexone or placebo. The labeling of the bottles was done arbitrarily by the pharmacy with this objective in mind" (Elizabeth Ralevski, 30 August 2013)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Medication was dispensed in blister packs, and the study was described as "double-blinded", although no information was provided to identify which parties were blinded Quote: "study medications were dispensed in blister packs (during the 2-week titration period for antidepressants) and packaged in separate bottles (after titration for 10 weeks), so subjects received two bottles, one labeled 'naltrexone/antidepressant study medication' and the other 'naltrexone study medication' "

Petrakis 2012 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study described as "double-blinded" without information identifying which parties were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The drop-out rate was significantly higher in the paroxetine than desipramine groups, with no comparison of differences in demographic/clinical profile of drop-outs in the different treatment arms
Selective reporting (reporting bias)	Unclear risk	It was not possible to determine whether all outcomes were reported, as the protocol for the study (clinicaltrials.gov/ct2/show/NCT00338962) did not contain information on specific outcomes
Other bias	Unclear risk	The numbers reported for study withdrawal from the individual treatment arms did not correspond exactly between the study flow chart (Figure 1) and the text.

Randall 2001b
Study characteristics

Methods	DESIGN Description: randomized, placebo-controlled double-blind, parallel-group flexible-dose design. Participants received a single individual session of motivation enhancement therapy targeted towards their alcohol abuse based on MATCH treatment manual BLINDING Participants: yes, medication and placebo tablets visually "matched" Assessors: yes, LSAS administrator blind to adverse effects Administrators: partially, clinician blind to LSAS and SPIN but not CGI-I ALLOCATION CONCEALMENT Method: institutional research pharmacy dispensed medications RANDOMIZATION Method: order pre-determined by pharmaceutical company
Participants	SAMPLE Description: 15 DSM-IV SAD with concurrent alcohol dependence (14 participants)/abuse (1 participant), 13.3% female, mean age: 35.8 years, LSAS total at baseline: 75.8 SCREENING Primary diagnosis: MINI - Plus, SCID, ≥ 15 standard drinks in past 30 days Comorbidity: SCID
Interventions	Paroxetine 20 mg/day (week 1), 40 mg/day (week 2), 60 mg/day (week 3+) versus placebo x 8 weeks. Single motivational therapy session for alcoholism also offered
Outcomes	Primary outcomes: LSAS, CGI-I for SAD, SPIN, TLFB (total drinks, drinks per drinking day, % days abstinent, % days drinking), CGI-I for social phobia and drinking Secondary outcomes: BDI, ASI, ADS Data estimation: LOCF
Notes	INDUSTRY SUPPORT Industry funded: yes Medication provided by industry: yes Any of the authors work for industry: no ADDITIONAL INFORMATION Drop-out rates: 1/16 (16.7%) participants in paroxetine and 1/9 (11.1%) participants in placebo groups

Risk of bias
Pharmacotherapy for anxiety and comorbid alcohol use disorders (Review)

Randall 2001b (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized according to a predetermined order prepared by the pharmaceutical company"
Allocation concealment (selection bias)	Low risk	Quote: "the institutional research pharmacy maintained the blind and dispensed all study medications"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded, as medication and placebo tablets visually "matched". Clinicians were also blinded to LSAS outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	LSAS assessment kept separate from administration of medication and adverse effects assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Quote: ".two participants received the first week's medication but failed to attend a medication management session, and one participant was determined by group consensus to be cognitively impaired and to have suspect data. These three subjects were excluded from all data analysis without breaking the study blind"</p> <p>The reasons for why the participants failed to attend the medication management session or which group they were assigned to was not clear</p> <p>Quote: "Five of the 6 patients in the paroxetine group and 8 of the 9 patients in the placebo group completed all 8 weeks of the trial"</p> <p>No information was provided on the causes of study withdrawal</p>
Selective reporting (reporting bias)	Unclear risk	It was not possible to determine whether all outcomes were reported, as no protocol for the study was available
Other bias	Unclear risk	It is not possible to rule out other sources of bias, based on the information contained in the report. The trial was industry funded. Quote: "This work was supported by an investigator-initiated award from SmithKline Beecham (to J.R.D.), who also supplied the drug and matched placebo"

Tollefson 1992
Study characteristics

Methods	DESIGN Description: randomized, double-blind, parallel-group flexible-dose design with a 1-week placebo run-in BLINDING Participants: unclear Assessors: yes Administrators: unclear ALLOCATION CONCEALMENT Method: unclear RANDOMIZATION Method: unclear
Participants	SAMPLE

Tollefson 1992 (Continued)

Description: 51 DSM-III GAD with concurrent alcohol dependence/abuse referred from chemical dependence treatment programmes, 27.5% female, mean age: 38.4 years, baseline HAM-A score: approximately 25 (from figure 2 in article)

SCREENING

Primary diagnosis: SCID, HAM-A score > 18, HAM-D score < 18, abstinence from alcohol consumption for at least 30 and not more than 90 days

Comorbidity: SCID

Interventions	Buspirone 15 mg/day (week 1), \geq 30 mg/day (week 2) to maximum 60 mg/day (3-4 week, after which held constant) versus placebo x 24 weeks
Outcomes	Primary outcomes: HAM-A treatment response (\geq 30% reduction on HAM-A total score and score < 18 = responders; \geq 30% reduction on HAM-A total score only = partial responders; otherwise classified as non-responders), CGI Secondary outcomes: ASI, HAM-D Data estimation: LOCF from 4 weeks for efficacy analyses
Notes	INDUSTRY SUPPORT Industry funded: yes Medication provided by industry: unclear Any of the authors work for industry: no ADDITIONAL INFORMATION Drop-out rates: 16/26 (61.5%) participants in buspirone and 21/25 (84%) in placebo groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects were randomised to either buspirone or placebo"
Allocation concealment (selection bias)	Unclear risk	No information on allocation is provided in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as "double-blinded", but no information provided on who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "anxiolytic efficacy was determined by blinded HAM-A score reduction"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although the proportion of participants who dropped at by 4 weeks was similar between groups (4/26 for buspirone and 5/25 for placebo), there were more drop-outs by study endpoint in the placebo (21/25 participants) than buspirone group (16/26 participants), with significantly more people in the placebo group dropping out due to lack of efficacy or worsening of symptoms accounting for this difference. Unfortunately, while the authors confirm in the study report that there was no difference in demographics or ratings on the Cloninger personality scale between all 51 randomized participants and the participants who completed at least 4 weeks of treatment, they did not report a similar analysis for study endpoint
Selective reporting (reporting bias)	High risk	Only reported examples of items on questionnaires such as the ASI that were significantly different between groups, without indicating how many comparisons were conducted altogether

