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Antidepressants for the treatment of people with co-occurring depression and alcohol dependence (Review)

Agabio R, Trogu E, Pani PP

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[Intervention Review]

Antidepressants for the treatment of people with co-occurring depression and alcohol dependence

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ABSTRACT

Background

Alcohol dependence is a major public health problem characterized by recidivism, and medical and psychosocial complications. The co-occurrence of major depression in people entering treatment for alcohol dependence is common, and represents a risk factor for morbidity and mortality, which negatively influences treatment outcomes.

Objectives

To assess the benefits and risks of antidepressants for the treatment of people with co-occurring depression and alcohol dependence.

Search methods

We searched the Cochrane Drugs and Alcohol Group Specialised Register (via CRSLive), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase from inception to July 2017. We also searched for ongoing and unpublished studies via ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

All searches included non-English language literature. We handsearched references of topic-related systematic reviews and the included studies.

Selection criteria

Randomized controlled trials and controlled clinical trials comparing antidepressants alone or in association with other drugs or psychosocial interventions (or both) versus placebo, no treatment, and other pharmacological or psychosocial interventions.

Data collection and analysis

We used standard methodological procedures as expected by Cochrane.

Main results

We included 33 studies in the review (2242 participants). Antidepressants were compared to placebo (22 studies), psychotherapy (two studies), other medications (four studies), or other antidepressants (five studies). The mean duration of the trials was 9.9 weeks (range 3 to 26 weeks). Eighteen studies took place in the USA, 12 in Europe, two in Turkey, and one in Australia. The antidepressant included in most of the trials was sertraline; other medications were amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mianserin, mirtazepine, nefazodone, paroxetine, tianeptine, venlafaxine, and viloxazine. Eighteen studies were conducted in

an outpatient setting, nine in an inpatient setting, and six in both settings. Psychosocial treatment was provided in 18 studies. There was high heterogeneity in the selection of outcomes and the rating systems used for diagnosis and outcome assessment.

Comparing antidepressants to placebo, low-quality evidence suggested that antidepressants reduced the severity of depression evaluated with interviewer-rated scales at the end of trial (14 studies, 1074 participants, standardized mean difference (SMD) -0.27, 95% confidence interval (CI) -0.49 to -0.04). However, the difference became non-significant after the exclusion of studies with a high risk of bias (SMD -0.17, 95% CI -0.39 to 0.04). In addition, very low-quality evidence supported the efficacy of antidepressants in increasing the response to the treatment (10 studies, 805 participants, risk ratio (RR) 1.40, 95% CI 1.08 to 1.82). This result became non-significant after the exclusion of studies at high risk of bias (RR 1.27, 95% CI 0.96 to 1.68). There was no difference for other relevant outcomes such as the difference between baseline and final score, evaluated using interviewer-rated scales (5 studies, 447 participants, SMD 0.15, 95% CI -0.12 to 0.42).

Moderate-quality evidence found that antidepressants increased the number of participants abstinent from alcohol during the trial (7 studies, 424 participants, RR 1.71, 95% CI 1.22 to 2.39) and reduced the number of drinks per drinking days (7 studies, 451 participants, mean difference (MD) -1.13 drinks per drinking days, 95% CI -1.79 to -0.46). After the exclusion of studies with high risk of bias, the number of abstinent remained higher (RR 1.69, 95% CI 1.18 to 2.43) and the number of drinks per drinking days lower (MD -1.21 number of drinks per drinking days, 95% CI -1.91 to -0.51) among participants who received antidepressants compared to those who received placebo. However, other outcomes such as the rate of abstinent days did not differ between antidepressants and placebo (9 studies, 821 participants, MD 1.34, 95% CI -1.66 to 4.34; low-quality evidence).

Low-quality evidence suggested no differences between antidepressants and placebo in the number of dropouts (17 studies, 1159 participants, RR 0.98, 95% CI 0.79 to 1.22) and adverse events as withdrawal for medical reasons (10 studies, 947 participants, RR 1.15, 95% CI 0.65 to 2.04).

There were few studies comparing one antidepressant versus another antidepressant or antidepressants versus other interventions, and these had a small sample size and were heterogeneous in terms of the types of interventions that were compared, yielding results that were not informative.

Authors' conclusions

We found low-quality evidence supporting the clinical use of antidepressants in the treatment of people with co-occurring depression and alcohol dependence. Antidepressants had positive effects on certain relevant outcomes related to depression and alcohol use but not on other relevant outcomes. Moreover, most of these positive effects were no longer significant when studies with high risk of bias were excluded. Results were limited by the large number of studies showing high or unclear risk of bias and the low number of studies comparing one antidepressant to another or antidepressants to other medication. In people with co-occurring depression and alcohol dependence, the risk of developing adverse effects appeared to be minimal, especially for the newer classes of antidepressants (such as selective serotonin reuptake inhibitors). According to these results, in people with co-occurring depression and alcohol dependence, antidepressants may be useful for the treatment of depression, alcohol dependence, or both, although the clinical relevance may be modest.

PLAIN LANGUAGE SUMMARY

Antidepressants for the treatment of people with co-occurring depression and alcohol dependence

Review question

This review investigated whether antidepressants reduce the severity of depression or alcohol dependence (or both) in people with co-occurring depression and alcohol dependence.

Background

The co-occurrence of major depression in people entering treatment for alcohol dependence is common and increases the severity of the condition reducing the effectiveness of treatments. Treatment of these people with medicines is challenging. In this review, we compared the results obtained by people with co-occurring depression and alcohol dependence treated with antidepressant medicines to those treated with placebo (a sham/pretend treatment) or other treatments.

Search date

The evidence is current up to July 2017.

Study characteristics

We identified 33 medical trials involving 2242 participants: 68% were male, and the mean age was 42 years.

Most studies compared antidepressants to placebo (22 studies), but some compared one antidepressant to antidepressant (five studies), to another type of medicine (four studies), or to psychotherapy (a talking treatment; two studies). The average duration of the trials

was 10 weeks (range 3 to 26 weeks). A total of 18 trials took place in the USA, and the others were in Europe, Turkey, and Australia. The antidepressant used in most of the trials was sertraline; the others were: amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mianserin, mirtazepine, nefazodone, paroxetine, tianeptine, venlafaxine, and viloxazine. The studies used 49 different rating scales and varied in terms of design, quality, participant characteristics, tested medicines, services provided, and treatments administered.

A total of 19 studies reported the source of funding (public funds: six studies; pharmaceutical industry: two studies; both funds: 10 studies).

Only four trials reported a declaration of the authors reporting possible conflicts of interest.

Key results

In the 22 studies comparing antidepressants to placebo, antidepressants may have reduced the severity of depression but we are uncertain whether it increased the number of people with clinical beneficial effects from the reduction of depression severity (response to treatment, i.e. people who halved the severity of depression). However, we found no difference between antidepressants and placebo in other relevant outcomes related to the severity of depression, such as the number of people without depression at the end of the trial (remission).

In addition, we found that the administration of antidepressants probably reduced alcohol consumption evaluated as the number of participants abstinent during the treatment (higher among participants who received antidepressants compared to placebo) and the number of drinks consumed per drinking days (lower among participants who received antidepressants compared to placebo). However, similarly to what we found for the severity of depression, we also observed that the administration of antidepressants did not affect other relevant outcomes related to alcohol dependence, such as the rate of abstinent days, number of heavy drinkers, and time before first relapse.

In terms of safety issues, the rate of people withdrawing from treatment due to side effects (undesirable effects such as dry mouth) may not differ between antidepressants and placebo.

There were few studies comparing one antidepressant to another antidepressant or to other interventions, and these had a small number of participants and the same comparison was not made by more than one study, and were therefore not informative.

Quality of evidence

The quality of the included studies was low or moderate for depression severity, abstinence from alcohol, rate of people withdrawal for medical reasons, and dropouts. In subgroup analyses, in the case of single types of medicines, and comparisons with other medicines, the findings of the review were limited by the small number of available studies.

Authors' conclusions

There is low-quality evidence supporting the use of antidepressants in the treatment of people with co-occurring depression and alcohol dependence. Antidepressants have positive effects on certain relevant outcomes related to depression and alcohol use but not on equally relevant other outcomes. However, the risk of developing side effects appears to be minimal, especially for the newer classes of antidepressants.

Summary of findings for the main comparison. Antidepressants compared to placebo: all studies for the treatment of people with co-occurring depression and alcohol consumption

Antidepressants compared to placebo: all studies

Patient or population: people with co-occurring depression and alcohol dependence

Settings: unknown
Intervention: antidepressants
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	Antidepressants				
Depression severity: final score (interviewer-rated scales)	-	The mean depression: final score (interviewer-rated scales) - all studies in the intervention groups was **0.27 standard deviations lower** (0.49 lower to 0.04 lower)	-	1074 (14 studies)	⊕⊕⊖⊖ **Low**[1,2]	-
Response to antidepressive treatment	**Study population**		**RR 1.40** (1.08 to 1.82)	805 (10 studies)	⊕⊖⊖⊖ **Very low**[3,4,5]	-
	481 per 1000	**674 per 1000** (520 to 876)				
	392 per 1000	**521 per 1000** (416 to 659)				
Consumption of alcohol: abstinent days (%)	-	The mean alcohol: abstinent days (%) - all studies in the intervention groups was **1.34 higher** (1.66 lower to 4.34 higher)	-	821 (9 studies)	⊕⊕⊖⊖ **Low**[6,7]	-
Consumption of alcohol: abstinent participants (number)	**Study population**		**RR 1.71** (1.22 to 2.39)	424 (7 studies)	⊕⊕⊕⊖ **Moderate**[8,9]	-
	199 per 1000	**340 per 1000** (243 to 476)				
	188 per 1000	**321 per 1000**				

		(229 to 449)				
Consumption of alcohol: drinks (per drinking days)	-	The mean alcohol: drinks (per drinking days) - all studies in the intervention groups was **1.13 lower** (1.79 lower to 0.46 lower)	-	451 (7 studies)	⊕⊕⊕⊖ **Moderate**[10]	-
Acceptability: dropouts	**Study population**		**RR 0.98** (0.79 to 1.22)	1159 (17 studies)	⊕⊕⊖⊖ **Low**[11,12]	-
	334 per 1000	**328 per 1000** (264 to 408)				
	307 per 1000	**301 per 1000** (243 to 375)				
Tolerability of treatment: withdrawal for medical reasons	**Study population**		**RR 1.15** (0.65 to 2.04)	947 (10 studies)	⊕⊕⊖⊖ **Low**[13,14]	-
	69 per 1000	**80 per 1000** (45 to 141)				
	32 per 1000	**37 per 1000** (21 to 65)				

*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).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Nine studies at unclear risk for selection bias; two studies at high risk and six at unclear risk for performance bias; 13 studies at unclear risk for detection bias (subjective); one study at high risk and two at unclear risk for attrition bias; three studies at high risk and one at unclear risk for reporting bias.
[2]Significant heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 39.01$, df = 13 (P = 0.0002); $I^2 = 67\%$.
[3]Ten studies at unclear risk for selection bias; one study at high risk and five at unclear risk for performance bias; nine studies at unclear risk for detection bias (subjective); two studies at high risk and two at unclear risk for attrition bias; two studies at high risk and two at unclear risk for reporting bias.
[4]Significant heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 31.63$, df = 9 (P = 0.0002); $I^2 = 72\%$.
[5]Funnel plot showed asymmetry in favour of 'positive' trials.
[6]Seven studies with unclear risk of selection bias; one study at high risk and five studies at unclear risk for performance bias; all studies at unclear risk for detection bias (subjective); one study at high risk and two at unclear risk for reporting bias.
[7]Significant heterogeneity: $Tau^2 = 9.16$; $Chi^2 = 39.42$, df = 8 (P < 0.00001); $I^2 = 80\%$.

[8]Four studies with unclear risk of selection bias; one study at high risk and two studies at unclear risk for performance bias; six studies at unclear risk for detection bias (subjective); one study at high risk and one at unclear risk for reporting bias.
[9]Total number of events was fewer than 300.
[10]Five studies with unclear risk of selection bias; one study at high risk and two studies at unclear risk for performance bias; six studies at unclear risk for detection bias (subjective); one study at high risk and two at unclear risk for reporting bias.
[11]Twelve studies with unclear risk of selection bias; one study at high risk and seven studies at unclear risk for performance bias; 16 studies at unclear risk for detection bias (subjective); four studies at high risk and three studies at unclear risk for attrition bias; five studies at high risk and two at unclear risk for reporting bias.
[12]Significant heterogeneity: $Chi^2 = 23.80$, df = 14 (P = 0.05); $I^2 = 41\%$.
[13]Six studies at unclear risk for selection bias; one study at high risk and three at unclear risk for performance bias; nine studies at unclear risk for detection bias (subjective); two studies at high risk and one at unclear risk for attrition bias; three studies at high risk and two at unclear risk for reporting bias.
[14]Optimal information size not met.

BACKGROUND

See Appendix 1 for a list of the abbreviations used in this review.

Description of the condition

Major depression disorder and alcohol dependence are among the most prevalent mental disorders worldwide, and their co-occurrence is common (APA 2013; Grant 1995; Grant 2015; Pettinati 2013). Depression is characterized by a low mood or diminished interest in normal activities on most days, for at least two weeks, as well as other symptoms such as significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of guilt or worthlessness, difficulty concentrating, and suicidal ideation (APA 2013). Diagnosis requires the presence of at least five of these symptoms (APA 2000; APA 2013). Alcohol dependence is characterized by bouts of excessive drinking, and inability to control alcohol consumption despite the awareness of its negative consequences (APA 2013). In the last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), diagnoses of alcohol dependence and alcohol abuse formerly classified as Alcohol Use Disorders have been replaced by a classification of Alcohol Use Disorder (AUD), which merges their criteria into a single set (APA 2000; APA 2013). AUD diagnosis requires repetitive alcohol-related problems in at least two out of 11 areas of life as described by a set of criteria that includes 'craving,' which is defined as a strong, obsessive, and irresistible desire to consume alcohol (APA 2013).

Epidemiological studies found that the 12-month prevalence of depression in the adult population was 5.3% and lifetime prevalence was 13.3% (Hasin 2005), and the 12-month prevalence of alcohol dependence was 13.9% and lifetime prevalence was 29.1% (Grant 2015). The prevalence of depression has been reported to be higher in people with alcohol dependence than in the general population as well as the prevalence of alcohol dependence in people with depression than in the general population (Regier 1990; Schuckit 1997). Each of these disorders alone is associated with a significant risk of developing the other, and their coexistence is a risk factor for morbidity and mortality, including death from suicide (Schneider 2009; Sher 2005; Wilcox 2004).

The co-occurrence of depression and alcohol dependence carries potential problems in the diagnostic process (Pettinati 2013; Schuckit 2006). Indeed, depression and alcohol dependence may represent two independent conditions, each requiring to be treated comprehensively (Schuckit 2006). Alternatively, one disorder may influence the development of the second condition. For instance, depression may be the first disorder and is a risk factor for the development of excessive alcohol consumption and the progression to alcohol dependence. In this case, depression is defined as the primary disorder and alcohol dependence is the secondary disorder (Schuckit 2006). However, when the two conditions are of significant duration or severity, both require treatment for as long as is necessary (Schuckit 2006). In contrast, temporary alcohol-induced depressive symptoms, resulting from the acute alcohol effects of intoxication or withdrawal (APA 2013) tend to spontaneously disappear within approximately one month of alcohol abstinence, without requiring antidepressant therapy (Pettinati 2013; Schuckit 2006).

Description of the intervention

People with alcohol dependence and depression may require different medical treatments depending to the different typology of co-occurrence. However, pharmacological treatment of people with alcohol dependence and depression constitutes a real challenge (Pettinati 2013).

Except in the case of temporary alcohol-induced depressive symptoms, people with co-occurrence of alcohol dependence and depression often receive a combination therapy consisting of medication for the treatment of depression and another for the treatment of alcohol dependence (Pettinati 2013). From a clinical standpoint, this practice is limited by two factors. The first is the extremely low use of medications approved for the treatment of alcohol dependence (Pettinati 2013). One epidemiological study found that less than 10% of people affected by alcohol dependence seek and receive a medical treatment other than 12-step groups (Grant 2015). The second limitation is the lack of clear evidence of the efficacy of antidepressants in people with alcohol dependence (Pettinati 2013). Usually, depression is considered as a disorder that is amenable to antidepressant treatment (O'Donnell 2011). The most commonly used medications are selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) (O'Donnell 2011). SSRIs and SNRIs are often referred to as second-generation antidepressants and are considered to be as effective and safer than the older first-generation antidepressants, such as monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) (O'Donnell 2011). A common characteristic of antidepressants is that three to four weeks are required following initiation of treatment before a therapeutic response is observed (O'Donnell 2011). In addition, 20% of people with depression may be refractory to multiple antidepressants at adequate doses (O'Donnell 2011).

The efficacy of antidepressants in the treatment of people with alcohol dependence and depression has been investigated in four systematic reviews and meta-analyses (Foulds 2015; Iovieno 2011; Nunes 2004; Torrens 2005). The first study analyzed 14 trials in which the efficacy of antidepressants was compared to that of placebo in people with dependence on alcohol or other substances of abuse (opioids or cocaine) (Nunes 2004). Among the selected trials, eight specifically investigated the efficacy of antidepressants in people with alcohol dependence and depression (Altamura 1990; Cornelius 1997; Mason 1996; McGrath 1996; Moak 2003; Pettinati 2001a; Roy 1998; Roy-Byrne 2000). The results of the meta-analysis revealed that antidepressants had a modest beneficial effect in people with depression who were dependent on alcohol or other substances. The second meta-analysis compared the efficacy of antidepressants in people who were dependent on substances of abuse, with and without depression (Torrens 2005). Nine studies investigated the efficacy of antidepressants in people with alcohol dependence and depression (Altamura 1990; Cornelius 1997; Gual 2003; Mason 1996; McGrath 1996; Moak 2003; Pettinati 2001a; Roy 1998; Roy-Byrne 2000). Two of these examined the efficacy of TCAs (Mason 1996; McGrath 1996), five of SSRIs (Cornelius 1997; Gual 2003; Moak 2003; Pettinati 2001a; Roy 1998), one of viloxazine (Altamura 1990), and one of nefazodone (Roy-Byrne 2000). Although five trials investigated the efficacy of SSRIs, the meta-analysis did not demonstrate a significant advantage associated with their use but found a significant effect of other antidepressants (Torrens 2005). The third meta-analysis analyzed

11 trials (Altamura 1990; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000), and compared the efficacy of antidepressants in people affected by depression or dysthymic disorder (or both) with and without alcohol dependence (Iovieno 2011). The results showed that antidepressants reduced the severity of depression, increasing the rate of responders in people with and without alcohol dependence, with no difference between these two groups; however, there was no effect on the rate of the responders with SSRIs alone. In addition, antidepressant treatment did not reduce alcohol consumption in people with depression and alcohol dependence (Iovieno 2011), which may be explained, at least in part, by the low number of trials reporting data on alcohol consumption. However, there have been conflicting reports on the effects of antidepressants on alcohol consumption in alcohol-dependent people (Naranjo 2001; Pettinati 2013): while some studies found that antidepressants did not alter consumption (Kranzler 2000; Pettinati 2004), others found that it was significantly reduced (Naranjo 2001), or increased in certain typologies of alcohol-dependent people (Kranzler 1996; Pettinati 2000). The last meta-analysis investigated differences in the response to treatment for depression in alcohol-dependent people according to depression type, independent or alcohol-induced depression (Foulds 2015). This study analyzed 22 clinical trials of which 13 compared the efficacy of antidepressants to placebo in people with alcohol dependence and depression (Adamson 2015; Altintoprak 2008; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Muhonen 2008; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000), while the other nine studies investigated the efficacy of other treatments (e.g. psychotherapy or medical management). Two of the 13 former studies were excluded from the meta-analysis (Altintoprak 2008; Mason 1996); the remaining 11 were divided into two groups, the first comprising trials in which depression was considered to be independent (Cornelius 1997; McGrath 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000), and the second in which depression was considered to be alcohol-induced or undifferentiated (Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; Pettinati 2001a). The results showed that treatment of depression in alcohol-dependent people was associated with a large early improvement in the severity of the depression, even when it was independent from drinking, and that the effect of antidepressants was modest but stronger in independent than in alcohol-induced depression (Foulds 2015).