Tollefson 1992 *(Continued)*

Other bias	Unclear risk	<p>Prior benzodiazepine exposure was greater in the buspirone than the placebo group, which may predict a less robust response to buspirone. The trial was industry funded</p> <p>Quote: "the authors wish to acknowledge...[.]...a concept grant from Mead-Johnson Pharmaceuticals</p>
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ADS: Alcoholism Dependency Scale ; ANCOVA: analysis of covariance; ANOVA: analysis of variance; ASI: Addiction Severity Index; BDI: Beck Depression Inventory; CAPS: Clinician Administered PTSD Scale; CBT: cognitive behaviour therapy; CGI: Clinical Global Impressions scale; DSM: Diagnostic and Statistical Manual; GAD: generalized anxiety disorder; HAM-A: Hamilton Anxiety scale; HAM-D: Hamilton Depression scale; IES: Impact of Event Scale; LSAS: Liebowitz Social Anxiety Scale (Clinician administered); LSAS-SR: Liebowitz Social Anxiety (Self Report); MATCH: Matching Alcoholism Treatment to Client Heterogeneity; MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; MISS: Civilian Mississippi Scales for PTSD; OCDs: Obsessive Compulsive Drinking Scale; PTSD: post-traumatic stress disorder; SAC: The Substance Abuse Calendar; SAD: social anxiety disorder; SCID: Structured Clinical Interview for DSM-IV; SPIN: Social Phobia Inventory; TLFB: Timeline Followback scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Batki 2011	Participants received concurrent psychotropic medication and study did not screen out comorbid diagnoses other than major depressive disorder and secondary anxiety disorders
Caponi 1985	Participants not diagnosed with anxiety disorders according to DSM-III+ criteria
Ciraulo 2013	Intervention was anxiety disorders including generalized anxiety disorder and panic disorder initiated after 5 days of abstinence attained, potentially confounding withdrawal effects with the anxiety disorders
Guardia 2012	No screening for anxiety disorder (investigators use score of ≥ 7 in the General Health Questionnaire-28 scale to screen for comorbid psychiatric symptoms)
Kranzler 1994	Participants not diagnosed with anxiety disorders according to DSM-III+ criteria and required to be abstinent for a minimum of 1 week only
Krupitsky 1993	Anxiety determined using Spielberger's tests and Taylor's Anxiety Scale of the Minnesota Multiphasic Personality Inventory
Krupitsky 2013	Participants not formally diagnosed with anxiety disorders according to DSM criteria
Liappas 2003	Participants not diagnosed with social anxiety disorder according to DSM criteria. Treatment was also not assigned randomly, but consecutively
Loo 1986	Participants were eligible for inclusion if diagnosed with "anxious states"
Malcolm 1992	Participants were required to only have been abstinent from alcohol for 2 weeks prior to initiation of study medication
Oluwadara 2013	Excluded as certain concurrent psychotropic medications were allowed; serious head injury was also allowed
Schadé 2005b	Participants receiving treatment for anxiety disorders were given choice of initiating treatment with an antidepressant (fluvoxamine). Pharmacotherapy was only administered to 22/47 participants

DSM: Diagnostic and Statistical Manual.

Characteristics of studies awaiting classification [ordered by study ID]

NCT00248612

Methods	Participants were randomized in a double-blind method (participant, carer, investigator and outcomes assessor all described as blinded) to 12 weeks of treatment with venlafaxine, CBT or placebo after participating in outpatient treatment for alcoholism. Study begins with 1-week placebo run-in, and ends with a 2-week taper. Outcome assessment took place at study endpoint and 3, 6, 9 and 12 months post-study
Participants	180 English-speaking adults, aged 18-65 years (inclusive), with DSM-IV diagnoses of alcohol dependence or abuse, and comorbid panic disorder, social phobia or generalized anxiety disorder
Interventions	Venlafaxine and CBT versus relaxation training and placebo (no dosage information provided)
Outcomes	Primary outcomes described as "drinking status over the course of treatment and during the treatment follow-up", with secondary outcome including treatment completion, remission rates, "anxiety-disorder free rates", abstinence rates and drinking frequency
Notes	

NCT00330239

Methods	Double-blind, placebo-controlled randomized assignment to 12 weeks of treatment with paroxetine
Participants	Adults aged 18-65 years with DSM-IV criteria for PTSD (chronic subtype, based on CAPS-1) and substance dependence disorder (last 3 months, excluding caffeine and nicotine)
Interventions	Paroxetine (Paxil CR) (12.5-50 mg/day) versus placebo (medication will be initiated at 12.5 mg and increased every 3 days as tolerated to the terminal dose in the double-blind phase)
Outcomes	Primary outcome measures: CAPS; Clinical Global Impressions Scale
Notes	Contacted authors on 17 February 2010 for information on inclusion of study, but after a few preliminary responses (from Drs Brady and Sonne), no additional responses received (GlaxoSmithKline sponsored study)

NCT00352469

Methods	Double-blind, placebo-controlled randomized assignment to 12 weeks of treatment with quetiapine
Participants	20 participants, aged 19-65 years (inclusive), with DSM-IV diagnosis of alcohol dependence and a comorbid anxiety disorder
Interventions	Quetiapine (50 mg on days 1-2, 150 mg on days 3-4 and 300-400 mg on days 5-42) versus placebo
Outcomes	Primary outcome: reduction in alcohol use and increase in duration of sobriety, measured by the Timeline Followback method and breathalyser test Secondary outcomes: Pennsylvania Craving Scale, HAM-A

NCT00352469 (Continued)

Notes

NCT01408641

Methods	Double-blind (participant, carer, investigator, outcomes assessor), placebo-controlled randomized assignment to 14 weeks of treatment with topiramate
Participants	30 veterans, aged 18-65 years (inclusive), with DSM-IV diagnosis of current PTSD and alcohol use disorders
Interventions	Topiramate uptitrated over 6 weeks to 400 mg or highest tolerated dose versus placebo in matching capsules
Outcomes	Primary outcome: number of days of heavy drinking Secondary outcomes: number of days abstinent, amount of PTSD symptoms, number of memory/cognitive complaints

Notes

NCT01518972

Methods	Randomized double-blind placebo-controlled clinical trial
Participants	60 participants (25% women) with current primary DSM-IV diagnosis of alcohol dependence and PTSD
Interventions	Prazosin titrated per study protocol vs. matched placebo for 6 weeks; with concomitant medical management based on the procedures of the COMBINE Study (Combining Medications and Behavioral Interventions for Alcoholism)
Outcomes	Primary outcomes: alcohol use during the 12-week medication phase of the study and reports of craving during the same time period; PTSD symptom severity (whether reductions in PTSD mediate the effect of prazosin)

Notes

The entry for the study lists 1 of the exclusion criteria as a "psychiatric disorder requiring any medication other than anti-depressants".

Contacted Dr. Simpson on 12 February 2014 to obtain clarification on what proportion of her current intake of participants were receiving antidepressants while receiving the intervention (if any)

Powell 1995

Methods	Participants in each of 3 diagnostic groups were randomized to bromocriptine or nortriptyline treatment arms, with participants in each arm subsequently re-randomized to receive either active medication or placebo. The diagnostic groups were: "pure" alcohol dependence, alcohol dependence with comorbid anxiety and affective disorders, and alcohol dependence and antisocial personality disorder with or without comorbid Axis I psychiatric disorders
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Powell 1995 *(Continued)*

Participants	216 male inpatient veterans with DSM-III-R diagnosis of alcohol dependence, mean age: 41.3 years (standard deviation 9.2). Participants diagnosed with comorbid anxiety and affective disorders, as well as antisocial personality disorder were also included
Interventions	Bromocriptine (3 x daily doses of 2.5 mg/day at study onset, increased to 5 mg/day by months 4-6) versus nortriptyline (25-75 mg/day at bedtime) x 6 months. Placebo dosing was matched to the respective medication arms (1 capsule increased to 2 capsules by months 4-6, 3 times daily, for bromocriptine and placebo capsules at bedtime for nortriptyline)
Outcomes	Alcohol Severity Scale, Severity of Alcohol Dependence Questionnaire (SADQ), visual analogue alcohol craving scale, Beck Depression Inventory, Beck Anxiety Inventory, Symptom Check List-90 and the Global Assessment Scale
Notes	It is unclear whether anxiety disorders were diagnosed according to DSM criteria

CAPS: Clinician Administered; CBT: cognitive behaviour therapy; DSM: Diagnostic and Statistical Manual; HAM-A: Hamilton Anxiety scale; PTSD: post-traumatic stress disorder.

Characteristics of ongoing studies *[ordered by study ID]*
NCT00585780

Study name	Effect of Prazosin on Alcohol Craving; Stress Dysregulation and Alcohol Relapse
Methods	Randomized, placebo-controlled, double-blind trial of 12 weeks of treatment with prazosin
Participants	75 participants with anxiety dependence and comorbid anxiety disorders (subtypes not specified)
Interventions	The alpha1-adrenergic antagonist prazosin (16 mg/day) versus placebo
Outcomes	Describe the short-term (12-week) and follow-up assessment of the effect of prazosin versus placebo on primary alcohol use outcomes and secondary outcomes including alcohol craving, negative mood symptoms, smoking and sleep
Starting date	September 2012
Contact information	Prof. Rajita Sinha, rajita.sinha@yale.edu
Notes	

NCT00744055

Study name	Prazosin for Treatment of Patients With Alcohol Dependence (AD) and Post Traumatic Stress Disorder (PTSD)
Methods	Randomized, placebo-controlled, double-blind (participant, carer and investigator were blinded) trial of 12 weeks of treatment with prazosin
Participants	120 (projected) DSM-IV PTSD and current comorbid alcohol dependence, heavy drinking episode within the last 14 days, aged 21-65 years (inclusive)
Interventions	Alpha1-adrenergic antagonist prazosin (16 mg/day) versus placebo
Outcomes	Information not provided

Pharmacotherapy for anxiety and comorbid alcohol use disorders (Review)

NCT00744055 (Continued)

Starting date	January 2009
Contact information	Elizabeth Ralevski, Ph.D. (+1)203-932-5711 ext. 4282, elizabeth.ralevski@yale.edu
Notes	

NCT01749215

Study name	A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans with PTSD
Methods	Double-blind (participant, investigator), placebo-controlled randomized assignment to 12 weeks of treatment with topiramate
Participants	150 veterans with PTSD, aged 18-65 years. Level of drinking must meet criteria for "at-risk " or "heavy" drinking by NIAAA threshold, and participants "must express a desire to reduce alcohol consumption with the possible long-term goal of abstinence"
Interventions	Topiramate vs. placebo, both up to 300 mg/day
Outcomes	Primary outcome: reduction in alcohol use assessed using the TLFB Secondary outcomes: reduction in PTSD severity on the PTSD Checklist (PCL). Other secondary outcomes include the effect of topiramate on impulsivity, risk-taking and decision-making, assessed using the Balloon Analogue Risk Task (BART) and Delay Discounting (DD) task
Starting date	February 2013
Contact information	Steven L. Batki, M.D. (+1)415-221-4810 ext. 3671, steven.batki@ucsf.edu ; Brooke A. Lasher, B.A. (+1)415-221-4810 ext. 4954, brooke.lasher@va.gov
Notes	

NCT01847469

Study name	Zonisamide in Addition to E-CPT-C for Veterans With PTSD and Comorbid Alcohol Dependence
Methods	Double-blind, placebo-controlled randomized assignment to 6 weeks' titration and 6 weeks' maintenance of treatment with zonisamide. Participants will receive E-CPT-C therapy for the 12 weeks of treatment. Randomization will be done using 3: 1 ratio and will be performed by the research pharmacy using a random assignment in blocks of 4, with 3 assigned to active medication and 1 to placebo
Participants	50 veterans with PTSD, aged 18-65 (inclusive), with DSM-IV diagnosis of current PTSD and alcohol use disorders
Interventions	Zonisamide (400 mg) or placebo
Outcomes	Primary outcomes: CAPS; TLFB assessment
Starting date	June 2013
Contact information	Elizabeth Ralevski, Ph.D. (+1)203-932-5711 ext. 4282, elizabeth.ralevski@yale.edu ; Diana Limoncelli, B.A. (+1)203-932-5711 ext. 5217, diana.limoncelli@yale.edu

Pharmacotherapy for anxiety and comorbid alcohol use disorders (Review)

NCT01847469 (Continued)