How the intervention might work

The effect of antidepressants on depression in alcohol-dependent people could depend on their interference with neurobiological substrates underlying depression, including noradrenaline, dopamine, and serotonin brain circuits (Artigas 2002; Stahl 2003). However, it may also be related to interference with the neurobiological pathways that support alcohol dependence (Carboni 2004; LeMoal 2007; Shirayama 2006). In fact, antidepressants have been proposed for the treatment of alcohol dependence, although their efficacy in this regard remains controversial (Torrens 2005): while some SSRIs have shown positive results in cases of less severe drinking (Pettinati 2001b), others have reported that antidepressants achieved even worse results than placebo (Chick 2004a; Kranzler 1996), especially when treating early-onset subtypes (Type B, Type II) of alcohol dependence (Babor 1992; Cloninger 1988). Consistent with the heterogeneous origin of depression in alcohol-dependent people, there are reports of depression symptoms abating spontaneously after alcohol detoxification (Brown 1995; Nunes 2004), and the lack of effect of antidepressants in people who are actively drinking (Pettinati 2004).

Why it is important to do this review

Several Cochrane Reviews on the use of antidepressants for depression are available. However, the generalization of their results to the treatment of people whose depression is complicated by alcohol dependence is limited since it is unknown whether depressive symptoms result from the effects of alcohol or constitute a separate mood disorder (Pettinati 2004). There are no Cochrane Reviews or protocols available on the efficacy of antidepressants in the treatment of people with co-occurring depression and alcohol dependence, and, although results from the few published reviews (including four meta-analyses; Foulds 2015; Iovieno 2011; Nunes 2004; Torrens 2005) are suggestive of the efficacy of antidepressants, there are no conclusive results. Therefore, the treatment of a clinical condition associated with significant mortality and morbidity is not yet supported by systematic evaluations of efficacy using rigorous Cochrane methodology. Thus, the evaluation of the efficacy and safety of antidepressants for the treatment of people with co-occurring depression and alcohol dependence represents a priority.

OBJECTIVES

To assess the benefits and risks of antidepressants for the treatment of people with co-occurring depression and alcohol dependence.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) and controlled clinical trials (CCTs) focused on the use of any antidepressant medication for the treatment of people with co-occurring depression and alcohol dependence. For cross-over studies, given possible carry-over effects and expected dropout rates, we considered only the first period of the trial.

Types of participants

People with co-occurring depression and alcohol dependence, irrespective of symptom severity. Alcohol dependence and depression were both diagnosed according to standardized criteria such as DSM or equivalent. However, we also accepted trials that did not use explicit diagnostic criteria.

We examined the effect of including people with uncertain diagnoses in the sensitivity analyses. Trials including people with additional diagnoses of dependence by other substances of abuse were also considered eligible. People under 18 years of age and pregnant women were excluded for the substantially different approach to clinical management of these people. People with other comorbid mental health conditions were included and considered in subgroup analysis.

Types of interventions

Experimental intervention

- **Monoamine oxidase inhibitors (MAOIs):** minaprine, moclobemide, phenelzine, selegiline.
- **Tricyclic antidepressants (TCAs) and TCA-related antidepressants:** amitriptyline, amoxapine, clomipramine, desipramine, dothiepin (also known as dosulepin), doxepin, imipramine, maprotiline, nomifensine, nortriptyline, protriptyline, trimipramine.
- **Selective serotonin reuptake inhibitors (SSRIs):** citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, zimelidine.
- **Serotonin-noradrenaline reuptake inhibitors (SNRIs):** desvenlafaxine, duloxetine, milnacipran, venlafaxine.
- **5-HT$_2$ antagonists:** mianserin, mirtazepine, nefazodone, trazodone.
- **Other antidepressants:** agomelatine, bupropion, reboxetine, tianeptine, viloxazine.

These antidepressants may have been administered alone or in combination with other medications for the treatment of alcohol dependence or with any psychosocial intervention.

Control intervention

- Placebo.
- No intervention.
- Other pharmacological interventions.
- Any psychosocial intervention.

Types of outcome measures

Primary outcomes

- Depression severity measured as group mean scores in continuous: interviewer-rated scales (e.g. Hamilton Rating Scale for Depression (HRSD)) and self-administered scales (e.g. Beck Depression Inventory (BDI)).
- Response to antidepressive treatment (defined using interviewer-rated scales as the number of people showing greater than 50% reduction in depression severity from baseline, according to the definition of the study authors, or a 'very much improved' or 'much improved' on the Clinical Global Impression (CGI) improvement scale).
- Full remission of depression (defined according to a prespecified score in interviewer-rated continuous depression scales).
- Consumption of alcohol as number of participants who reported use during treatment, or number of participants with positive breath alcohol analysis or urine analyses positive for alcohol, or both.
- Liver enzyme levels (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT)).
- Acceptability indicated by all-cause dropouts from the treatment as number of participants who did not complete treatment.
- Tolerability of treatment as withdrawal for medical reasons, total number of adverse events, and type of adverse events experienced during treatment.
- Suicide and suicide attempts.

Where possible, indices of effectiveness at different time points in the course of treatment were pooled.

Secondary outcomes

- Use of other substances of abuse as number of participants who reported use during treatment, or number of participants with urine analyses positive for other substances of abuse, or both; self-reported quantity and frequency of use of other substances of abuse.
- Craving as measured by validated scales (e.g. Brief Substance Craving Scale (BSCS), Visual Analogue Scale (VAS), Obsessive Compulsive Drinking Scale (OCDS)).
- Severity of dependence as measured by validated scales (e.g. Addiction Severity Index (ASI), CGI, Severity of Dependence Scale (SDS), Drinker Inventory of Consequences scale (DrInC)).
- Psychiatric symptoms/psychological distress diagnosed using standard criteria (e.g. DSM) or measured by validated scales (e.g. Positive and Negative Syndrome Scale (PANSS); Symptoms Check List-90 (SCL-90)).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases.

- Cochrane Drugs and Alcohol Group (CDAG) Specialised Register (inception to 4 July 2017), using the search strategy outlined in Appendix 2.
- Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 7), using the search strategy outlined in Appendix 3.
- MEDLINE (via PubMed) (January 1966 to 4 July 2017), using the search strategy outlined in Appendix 4.
- Embase (Elsevier, embase.com) (January 1974 to 4 July 2017), using the search strategy outlined in Appendix 5.

We searched for ongoing clinical trials and unpublished trials via Internet searches on the following websites.

- ClinicalTrials.gov (www.clinicaltrials.gov) (4 July 2017).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) (4 July 2017).

All searches included non-English language literature and studies with English abstracts were assessed for inclusion. When considered likely to meet inclusion criteria, studies were translated.

Searching other resources

We searched the reference lists of all relevant papers to identify additional studies, and conference proceedings that were likely to contain trials relevant to the review. We also contacted investigators to seek information about unpublished or incomplete trials.

Data collection and analysis

Selection of studies

Two authors (RA, ET) inspected the search hits by reading titles and abstracts. Two authors (RA, ET) obtained each potentially relevant study identified in the search in full text and independently

assessed them for inclusion. We resolved disagreements by discussion or consultation with the third author (PP).

Data extraction and management

Two authors (RA, ET) independently extracted data and used a standardized checklist to collect information on methodology, participants (sociodemographic and clinical information relevant to the review aims), interventions (medications and non-pharmacological interventions), and primary and secondary outcomes. We resolved disagreements by discussion and, for those that persisted, by consultation with the third author (PP).

Assessment of risk of bias in included studies

Two authors (RA, ET) assessed study quality according to the criteria listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or consultation with the third author (PP). We assessed the risk of bias for RCTs and CCTs according the five criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The approach recommended for assessing the risk of bias in studies included in a Cochrane Review involves a two-part tool addressing seven specific domains, namely, sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part involves assigning a judgement relating to the risk of bias for that entry in terms of low, high, or unclear risk. To make these judgements, we used the criteria listed in the *Cochrane Handbook for Systematic Reviews of Interventions* adapted to the addiction field (see Appendix 6).

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

Blinding of participants and personnel (avoidance of performance bias) was judged to interfere with both subjective and objective outcomes pertaining to the behaviour of participants (such as retention in treatment) and was addressed by a single entry for each study.

Blinding of outcome assessor (avoidance of detection bias) was considered separately for objective outcomes (e.g. retention in treatment, use of substances of abuse measured by breath or urine analysis), and subjective outcomes (e.g. severity of depression, other psychiatric symptoms/psychological distress, severity of dependence).

Incomplete outcome data (avoidance of attrition bias) was considered for all outcomes except for the dropout from the treatment, which is often the primary outcome measure in addiction studies.

To incorporate assessment in the review process, we first plotted intervention effects estimates for different outcomes stratified for risk. If there were differences in results among studies with different risks of bias, we performed a sensitivity analysis excluding studies with high risk of bias in one or more domains.

We also performed subgroup analysis for studies with low and unclear risk of bias.

Measures of treatment effect

We analyzed dichotomous outcomes (e.g. number of participants showing improvement in depression at follow-up) calculating the risk ratio (RR) for each trial, with the uncertainty of each result expressed as a 95% confidence interval (CI). Continuous outcomes (e.g. severity of depression according to final scores archived in continuous interviewer-rated scales) were analyzed by calculating the mean difference (MD) with 95% CI, which were calculated by comparing and pooling mean score differences from the end of treatment to baseline for each group. In case of missing data on the standard deviation (SD) of the changes, we used the SD at the end of treatment for each group. We used the standardized mean difference (SMD) when the studies employed different instruments.