Notes

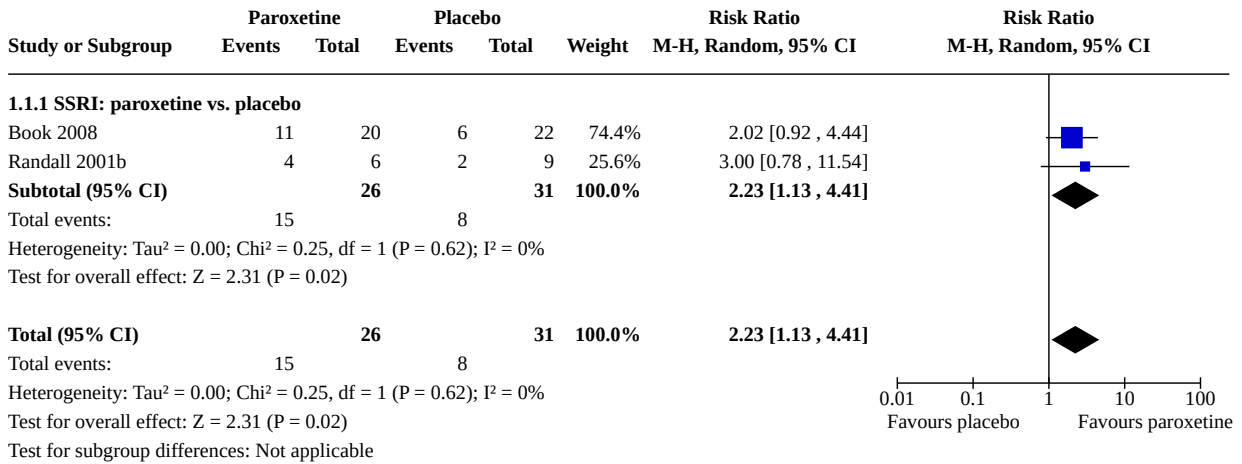
CAPS: Clinician Administered PTSD Scale; DSM: Diagnostic and Statistical Manual; PTSD: post-traumatic stress disorder; TLFB: Timeline Followback.

DATA AND ANALYSES

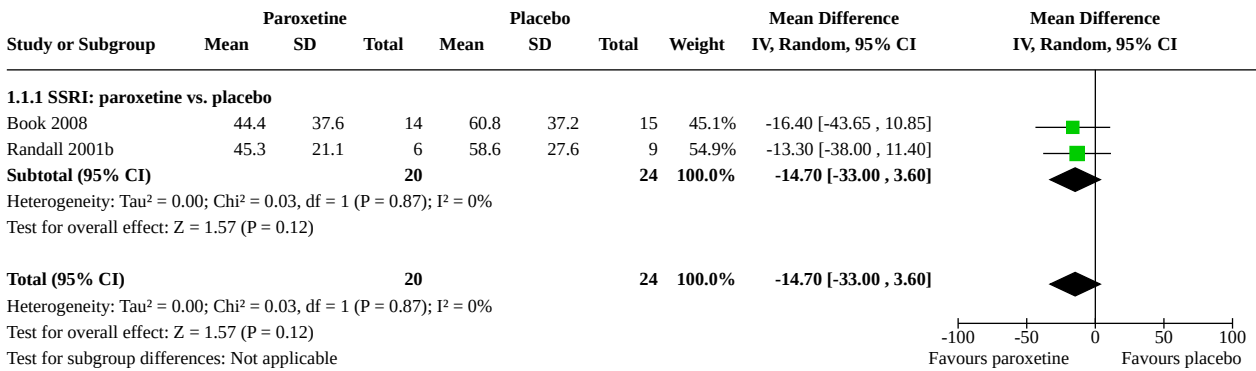
Comparison 1. Medication versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Treatment response	2	57	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.13, 4.41]
1.1.1 SSRI: paroxetine vs. placebo	2	57	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.13, 4.41]
1.2 Symptom severity reduction	2	44	Mean Difference (IV, Random, 95% CI)	-14.70 [-33.00, 3.60]
1.2.1 SSRI: paroxetine vs. placebo	2	44	Mean Difference (IV, Random, 95% CI)	-14.70 [-33.00, 3.60]
1.3 Treatment acceptability	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 SSRI: paroxetine vs. placebo	2	57	Risk Ratio (M-H, Random, 95% CI)	3.29 [0.14, 76.33]
1.3.2 SSRI: sertraline vs. placebo	1	94	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3.3 5-HT partial agonist: buspirone vs. placebo	1	51	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.32, 25.92]
1.4 Proportion of days abstinent	2	54	Mean Difference (IV, Random, 95% CI)	0.08 [-0.26, 0.43]
1.4.1 SSRI: paroxetine vs. placebo	2	54	Mean Difference (IV, Random, 95% CI)	0.08 [-0.26, 0.43]
1.5 Drinks per drinking day	2	54	Mean Difference (IV, Random, 95% CI)	-2.42 [-4.97, 0.14]
1.5.1 SSRI: paroxetine vs. placebo	2	54	Mean Difference (IV, Random, 95% CI)	-2.42 [-4.97, 0.14]

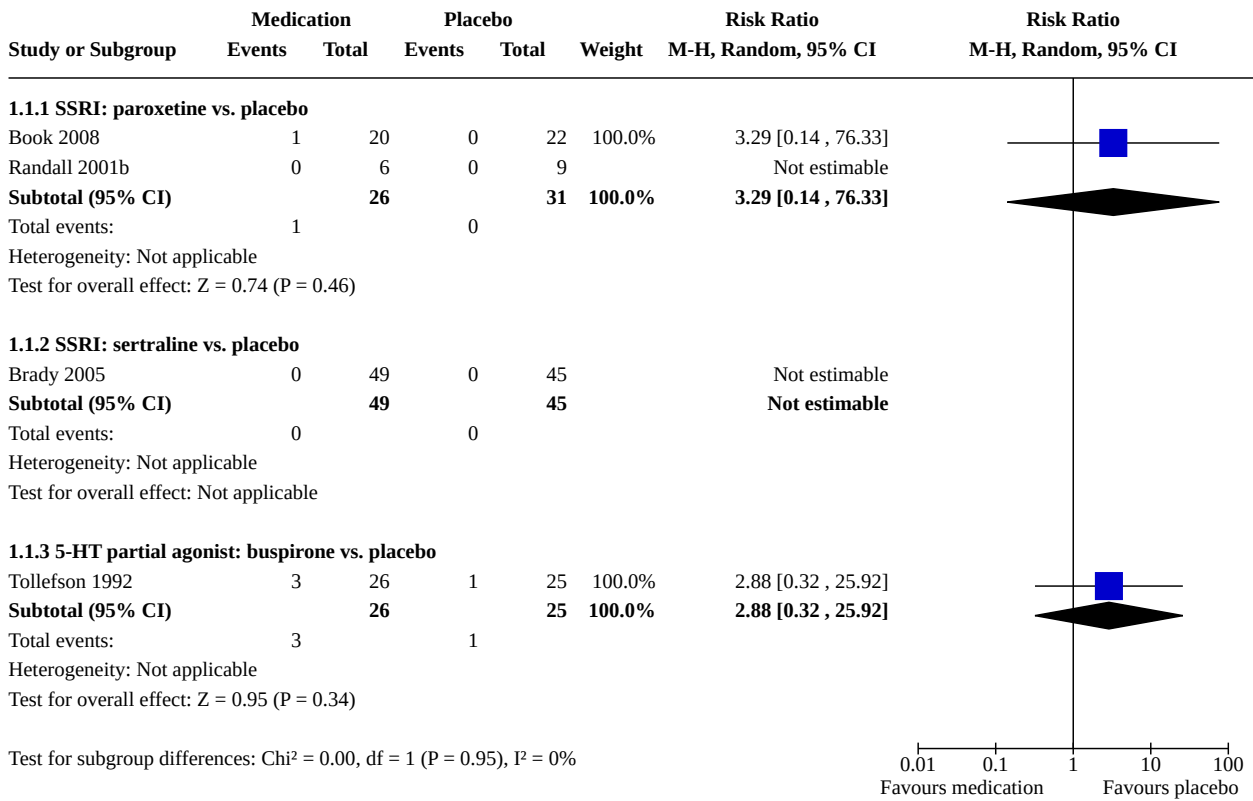
Analysis 1.1. Comparison 1: Medication versus placebo, Outcome 1: Treatment response



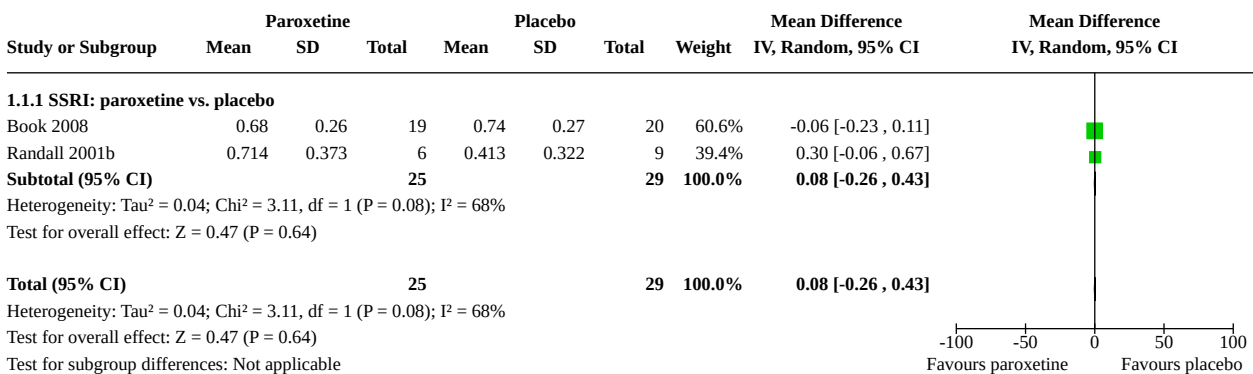
Analysis 1.2. Comparison 1: Medication versus placebo, Outcome 2: Symptom severity reduction



Analysis 1.3. Comparison 1: Medication versus placebo, Outcome 3: Treatment acceptability



Analysis 1.4. Comparison 1: Medication versus placebo, Outcome 4: Proportion of days abstinent



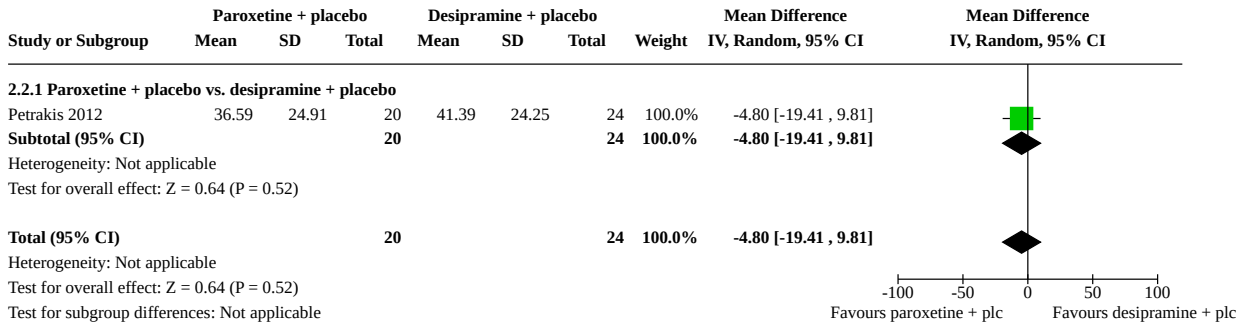
Analysis 1.5. Comparison 1: Medication versus placebo, Outcome 5: Drinks per drinking day

Study or Subgroup	Paroxetine		Placebo			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD			
1.1.1 SSRI: paroxetine vs. placebo								
Book 2008	5.25	3.57	19	6.92	6.49	20	61.4%	-1.67 [-4.94, 1.60]
Randall 2001b	4.2	3.6	6	7.8	4.5	9	38.6%	-3.60 [-7.72, 0.52]
Subtotal (95% CI)			25			29	100.0%	-2.42 [-4.97, 0.14]
Heterogeneity: Tau ² = 0.00; Chi ² = 0.52, df = 1 (P = 0.47); I ² = 0%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Total (95% CI)			25			29	100.0%	-2.42 [-4.97, 0.14]
Heterogeneity: Tau ² = 0.00; Chi ² = 0.52, df = 1 (P = 0.47); I ² = 0%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Test for subgroup differences: Not applicable								