Unit of analysis issues

We did not use data presented as a number of positive urine or breath alcohol tests relative to the total number of tests in the experimental and control groups as a measure of substance use. This decision was made because using the number of tests instead of the number of participants as a unit of analysis violates the assumption of the independence of observations. In fact, the results of the tests performed for each participant were not independent.

If multi-arm studies were included in the meta-analyses and one arm was considered more than once in the same comparison, we combined groups according to the approaches suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). That is, if one arm (e.g. control group) was compared with different groups in which participants received different doses of the same antidepressant, we combined all the experimental groups (different doses of the same antidepressant) into a single group, which was then compared with the control group. If one arm (e.g. control group) was compared with different experimental groups in which participants received different antidepressants, we planned to split the 'shared' control group into two or more groups with smaller sample sizes, and compared these smaller control groups with the different experimental groups. While this last approach avoided the repeated use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial, it decreased the precision of the pooled estimate. Both approaches avoided the double counting of participants in the control groups.

Dealing with missing data

We contacted the original investigators to request information on data missing from the studies. In the absence of supplemental data from the study authors, we obtained missing data according to procedures suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Whenever the assumption that random data were missing was supported by available information, we analyzed only available data; on the contrary case, other approaches, such as the last observation carried forward or the assumption that missing data corresponded to poor outcomes, were pursued. To assess the sensitivity of the results to changes made in the assumptions, we carried out a sensitivity analysis. The potential impact of missing data on the findings of the review is addressed in the Discussion.

Assessment of heterogeneity

We analyzed heterogeneity using the I^2 statistic and the Chi^2 test. As suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), according to I^2 values, evidence of heterogeneity may be classified into no important (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%). In the present meta-analysis, we considered the following cut-off values: I^2 value 50% or greater; P value for the Chi^2 test 0.1 or less for significant evidence of heterogeneity.

Assessment of reporting biases

We used a funnel plot (plot of the effect estimate from each study against sample size or effect standard error) to evaluate the potential for bias related to the size of the trials.

Data synthesis

Whenever possible, we combined the outcomes from individual trials in a meta-analysis (comparing intervention and outcomes between trials) using a fixed-effect model; when there was significant heterogeneity, we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for studies with low and unclear risk of bias and for classes of antidepressants. Moreover, we performed subgroup analyses to take into account the following confounders/effect modifiers, when possible.

- Setting (inpatient or outpatient treatment).
- Starting dose/rate and pattern of dose reduction.
- Scheduled duration of treatment.
- Severity of depression.
- Severity of alcohol dependence.
- Being actively drinking.
- Length of abstinence.
- Other psychiatric comorbidity.
- Other pharmacological treatment offered.
- Other psychosocial treatment offered.

Sensitivity analysis

To incorporate assessment into the review process, we first plotted intervention effects estimates stratified for risk of bias for each relevant domain. If there were differences in the results among studies at different risks of bias, we performed a sensitivity analysis excluding the studies with a high risk of bias. The effect of including people with uncertain diagnoses was evaluated with the sensitivity analysis; other issues suitable for sensitivity analysis were identified during the review process based on idiosyncrasies of the examined studies.

'Summary of findings' table

We assessed the overall quality of the evidence for the primary outcomes using the GRADE system. The GRADE Working Group developed a system for grading the quality of evidence (GRADE 2004; Guyatt 2008; Guyatt 2011; Schünemann 2006), which takes into account issues related to internal validity and to external validity, such as directness of results. The 'Summary of findings' table presents the main findings of a review in a transparent and simple tabular format. In particular, it provides key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes.

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

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

Grading is decreased for the following reasons.

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

RESULTS

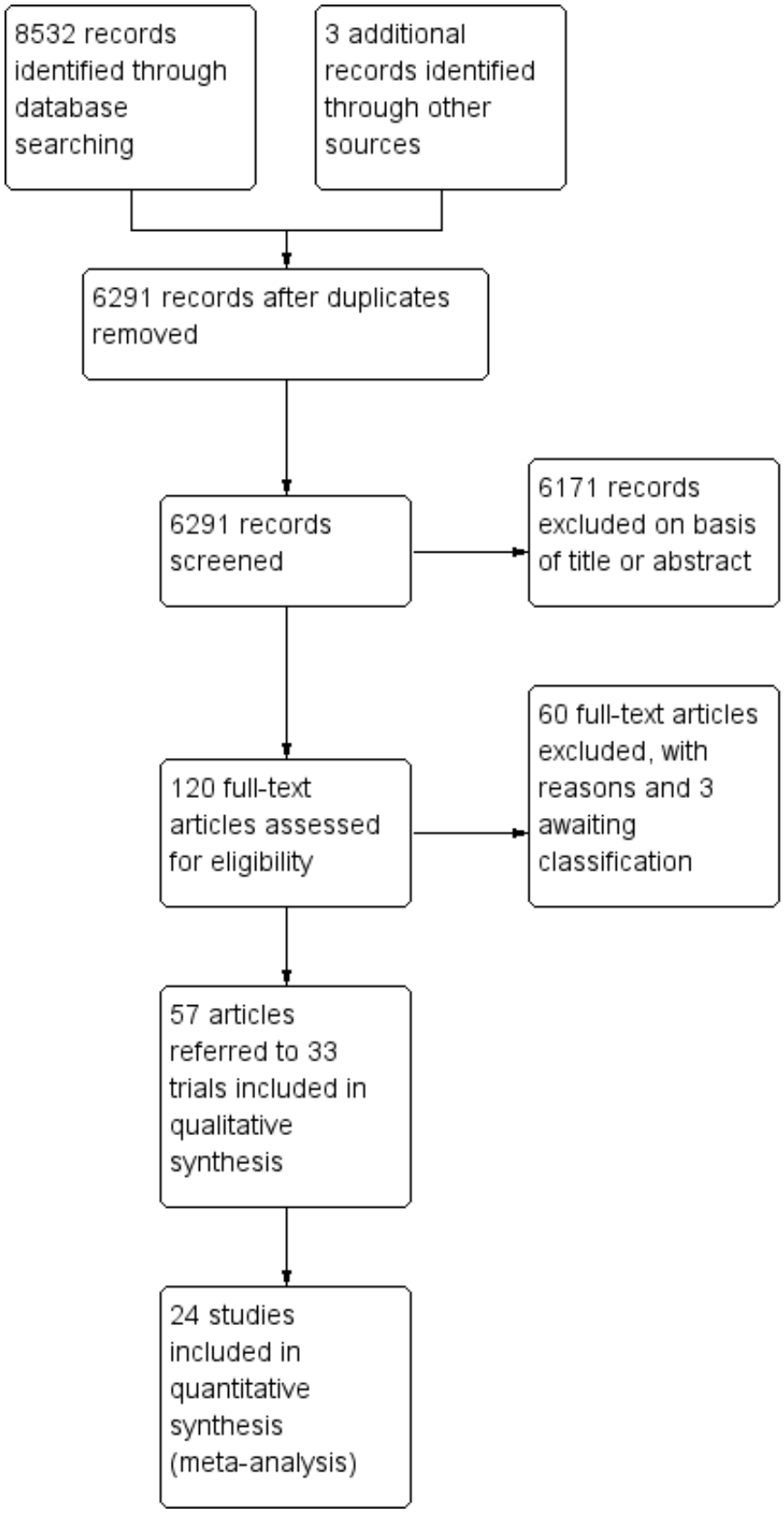
Description of studies

For substantive descriptions of studies see Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies tables.

Results of the search

The searches of the four databases (see Electronic searches) retrieved 8532 records (see Figure 1). Our searches of other resources identified three additional records that appeared to meet the inclusion criteria. Therefore, there was a total of 8535 records.

Figure 1. Study flow diagram.



Once duplicates had been removed, there were 6291 records. We excluded 6171 records based on titles and abstracts. We obtained the full text of the remaining 120 records. We excluded 60 records (see Characteristics of excluded studies table). We added three records to the Characteristics of studies awaiting classification table pending information from the authors.

We included 33 studies reported in 57 references. For a further description of our screening process, see the study flow diagram (Figure 1).

Included studies

Thirty-three studies with 2242 participants met the inclusion criteria (see Characteristics of included studies table).

It was not possible to extract and combine the results of nine studies as their comparisons were not evaluated by more than one study. We extracted data from the other 24 studies (1498 participants) (see Figure 1).

Duration of trials

The mean duration of the trials was 9.9 weeks (range 3 to 26 weeks).

Treatment regimens and setting

Medications evaluated: sertraline (eight studies); amitriptyline (five studies); mirtazapine (four studies); doxepin (three studies); imipramine (three studies); nefazodone, tianeptine, and venlafaxine (two studies each); and citalopram, desimipramine, escitalopram, fluoxetine, fluvoxamine, mianserine, paroxetine, and viloxazine (one study each).

Twenty-two studies (1438 participants) compared the efficacy of an antidepressant versus placebo, two (60 participants) compared the efficacy of an antidepressant versus psychotherapy, five compared the efficacy of one antidepressant versus another (mirtazapine versus amitriptyline; mirtazapine versus venlafaxine; paroxetine versus amitriptyline; tianeptine versus amitriptyline; tianeptine versus fluvoxamine), four compared the efficacy of antidepressants versus other medications (amitriptyline versus diazepam (one study); doxepin versus diazepam (two studies); escitalopram versus memantine (one study)).

In total, 18 trials were conducted in an outpatient setting, 12 in an inpatient setting, and three trials initially in an inpatient setting and then in an outpatient setting. Eighteen studies took place in the USA, 12 in Europe, two in Turkey, and one in Australia.

Eighteen trials administered psychosocial treatment in conjunction with antidepressants, including cognitive behavioural psychotherapy or relapse prevention therapy (14 trials) and manualized clinical case management or unspecified psychotherapy (four studies).