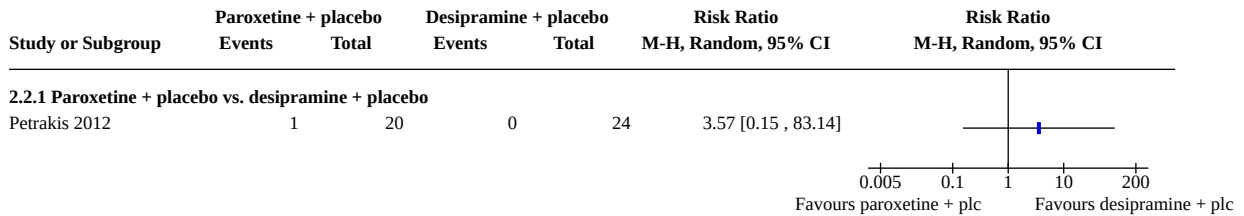
Comparison 2. Medication versus other medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Symptom severity reduction	1	44	Mean Difference (IV, Random, 95% CI)	-4.80 [-19.41, 9.81]
2.1.1 Paroxetine + placebo vs. desipramine + placebo	1	44	Mean Difference (IV, Random, 95% CI)	-4.80 [-19.41, 9.81]
2.2 Treatment acceptability	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.2.1 Paroxetine + placebo vs. desipramine + placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.3 Mean number of drinking days	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3.1 Paroxetine + placebo vs. desipramine + placebo	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.4 Drinks per drinking day	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.4.1 Paroxetine + placebo vs. desipramine + placebo	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5 Proportion heavy drinking days	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5.1 Paroxetine + placebo vs. desipramine + placebo	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.6 Reduction in depression symptoms	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.6.1 Paroxetine + placebo vs. desipramine + placebo	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

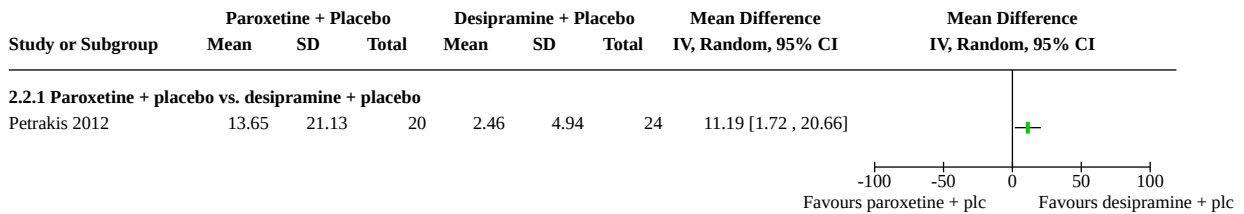
Analysis 2.1. Comparison 2: Medication versus other medications, Outcome 1: Symptom severity reduction



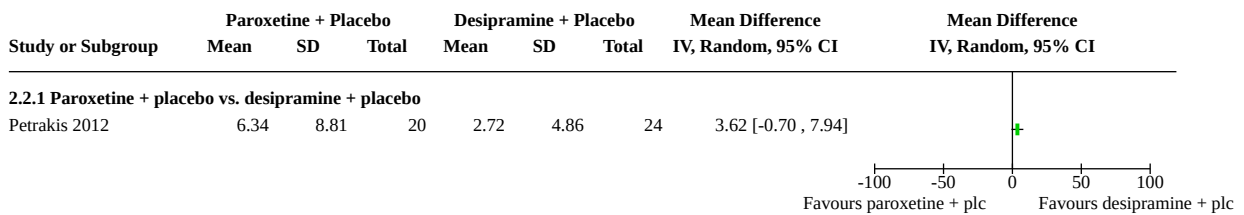
Analysis 2.2. Comparison 2: Medication versus other medications, Outcome 2: Treatment acceptability



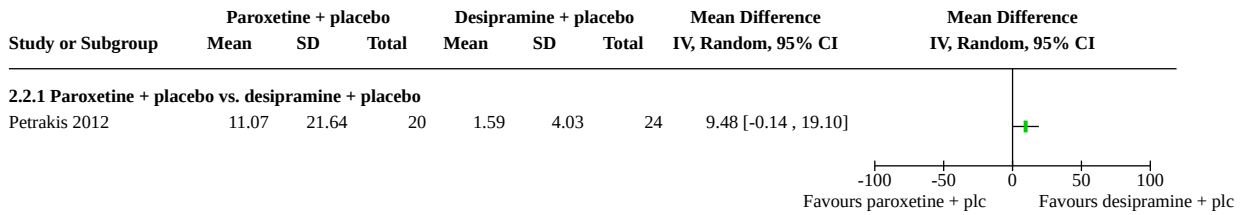
Analysis 2.3. Comparison 2: Medication versus other medications, Outcome 3: Mean number of drinking days



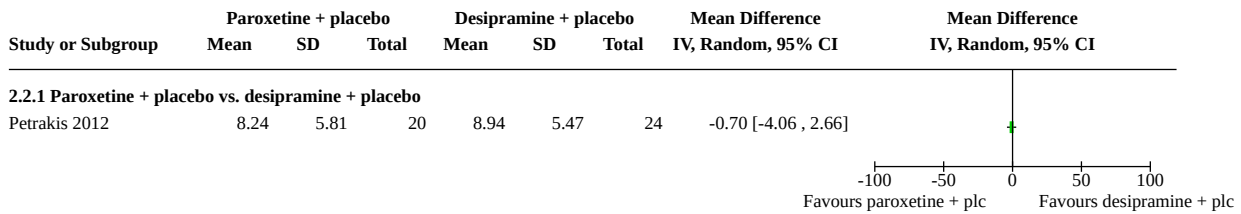
Analysis 2.4. Comparison 2: Medication versus other medications, Outcome 4: Drinks per drinking day



Analysis 2.5. Comparison 2: Medication versus other medications, Outcome 5: Proportion heavy drinking days



Analysis 2.6. Comparison 2: Medication versus other medications, Outcome 6: Reduction in depression symptoms



APPENDICES

Appendix 1. The Cochrane Collaboration Depression, Anxiety and Neurosis Group's Specialized Register (CCDANCTR)

The Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies based register. The CCDANCTR-References Register contains over 35,000 reports of randomized controlled trials in depression, anxiety and neurosis. Approximately 60% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Co-ordinator for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), ClinicalTrials.gov, drug companies, the handsearching of key journals, conference proceedings, and other (non-Cochrane) systematic reviews and meta-analyses.

Details of [CCDAN's generic search strategies](#) can be found on the Group's website.

CCDANCTR-Studies was searched (to 16 January 2014) using the following strategy:
Condition = (anxiety or panic or phobic or obsessive or compulsive or "post-traumatic") AND
Condition or Co-morbidity = (alcohol*)

CCDANCTR-References was searched (to 16 January 2014) using a more sensitive set of terms to find additional untagged/uncoded reports of RCTs:
((anxi* or *phobi* or PTSD or post-trauma* or posttrauma or "post trauma*" or "combat disorder" or panic or OCD or obsess* or compulsi* or GAD or "stress disorder" or "stress reaction" or "acute stress" or neurosis or neuroses or neurotic or psychoneuro*) AND ((alcoholi* or "alcohol use*") or (alcohol and (addict* or comorbid* or co-morbid* or co-occur* or depend* or concurren* or secondary or misus* or abus* or problem*)))):ti,ab,kw,ky,emt,mh,mc

Key to field tags: ti: title; ab: abstract; kw: keywords; ky: additional keywords; emt: EMTREE headings; MH: MeSH Headings; MC: MeSH check words

Appendix 2. The Cochrane Drugs and Alcohol Group's Specialized Register (CDAG)

Search conducted in November 2011 (records current until to November 2011):
Search strategy: anxiety AND alcohol*

Updated search conducted in March 2013 (records current to March 2013):
Search strategy: (alcohol* OR drink*) searched in title, abstract, keywords, intervention, diagnosis AND

(anxiety OR anxious OR gad OR phobic OR phobia* OR agoraphobi* OR claustrophobi* OR panic OR (obsess* AND compulsi*) OR ocd OR post-trauma* OR posttrauma* OR ptsd OR 'stress disorder' OR neurosis OR neuroses OR neurotic OR psychoneuro*) in all fields AND date >=2011

Appendix 3. PubMed

Search conducted in August 2013 (records from 1966 to August 2013)

Search strategy:

1. Alcohol-Related Disorders [mesh]
2. alcohol* [tiab]
3. dependen* or disorder* or drink* or misuse or abuse* or consumption [tiab]
4. #2 AND #3
5. alcoholism [mesh]
6. exp drinking behaviour
7. #1 or #4 or #5 or #6
8. Anxiety* [tiab]
9. Anxiety Disorders [mesh]
10. #8 OR #9
11. randomized controlled trial [pt]
12. controlled clinical trial [pt]
13. random* [tiab]
14. placebo [tiab]
15. drug therapy [mesh]
16. trial [tiab]
17. groups [tiab]
18. #11 or #12 or #13 or #14 or #15 or #16 or #17
19. Animals[mesh] NOT humans [mesh]
20. #18 NOT #19
21. #4 AND #10 AND #20

Appendix 4. EMBASE

Search conducted in August 2013 (records from 1966 to August 2013)

Search strategy: 'anxiety disorder'/exp OR 'anxiety'/exp OR anxiety:ab,ti OR anxious:ab,ti OR gad:ab,ti OR phobic:ab,ti OR phobia*:ab,ti OR agoraphobi*:ab,ti OR claustrophobi*:ab,ti OR panic:ab,ti OR obsess*:ab,ti OR compulsi*:ab,ti OR ocd:ab,ti OR (post NEAR/1 trauma*):ab,ti OR posttrauma*:ab,ti OR ptsd:ab,ti OR 'stress disorder' OR neurosis:ab,ti OR neuroses:ab,ti OR neurotic:ab,ti OR psychoneuro*:ab,ti AND ('alcoholism'/exp OR alcoholi*:ab,ti OR ('drinking behavior'/exp OR 'alcohol'/de OR alcohol AND ('comorbidity'/exp OR addict* OR comorbid* OR depend* OR concurren* OR secondary OR misus* OR abus* OR problem OR (co NEXT/1 (morbid* OR occur*)):ab,ti))) AND ('crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR placebo:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR random*:ab,ti OR factorial*:ab,ti OR crossover:ab,ti OR (cross:ab,ti AND over:ab,ti) OR 'randomized controlled trial'/exp) AND [humans]/lim AND [embase]/lim AND [1-11-2011]/sd

Appendix 5. PsycINFO

Search conducted in August 2013 (records from 1970 to August 2013)

Search strategy: (random* or controlled) and anxiety and alcohol

Appendix 6. Alcohol and Alcohol Problems Science database (ETOH)

Search conducted in August 2013 (records from 1977 to 2003)

Search strategy: "anxiety disorder*"/"posttraumatic stress disorder"/PTSD/"specific phobia"/"simple phobia"/"social phobia"/"social anxiety disorder"/"panic disorder"/"generalized anxiety disorder"/"obsessive compulsive disorder"/OCD

WHAT'S NEW

Date	Event	Description
26 November 2020	Amended	A typo has been corrected.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 1, 2015

Date	Event	Description
12 November 2020	Amended	Clarification message from the Co-ordinating Editor added to the Declarations of interest statement about the review's compliance with the Cochrane conflict of interest policy , which includes the relevant parts of the Cochrane Commercial Sponsorship Policy .

CONTRIBUTIONS OF AUTHORS

Jonathan Ipser wrote the initial draft of the protocol, provided feedback on the methodological components of the review, analysed the data and contributed towards the writing of the review.

Don Wilson helped coordinate the protocol and provided subject expertise in the writing of its background section.

Don Wilson and Taiwo Akindipe were responsible for study selection and data extraction, contributed towards the discussion and conclusion sections of the review, and prepared the abstract and plain language summary.

Carli Sager co-ordinated the initial database search for eligible studies and made final changes in response to reviewer comments.

Dan Stein conceived the idea of the review, and provided feedback on drafts of the protocol and review.

Jonathan Ipser stands as guarantor of the review.

DECLARATIONS OF INTEREST

Potential conflicts of interest for individual review authors:

Jonathan Ipser has no known conflicts of interest.

Don Wilson is employed by the University of Cape Town and the Western Cape Provincial government. As part of his duties, he occasionally conducts clinical trials, some of which are funded by pharmaceutical companies (including GlaxoSmithKline and Organon). He has presented on behalf of Sanofi-Synthelabo and Eli Lilly in the past. He has previously participated in industry-sponsored trials in mood disorders. From 2011-2014, Dr. Wilson received no research grants or consultancy honoraria. Dr. Wilson was involved in a Servier-sponsored trial of agomelatine for depression, which ended in 2014, for which his department/faculty received reimbursement. He also gave lectures at meetings sponsored by Sanofi-Synthelabo and Eli Lilly.

Taiwo Akindipe has no known conflicts of interest.

Carli Sager is currently contracted to Parexel International and sub contracted to MSD and Eli Lilly. Carli Sager had no known conflicts of interest while retrieving studies for inclusion in this review.

Dan Stein received research grants or consultancy honoraria (or both) from AMBRF, Biocodex, Cipla, Lundbeck, National Responsible Gambling Foundation, Novartis, Servier and Sun from 2011-2014.

Clarification statement added from the Co-ordinating Editor on 12 November 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the [Cochrane conflict of interest policy](#), which includes the relevant parts of the [Cochrane Commercial Sponsorship Policy](#). It will be updated within 12 months. The update will have a majority of authors and lead author free of conflicts.