Studies assessed compliance as the return of unused medications (six studies), trough plasma concentrations (two studies), and use of an electronic monitoring device that recorded the date and time of bottle cap openings (two studies). The remaining 19 studies did not report this information. For more information see Appendix 7.

Rating instruments

The rating instruments used in the included studies are listed in Appendix 8.

Participants

The analysis included 2242 participants affected by alcohol dependence and depression according to DSM criteria (Diagnostic and Statistic Manual of Mental Disorders III - Revised (DSM-III-R); Diagnostic and Statistic Manual of Mental Disorders IV - Revised (DSM-IV-R)) or other criteria (see Appendix 8).

The sex of 156 participants was unknown; among the remaining 2086 participants, 1425 were men (68.3%), and 661 were women (31.7%). The mean age was 41.7 years (data from 28/33 studies).

Sources of funding

Only 19 trials reported the source of funding for their research. Six trials received funds only from public Institutes; 10 studies were partly supported by both a public institute and a private pharmaceutical company; and two were only partially supported by a private pharmaceutical company.

Declaration of interest

Four trials reported a possible conflict of interest.

Outcomes

For some reported outcomes, it was difficult to make comparisons and pool results due to the different modes of measurement, the selected cut-off value, and the availability of data from the study or the primary investigator. This was particularly true for use of alcohol and alcohol abstinence, which were expressed in various ways (i.e. rate of drinking days, cumulative number of drinking days, number of drinks per drinking day, weekly number of heavy drinking days, rate of heavy drinkers, number of heavy drinkers, number of participants abstaining during the trial, rate of abstinence days, cumulative abstinence days). Appendix 9 shows the list of outcomes.

Primary outcomes

Depression severity

- Twenty-three studies reported the **final score of an interviewer-rated scale** (see Primary outcomes) (Adamson 2015; Altamura 1990; Altintoprak 2008; Butterworth 1971a; Gual 2003; Habrat 2006; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Lôo 1988; Mason 1996; McGrath 1996; Moak 2003; Muhonen 2008; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1796 participants) (see Appendix 8; Appendix 9). Nineteen studies used the HRSD (Altamura 1990; Altintoprak 2008; Gual 2003; Habrat 2006; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Mason 1996; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1410 participants); five studies used the Montgomery and Åsberg Depression Rating Scale (MADRS) (Adamson 2015; Gual 2003; Krupitsky 2012; Lôo 1988; Muhonen 2008; 490 participants), and one study used the Brief Psychiatric Rating Scale (BPRS) (Butterworth 1971a; 39 participants). Two studies reported data of two interviewer-rated scales (MADRS and HRSD) and only included data obtained using the HRSD (Gual 2003; Krupitsky 2012; 143 participants). One study excluded data because they were expressed as medians and interquartile ranges (Mason 1996; 22 participants).

- Thirteen studies reported the **final score of a self-administered scale** (see Primary outcomes) (Adamson 2015; Butterworth 1971a; Cocchi 1997; Cornelius 2016; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012; Lôo 1988; McLean 1986; Moak 2003; Muhonen 2008; Pettinati 2001a; Roy 1998; 825 participants) (see Appendix 8; Appendix 9). Among them, five studies used the BDI scale (Cornelius 2016; Moak 2003; Muhonen 2008; Pettinati 2001a; Roy 1998; 241 participants), one study used the HRSD scale (McLean 1986; 27 participants), two studies used the SCL-90 scale (Adamson 2015; Lôo 1988; 267 participants), and five studies used the Zung Self-Assessment Depression Scale (ZUNG) scale (Butterworth 1971a; Cocchi 1997; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012; 282 participants). Two studies reported data obtained using the Minnesota Multiphasic Personality Inventory (MMPI) and ZUNG and only included data obtained with ZUNG (Krupitsky 1993 arm A; Krupitsky 1993 arm B; 41 participants).
- Six studies reported the **difference between the baseline and final score of an interviewer-rated scale** (see Primary outcomes) (Butterworth 1971b; Cornelius 1997; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; Pettinati 2001a; 476 participants) (see Appendix 8; Appendix 9). Five studies used the HRSD (Cornelius 1997; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; Pettinati 2001a; 436 participants), and one trial used the Lehmann Depression Rating Scale (LDRS) (Butterworth 1971b; 40 participants). We excluded data from one study because they were expressed as medians and interquartile ranges (Mason 1996; 28 participants).
- Four studies reported the **difference between the baseline and final score of a self-administered scale** (see Primary outcomes; Appendix 8; Appendix 9) (Cornelius 1997; Cornelius 2016; McLean 1986; Pettinati 2001a; 129 participants). Among them, three studies used the BDI (Cornelius 1997; Cornelius 2016; Pettinati 2001a; 94 participants), and one study used a self-rating scale based on the HRSD (McLean 1986; 35 participants).

Response

Fourteen studies reported the response to antidepressive treatment (see Primary outcomes) (Butterworth 1971b; Butterworth 1971a; Gallant 1969 arm a; Gallant 1969 arm b; Gual 2003; Habrat 2006; Kranzler 2006 arm A; Kranzler 2006 arm B; Lôo 1988; Mason 1996; McGrath 1996; Moak 2003; Roy 1998; Roy-Byrne 2000; 1284 participants) (see Appendix 8; Appendix 9). The studies used different interviewer-rated scales: five studies used CGI (Butterworth 1971b; Gallant 1969 arm a; Gallant 1969 arm b; Roy 1998; Roy-Byrne 2000; 240 participants); two studies used MADRS (Gual 2003; Lôo 1988; 212 participants); six studies used HRSD (Habrat 2006; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; 793 participants); and one study used BPRS (Butterworth 1971a; 39 participants). One study reported data obtained using both CGI and HRSD and we only used data obtained using CGI (Roy 1998; 36 participants). One study reported data for significant depression that were converted into response (Moak 2003; 82 participants). Two studies reported response criteria using self-administered scales; these data were not included in the analyses (Cocchi 1997; Roy 1998).

Remission

Five studies reported remission (see Primary outcomes) (Adamson 2015; Gual 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000; 455 participants) (see Appendix 8; Appendix 9). The studies used different interviewer-rated scales or different cut-off values of the same scale: one study used MADRS, final score less than 10 (Adamson 2015; 138 participants), one study used MADRS, final score less than 7 (Gual 2003; 83 participants), one study used HRSD, final score less than 8 (Roy-Byrne 2000; 64 participants), and two studies used HRSD, final score 9 or less (Pettinati 2010 arm A; Pettinati 2010 arm B; 170 participants). Two studies reported remission criteria using self-administered scales and we did not include these data in the analyses (Cocchi 1997; McLean 1986).

Alcohol consumption

The studies included in the present meta-analysis did not report information on alcohol consumption as number of participants who reported use during treatment, or number of participants with positive breath alcohol analysis or urine analyses positive for alcohol (or alcohol consumption and positive breath alcohol analysis or urine analyses) (see Primary outcomes). Conversely, at least two studies reported the following information (see Characteristics of included studies table; Appendix 8; Appendix 9).

- Nine studies reported the **rate of abstinent days** (Adamson 2015; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; McGrath 1996; Moak 2003; Pettinati 2001a; 821 participants).
- Eight studies reported the **number of abstinent participants** during the trials (Cornelius 1997; Hernandez-Avila 2004; McGrath 1996; Muhonen 2008; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000), 504 participants)
- Two studies reported the **number of drinking days per week** (Cornelius 2016; Hernandez-Avila 2004; 55 participants).
- Seven studies reported the **number of drinks per drinking days** (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003; Roy-Byrne 2000; 451 participants).
- Two studies reported the **number of drinks per week** (Cornelius 2016; Hernandez-Avila 2004; 55 participants).
- Five studies reported the **number of heavy drinking days per week** (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; 513 participants) or it was calculated by other outcomes reported by the studies.
- Seven studies reported the **number of heavy drinkers** (Gual 2003; Krupitsky 2012; Mason 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; 459 participants).
- Six studies reported the **time to the first relapse** in days (Cornelius 1997; Gual 2003; Krupitsky 2012; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; 393 participants) or it was calculated by other outcomes reported by the studies.

Liver enzyme levels

The studies included in the present meta-analysis did not report information on ALT and AST (see Primary outcomes). Two studies reported the **final levels of GGT** (Hernandez-Avila 2004; Krupitsky 2012; 101 participants) (see Appendix 8 and Appendix 9).

Three studies reported a **global response both in depression and in alcohol consumption** (Krupitsky 2012; McGrath 1996; Nunes 1993; 152 participants) (see Appendix 8 and Appendix 9).

Acceptability

Seventeen studies reported acceptability indicated by all-cause dropouts (see Primary outcomes) (Altamura 1990; Butterworth 1971b; Cornelius 2016; Gallant 1969 arm a; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1156 participants) (see Appendix 8; Appendix 9).

Tolerability

Several studies evaluated tolerability of the treatment as number and type of adverse events experienced during the treatment (see Primary outcomes) (see Appendix 8; Appendix 9). Among the different adverse events, the following were reported by at least two studies:

- Blurred vision evaluated by two studies (Butterworth 1971a; Roy-Byrne 2000; 103 participants).
- Constipation evaluated by four studies (Altintoprak 2008; Butterworth 1971a; Kranzler 2006 arm A; Roy-Byrne 2000; 336 participants).
- Depression evaluated by two studies (Kranzler 2006 arm A; Moak 2003; 413 participants).
- Diarrhoea evaluated by two studies (Gual 2003; Roy-Byrne 2000; 139 participants).
- Dizziness evaluated by three studies (Altintoprak 2008; Gual 2003; Roy-Byrne 2000; 183 participants).
- Dry mouth evaluated by five studies (Altintoprak 2008; Butterworth 1971a; Gallant 1969 arm a; Gallant 1969 arm b; Roy-Byrne 2000; 286 participants).
- Headache evaluated by three studies (Gual 2003; Kranzler 2006 arm A; Roy-Byrne 2000; 470 participants).
- Increase in body weight reported by two studies (Altintoprak 2008; Cornelius 2016; 58 participants).
- Insomnia evaluated by four studies (Adamson 2015; Butterworth 1971b; Kranzler 2006 arm A; Roy-Byrne 2000; 564 participants).
- Nausea evaluated by three studies (Adamson 2015; Gual 2003; Roy-Byrne 2000; 277 participants).
- Sedation evaluated by two studies (Altintoprak 2008; Roy-Byrne 2000; 108 participants).
- Total adverse effects evaluated by eight studies (Adamson 2015; Butterworth 1971b; Butterworth 1971a; Gallant 1969 arm a; Gallant 1969 arm b; Habrat 2006; Kranzler 2006 arm A; Krupitsky 2012; 1041 participants).
- Total serious adverse events evaluated by seven studies (Adamson 2015; Butterworth 1971b; Cornelius 2016; Kranzler 2006 arm A; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; 774 participants).
- Withdrawal for medical reasons evaluated by ten studies (Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Krupitsky 2012; Mason 1996; McGrath 1996; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 947 participants).
- Worsening of clinical condition because of relapse evaluated by two studies (Kranzler 2006 arm A; Moak 2003; 413 participants).

Suicide and suicide attempts

Five studies evaluated suicide and suicidal attempts (see Primary outcomes) (Adamson 2015; Cornelius 1997; Habrat 2006; Kranzler 2006 arm A; Moak 2003; 888 participants) (see Appendix 8; Appendix 9).

Secondary outcomes

- Participants with substance use disorders were excluded by most studies (see Characteristics of included studies table). Participants with substance use disorders were included by two studies (Adamson 2015; McGrath 1996; 83 participants). Two studies excluded participants with substance use disorders but included participants with abuse of other substances (Cornelius 1997; Roy-Byrne 2000; 87 participants).
- Four studies reported **craving** (see Secondary outcomes) (Altintoprak 2008; Cornelius 2016; Habrat 2006; Krupitsky 2012; 404 participants). They used different scales. One study used a questionnaire prepared by the authors (Altintoprak 2008; 44 participants). Three studies used the Obsessive-Compulsive Drinking Scale (OCDS) (Cornelius 2016; Habrat 2006; Krupitsky 2012; 360 participants) (see Appendix 8; Appendix 9). One study used different scales but data obtained only with the OCDS were used (Krupitsky 2012; 60 participants).
- Several studies reported **severity of alcohol dependence** (see Secondary outcomes) but as**baseline** characteristics of recruited participants (see Characteristics of included studies table; Appendix 9). Three studies reported **final** data on the **severity of alcohol dependence** (see Appendix 8) (Adamson 2015; Hernandez-Avila 2004; Muhonen 2008; 259 participants). Studies used different interviewer-rated scales: Alcohol Use Disorders Identification Test (AUDIT) (Muhonen 2008; 80 participants), DrInC (Hernandez-Avila 2004; 41 participants), and Leeds Dependence Questionnaire (LDQ) (Adamson 2015; 138 participants).
- Studies reported baseline characteristics of recruited participants for **psychiatric symptoms/psychological distress** (see Secondary outcomes; Characteristics of included studies table). Eleven studies reported **final score of anxiety severity** (Altintoprak 2008; Habrat 2006; Hernandez-Avila 2004; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Lôo 1988; Muhonen 2008; 761 participants). Studies used several scales: an interviewer-rated scale (see Appendix 8): Hamilton Anxiety Rating Scale (HRSA) (Habrat 2006; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Lôo 1988; Muhonen 2008; 615 participants), and three self-administered scales: Beck Anxiety Inventory (BAI) (Muhonen 2008; 80 participants), MMPI (Krupitsky 1993 arm A; Krupitsky 1993 arm B; 61 participants), and STAI (Altintoprak 2008; Hernandez-Avila 2004; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012; 206 participants).

Comparisons

- Antidepressants versus placebo: 22 studies (Adamson 2015; Altamura 1990; Butterworth 1971b; Cornelius 1997; Cornelius 2016; Gallant 1969 arm a; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 1993 arm A; Krupitsky 2012; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Nunes 1993; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1438 participants).
- Antidepressants versus psychotherapy: two studies (Liappas 2005 arm A; Liappas 2005 arm B; 60 participants) compared the efficacy of mirtazapine (Liappas 2005 arm A) or venlafaxine

(Liappas 2005 arm B) versus psychotherapy for three weeks. Both studies had a high risk of bias.

- Antidepressants versus other medications: four studies compared the efficacy of antidepressants to that of another medication (Butterworth 1971a; Gallant 1969 arm b; Krupitsky 1993 arm B; Muhonen 2008; 228 participants). Of these, one study compared amitriptyline to diazepam (Krupitsky 1993 arm B; 29 participants), two studies doxepin to diazepam (Butterworth 1971a; 39 participants; Gallant 1969 arm b; 71 participants), and one study escitalopram to memantine (Muhonen 2008; 80 participants). In this comparison, we included only the three studies comparing an antidepressant to diazepam (Butterworth 1971a; Gallant 1969 arm b; Krupitsky 1993 arm B; 148 participants). Only the final score of the severity of depression was reported by at least two of these studies.
- An antidepressant versus another antidepressant: five studies compared the efficacy of an antidepressant versus another antidepressant (Altintoprak 2008; Cocchi 1997; Habrat 2006; Liappas 2005 arm A; Lôo 1988; 621 participants). Of these, one study compared mirtazapine (up to 60 mg/day) to amitriptyline (up to 150 mg/day) for eight weeks (Altintoprak 2008; 44 participants); one study mirtazapine (up to 60 mg/day) to venlafaxine (up to 300 mg/day) for three weeks (Liappas 2005 arm A; 40 participants); one study paroxetine (20 mg/day) to amitriptyline (25 mg/day) for three to four weeks (Cocchi 1997; 122 participants); one study tianeptine (37.5 mg/day) to amitriptyline (75 mg/day) for four to eight weeks (Lôo 1988; 129 participants); and one study tianeptine (37.5 mg/day) to fluvoxamine (100 mg/day) for six weeks (Habrat 2006; 286 participants). As the same comparison was not made by more than one study, it was not possible to conduct any analyses.

Subgroup analysis

We conducted subgroup analyses **only for the comparison between antidepressants and placebo**.

- Twenty-two studies reported the **setting** (see Subgroup analysis and investigation of heterogeneity): 15 studies were conducted in an outpatient setting (Adamson 2015; Cornelius 2016; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; Moak 2003; Nunes 1993; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000; 1129 participants), four studies in inpatient setting (Butterworth 1971b; Gallant 1969 arm a; Krupitsky 1993 arm A; McLean 1986; 192 participants), and three studies initially in an inpatient setting and then as outpatients (Altamura 1990; Cornelius 1997; Roy 1998; 117 participants). We investigated the possible role of this confounder factor for each analysis.
- Sixteen studies reported the **use of a lower starting dose** (see Subgroup analysis and investigation of heterogeneity) (Adamson 2015; Butterworth 1971b; Cornelius 1997; Cornelius 2016; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000; 1172 participants). No study described a pattern of dose reduction. The possible protective role of a lower starting dose in reducing the risk of appearance of adverse events has not been investigated because there were no differences in number and types of adverse events between antidepressants and placebo.
- All studies reported the **duration of treatment** (see Subgroup analysis and investigation of heterogeneity): 19 studies had a duration of four weeks or greater (Adamson 2015; Altamura 1990; Cornelius 1997; Cornelius 2016; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Nunes 1993; Pettinati 2001aPettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1281 participants), and three studies had a duration of less than four weeks (Butterworth 1971b; Gallant 1969 arm a; Krupitsky 1993 arm A; 157 participants). We investigated the possible role of this confounder factor for each analysis.
- Fifteen studies evaluated **the severity of depression** at baseline using **an interviewer-rated scale** (Adamson 2015; Altamura 1990; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1180 participants). One of these studies used the MADRS (Adamson 2015; 138 participants); the other 14 studies used the HRSD (Altamura 1990; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1042 participants) (see Characteristics of included studies table). According to these values, in five studies, the severity of depression ranged from the absence of depression or mild depression to severe or very severe (Cornelius 1997; Gual 2003; Krupitsky 2012; Mason 1996; McGrath 1996; 291 participants); in other eight studies, the severity of depression ranged from moderate to severe or very severe (Adamson 2015; Hernandez-Avila 2004; Kranzler 2006 arm A; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 720 participants). Only one study included people with very severe depression (Altamura 1990; 30 participants), and another study with mild or moderate depression (Kranzler 2006 arm B; 139 participants). Accordingly, we did not evaluate this possible confounder factor.
- Studies were divided according to the **typology of depression**, into studies with primary depression and with depression induced by alcohol consumption. Eleven studies recruited participants with primary depression (Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Krupitsky 1993 arm A; McGrath 1996; Moak 2003; Nunes 1993; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998 arm A; Roy-Byrne 2000; 842 participants); three studies recruited participants with depression induced by alcohol consumption (Kranzler 2006 arm B; Mason 1996; Roy 1998 arm B; 188 participants). The other studies did not report typology of depression and we excluded them from these analyses).
- Three studies evaluated **the severity of alcohol dependence** at baseline using the number of positive diagnostic criteria (Cornelius 1997; Kranzler 2006 arm A; Kranzler 2006 arm B; 379 participants) (see Characteristics of included studies). One study used the DSM-III criteria and reported a baseline severity ranging from 3.9 to 7.7 positive criteria (Cornelius 1997; 51 participants); the other two studies used the DSM IV criteria and reported a baseline severity ranging from 3.4 to 6.4 (Kranzler 2006 arm A; Kranzler 2006 arm B; 328 participants). Accordingly, it was not feasible to evaluate this possible confounder factor.
- Twenty studies reported if **participants were actively drinking alcohol at the beginning of the trial** (see Subgroup

analysis and investigation of heterogeneity): in 12 studies, participants were actively drinking (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000; 986 participants) and in eight studies, participants were not actively drinking (Butterworth 1971b; Gual 2003; Krupitsky 1993 arm A; Krupitsky 2012; Mason 1996; McLean 1986; Nunes 1993; Roy 1998; 346 participants). The other studies did not report this information. We investigated the possible role of this confounder factor for each analysis.