SOURCES OF SUPPORT

Internal sources

- University of Cape Town, Cape Town, South Africa

External sources

- MRC Research Unit on Anxiety and Stress Disorders, South Africa

Partial funding for this review was provided by the MRC.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review included the description of a strategy to identify ongoing trials through browsing records listed on the clinicaltrials.gov website, under the categories of "anxiety disorders", "alcohol-related disorders" and "alcoholism". We subsequently regarded this search as unnecessary given the inclusion of records from the clinicaltrials.gov database in the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/trialsearch/), another electronic register that was searched for ongoing trials for this review. We omitted the planned search of the metaRegister of Controlled Trials database (mRCT) (www.controlled-trials.com) as searches using the NIH RePORTER and WHO ICRP databases was regarded as adequate for identifying unpublished studies. In addition, we excluded the Cochrane Central Register of Controlled Trials (CENTRAL) from the search strategy described in the original protocol, as results from a search of CENTRAL are included on a quarterly basis in the specialized registers for the CCDAN and CDAG review groups.

The original protocol restricted inclusion to trials in which participants were diagnosed with alcohol dependence rather than alcohol abuse, given consistent findings of the greater reliability of the diagnosis of alcohol dependency ([Hasin 2003](#)), and a stronger relationship between dependence and anxiety disorders ([Kessler 1997](#)). We decided to omit this requirement, given that it would have excluded a number of otherwise eligible studies that did not explicitly indicate that they excluded participants with alcohol abuse from their sample. Accordingly, we changed the title of the protocol from "Pharmacotherapy for anxiety disorders and comorbid alcohol dependency" to "Pharmacotherapy for anxiety and comorbid alcohol use disorders". In addition, we revised the original protocol to include participants with major depressive disorder (MDD), given the frequent co-occurrence of MDD in this comorbid population.

The protocol included a planned sensitivity analysis to determine whether treatment response varies as a function of the use of treatment response versus non-response as an outcome statistic. This comparison may be necessary in the light of evidence that treatment response may result in less consistent outcome statistics than non-response ([Deeks 2002](#)) when the control group event rate is higher than 50%. We did not perform this analysis, as the proportion of responders on the Clinical Global Impressions (CGI-I) in the control group (26%) in the only meta-analysis of global clinical response conducted as part of this review was lower than 50%.

We also planned a 'worst-case/best-case' analysis as part of the protocol to determine whether the exclusion of participants who were lost to follow-up (LTF) influenced the findings of treatment efficacy ([Deeks 2011](#)). In this analysis, all the missing data for the treatment group are recorded as non-responders in the worst-case scenario, whereas in the best case, all missing data in the control group are treated as non-responders. Should the conclusions regarding treatment efficacy not differ between these two comparisons, it can be assumed that missing data in trial reports do not have a significant influence on outcome. We did not conduct this analysis since the trials that provided data on the CGI-I did so for their entire samples.

The protocol included eligibility criteria for studies employing cross-over designs, although none was found for the current review. Cross-over trials will only be included in the meta-analytic component of future versions of this review when it is possible to extract medication and placebo/comparator data from the first treatment period, or when the inclusion of data from both treatment periods is justified through a wash-out period of sufficient duration as to minimize the risk of carry-over effects. An adequate wash-out period is defined in accordance with clinical practice as at least two weeks for all drugs, with the exception of fluoxetine, for which a minimum wash-out period of four weeks will be required, given the long plasma half-life of this drug. For trials in which we regard the wash-out period as adequate, we will include data from both periods only when it is possible to determine the SE of the MD in response between groups ([Elbourne 2002](#)). We will obtain the summary statistics required to derive the SE of interest from the trial report. For trials for which this information is missing, we will impute the summary statistics through averaging the relevant statistic from other included cross-over trials with comparable control conditions. In cases in which the wash-out period is of an insufficient duration, or in which the small number of cross-over trials does not justify the separate analysis of the summary statistics, we will combine only treatment and placebo/comparator data from the first treatment period with the data from parallel randomized controlled trials (RCTs).

In the protocol, we stated that the primary outcome comparisons would be stratified by medication class, in recognition of the possibility of differential effects for different medications. Individual drugs were to be classified as selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reversible monoamine oxidase inhibitors (RIMAs), benzodiazepines or "other medication". Instead of employing this categorical schema, we added a list of medication classes consistent with a schema based on medication class and year of introduction recommended by the CCDAN review group to the section on [Data extraction and management](#). We only combined outcome data for drugs within each of these medication classes in the meta-analysis on the proviso that they were administered for the treatment of the same anxiety disorder, given that the particular anxiety disorder treated may have implications for the relative time of onset of comorbid alcohol use disorders, as well as the prognosis when treating the anxiety disorder.

We did not conduct planned analyses of potential clinical and methodological moderators of treatment response due to an insufficient number of trials that satisfied inclusion criteria for this review. Future updates of this review will group trials according to the following clinical sources of heterogeneity (number of trials permitting):

- gender of participants. Primary outcomes will be compared between trials that consist predominantly of men or women (defined arbitrarily as constituting greater than 70% of the total sample);
- whether the sample included people diagnosed with major depression. Such an analysis might assist in determining the extent to which the efficacy of a medication in treating post-traumatic stress disorder (PTSD) is independent of its ability to reduce symptoms of depression, an important consideration given the classification of many of these medications as antidepressants.

In addition, we will use the following criteria in future versions of this review to assess the extent of methodological sources of heterogeneity:

- the involvement of participants from a single centre or multiple centres. Single centre trials are more likely to be associated with lower sample size but less variability in clinician ratings;
- whether trials were industry funded. In general, published trials that are sponsored by pharmaceutical companies appear more likely to report positive findings than trials that are not supported by for-profit companies ([Als-Nielsen 2003](#); [Baker 2003](#));
- the relative order of implementing treatment for anxiety disorders and alcohol dependence. We will conduct comparisons between treatment effects for trials that employ treatment for the anxiety disorder first, alcohol dependence first, or that implement treatment for both disorders simultaneously;
- whether psychotherapy was implemented concurrently with pharmacotherapy.

INDEX TERMS

Medical Subject Headings (MeSH)

Alcohol-Related Disorders [*drug therapy] [epidemiology]; Anxiety [*drug therapy] [epidemiology]; Anxiety Disorders [drug therapy] [epidemiology]; Buspirone [therapeutic use]; Comorbidity; Desipramine [therapeutic use]; Paroxetine [therapeutic use]; Phobia, Social [drug therapy] [epidemiology]; Publication Bias; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [*therapeutic use]; Sertraline [therapeutic use]; Stress Disorders, Post-Traumatic [drug therapy] [epidemiology]

MeSH check words

Humans