- Nine studies reported the **length of abstinence** (see Subgroup analysis and investigation of heterogeneity) (Butterworth 1971b; Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 1993 arm A; Krupitsky 2012; Mason 1996; Nunes 1993; Roy 1998; 639 participants). Its possible confounder role has not been evaluated because it ranged from a minimum of few days (Butterworth 1971b) to a maximum of 12 weeks (Nunes 1993), also within the same study (Mason 1996).
- Fourteen studies used the **presence of other psychiatric disorders, including bipolar disorder** as an exclusion criterion (see Subgroup analysis and investigation of heterogeneity) (Adamson 2015; Butterworth 1971b; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998). The majority of the other studies did not report information on possible comorbid psychiatric disorders. Accordingly, it was not feasible to evaluate this possible confounder factor.
- Three studies allowed the **use of other pharmacological treatments** (see Subgroup analysis and investigation of heterogeneity) (Adamson 2015; Butterworth 1971b; McLean 1986). The low number of studies precluded the possibility to evaluate this possible confounder factor.
- Fifteen studies offered a**psychosocial treatment** to participants (see Subgroup analysis and investigation of heterogeneity and Appendix 10) (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000; 1109 participants). Two studies did not offer a psychosocial treatment to participants (Butterworth 1971b; Krupitsky 1993 arm A; 81 participants), whereas the other studies did not provide information on this issue. We investigated the possible role of this confounder factor for each analysis.

Excluded studies

We excluded 55 published articles for the following reasons: the study design did not meet the inclusion criteria (26 studies); the study relied on the same database as used in another (not included trial; one study); the study population did not meet the inclusion criteria (23 studies); and there was a lack of information (five studies). For details, see Characteristics of excluded studies table.

Risk of bias in included studies

All 33 studies were RCTs.

Allocation

We judged the random sequence generation adequately prevented (i.e. there was a low risk of bias) in 14 studies. For the remaining 19 studies, the risk of selection bias was unclear. There was no study in which the random sequence generation was inadequate (i.e. there was a high risk of bias).

Nine studies had adequately prevented (low risk) allocation concealment. In the other 24 studies, the details provided did not allow a specific evaluation of the procedures adopted to prevent participants and investigators from foreseeing the assignment.

Blinding

We judged the blinding of participants and personnel (performance bias) as low risk in 15 studies, as high risk in seven studies, and as unclear risk in the remaining 11 studies.

We judged the blinding of outcome assessment (detection bias; objective outcomes) as low risk in all 33 studies, whereas blinding of outcome assessment (detection bias; subjective outcomes) was at low risk in two studies, at high risk in six studies, and as unclear risk in the remaining 25 studies.

Incomplete outcome data

The risk of incomplete outcome data (attrition bias) was at low risk in 15 studies, at high risk in 13 studies, and at unclear risk in the remaining five studies.

Selective reporting

We judged missing data on at low risk in 13 studies, high risk in nine studies, and as having unclear risk in the other 11 studies.

For all se Figure 2; Figure 3

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

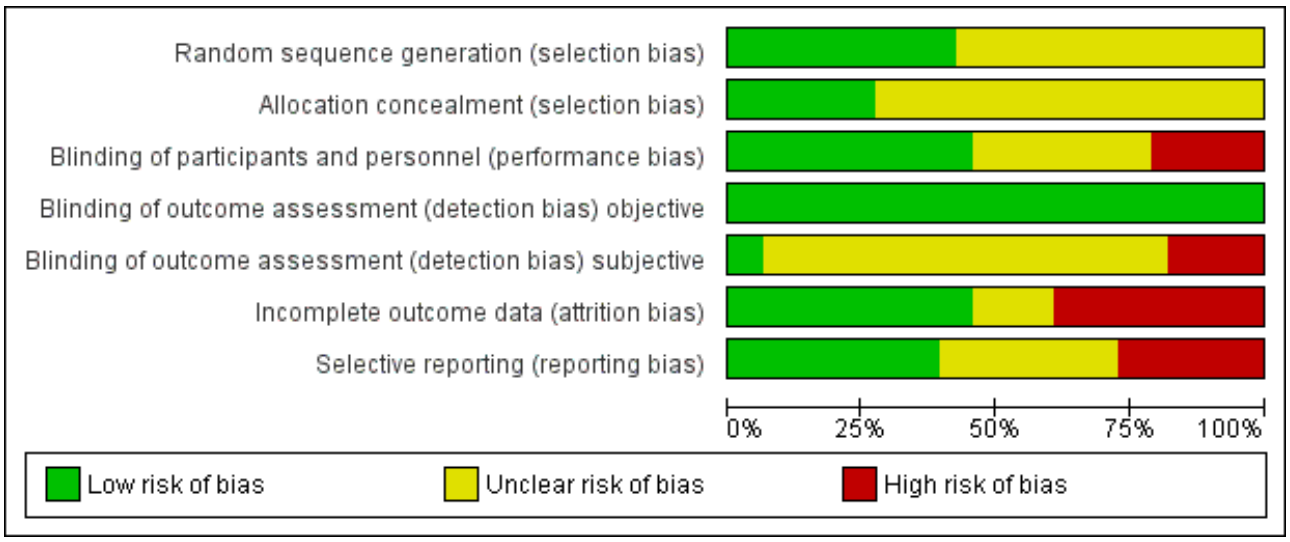


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

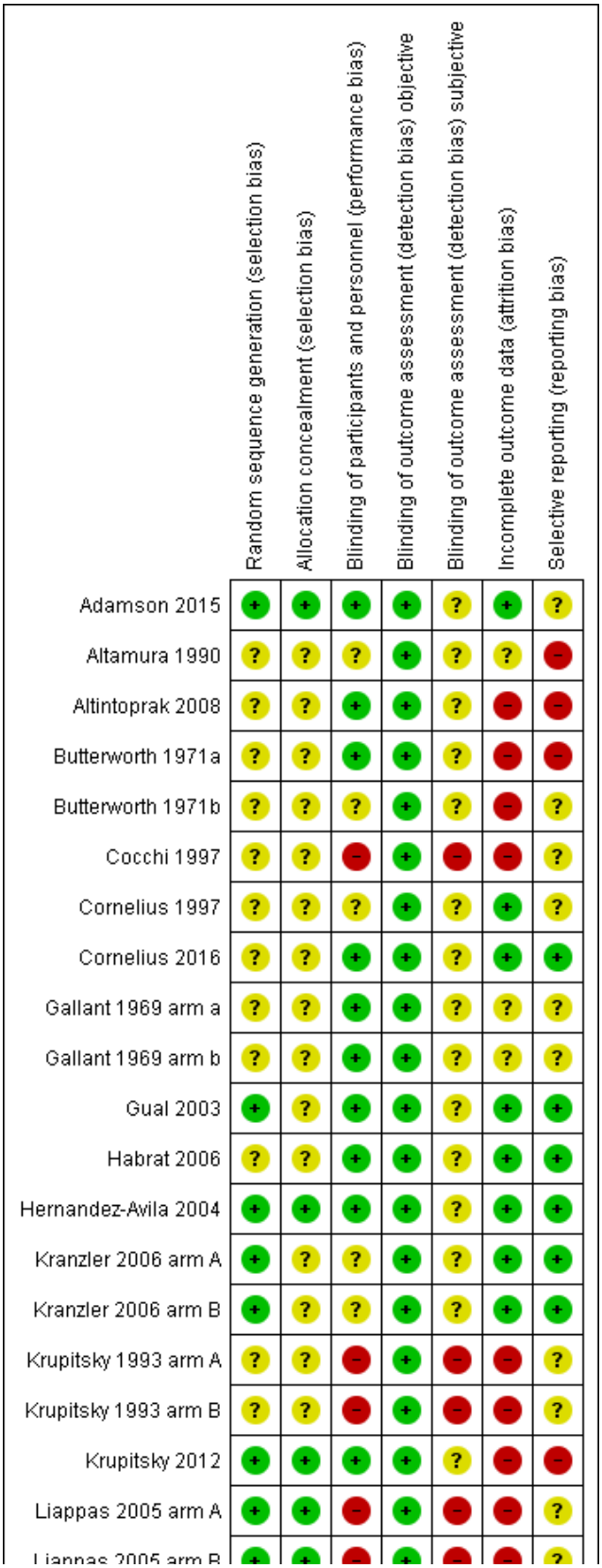
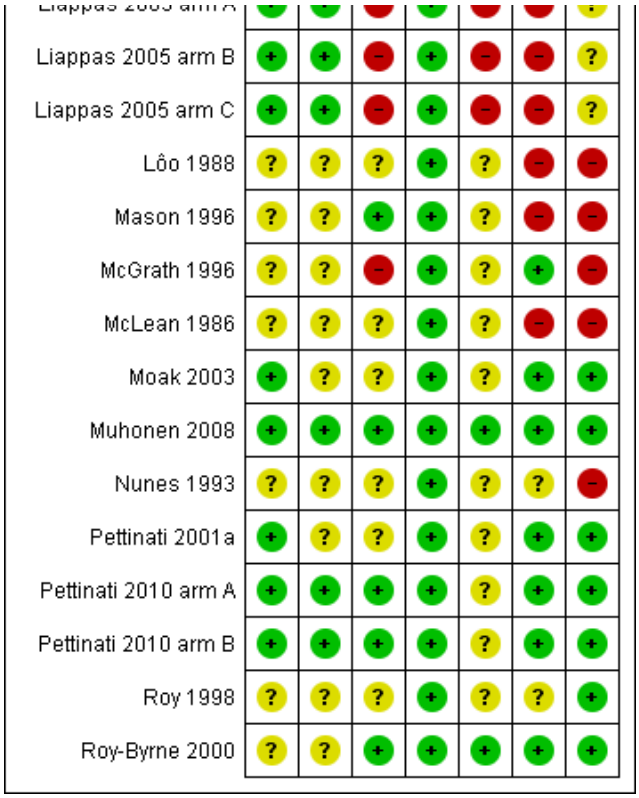


Figure 3. (Continued)



Effects of interventions

See: **Summary of findings for the main comparison** Antidepressants compared to placebo: all studies for the treatment of people with co-occurring depression and alcohol consumption

We compared quantitative data where at least two of the included studies reported the same outcome measures (see Appendix 8; Appendix 9). For some outcomes, it was impossible to pool data due to variations in the reporting of results, for instance different rating methods and the fact that authors did not identify the data required to proceed with the meta-analysis. If there was significant heterogeneity, the results of the comparisons were first reported by including all studies, and thereafter by excluding studies with high risk of bias in one or more domains.

Antidepressants versus placebo

Primary outcome: depression severity

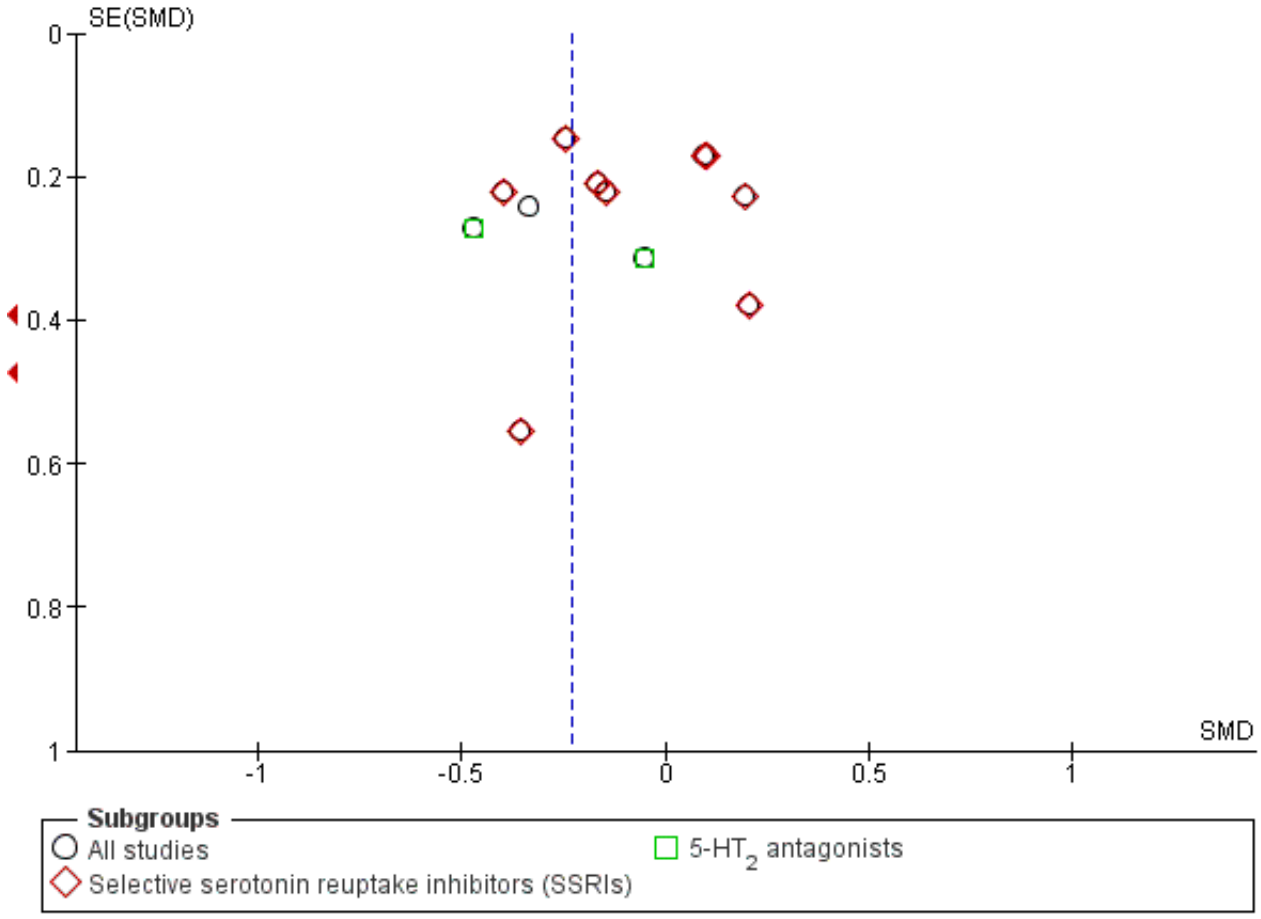
Final score (interviewer-rated scales)

The studies used different interviewer-rated scales, therefore, we used SMDs (see Appendix 8; Appendix 9). Two studies reported data of two interviewer-rated scales (MADRS and HRSD) and we included only data obtained using HRSD (Gual 2003; Krupitsky 2012).

All studies

The analysis found low-quality evidence of a significantly lower final score among participants treated with antidepressants compared to placebo (P = 0.02), with substantial evidence of heterogeneity (14 studies; 1074 participants; SMD -0.27, 95% CI -0.49 to -0.04; $Tau^2 = 0.11$; $Chi^2 = 39.01$, degrees of freedom (df) = 13 (P = 0.0002); $I^2 = 67\%$; Analysis 1.1; Summary of findings for the main comparison; Figure 4) (Adamson 2015; Altamura 1990; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000).

Figure 4. Funnel plot of comparison: 1 Antidepressants versus placebo: all studies, outcome: 1.1 Depression severity: final score (interviewer-rated scales).



Different classes of antidepressants and single antidepressant

The subgroup analyses found no differences in final score between SSRIs and placebo (10 studies; 881 participants; Analysis 1.1; Figure 4) (Adamson 2015; Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998), and 5-HT_2 antagonists and placebo (2 studies; 97 participants; Analysis 1.1; Figure 4) (Hernandez-Avila 2004; Roy-Byrne 2000).

There were no differences in final score between sertraline and placebo (8 studies; 728 participants; analysis not shown) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998) and nefazodone and placebo (2 studies; 97 participants ; analysis not shown) (Hernandez-Avila 2004; Roy-Byrne 2000).

Confounder factors

The analyses found a significantly lower final score for antidepressants among the studies with a duration four weeks or greater (P = 0.02), with substantial evidence of heterogeneity (14 studies; 1074 participants; SMD -0.27, 95% CI -0.49 to -0.04; Tau^2 = 0.11; Chi^2 = 39.01, df = 13 (P = 0.0002); I^2 = 67%; Analysis 1.1) (Adamson 2015; Altamura 1990; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000).

There was a significantly lower final score for antidepressants among the studies conducted in inpatient and outpatient settings (P < 0.00001) (2 studies; 63 participants; SMD -1.74, 95% CI -2.33 to -1.15) (Altamura 1990; Roy 1998). One of the studies had a high risk of bias (Altamura 1990).

There were no differences in final score between antidepressants and placebo among the studies:

- without high risk of bias (11 studies; 963 participants) (Adamson 2015; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000);
- conducted in an outpatient setting (12 studies; 1011 participants; SMD -0.11, 95% CI -0.24 to 0.01), with no evidence of heterogeneity (Adamson 2015; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000);
- with primary depression (8 studies; 719 participants; SMD -0.14, 95% CI -0.28 to 0.01), with no evidence of heterogeneity (Adamson 2015; Kranzler 2006 arm A; McGrath 1996; Moak 2003;

Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998 arm A; Roy-Byrne 2000);
- with secondary depression (2 studies; 160 participants) (Kranzler 2006 arm B; Roy 1998 arm B);
- with participants who were actively drinking at the beginning of the trial (10 studies; 913 participants) (Adamson 2015; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000);
- with participants who were not actively drinking at the beginning of the trial, with substantial evidence of heterogeneity (3 studies; 134 participants; SMD -0.80, 95% CI -1.65 to 0.005; $Tau^2 = 0.42$; $Chi^2 = 8.08$, df = 2 (P = 0.02); $I^2 = 75\%$) (Gual 2003; Krupitsky 2012; Roy 1998); and
- with psychotherapy (11 studies; 928 participants) (Adamson 2015; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; McGrath 1996; Moak 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000).

Final score (self-administered scales)

The studies used different interviewer-rated scales, therefore, we used SMDs. One study reported data obtained using the MMPI and ZUNG and we included only data obtained with ZUNG (Krupitsky 1993 arm A; 41 participants).

All studies

The analysis found no significant difference in final score between antidepressants and placebo with substantial evidence of heterogeneity (8 studies; 373 participants; SMD -0.29, 95% CI -0.64 to 0.07; $Tau^2 = 0.13$; $Chi^2 = 15.94$, df = 7 (P = 0.03); $I^2 = 56\%$; Analysis 1.2) (Adamson 2015; Cornelius 2016; Krupitsky 1993 arm A; Krupitsky 2012; McLean 1986; Moak 2003; Pettinati 2001a; Roy 1998).

Different classes of antidepressants and single antidepressant

The subgroup analyses found no difference in final score between SSRIs and placebo (5 studies; 300 participants; Analysis 1.2) (Adamson 2015; Krupitsky 2012; Moak 2003; Pettinati 2001a; Roy 1998), and 5-HT_2 antagonists and placebo (2 studies; 41 participants; Analysis 1.2) (Cornelius 2016; McLean 1986). There were no other comparisons with at least two studies.

There were no differences in final score between sertraline and placebo (3 studies; 147 participants; analysis not shown) (Moak 2003; Pettinati 2001a; Roy 1998). There were no other comparisons with at least two studies.

Confounder factors

There were no differences in final score between antidepressants and placebo among the studies:

- without high risk of bias (5 studies; 299 participants) (Adamson 2015; Cornelius 2016; Moak 2003; Pettinati 2001a; Roy 1998);
- with a duration of four weeks or greater (6 studies; 259 participants) (Adamson 2015; Cornelius 2016; Krupitsky 2012; McLean 1986; Pettinati 2001a; Roy 1998);
- conducted in an outpatient setting (5 studies; 278 participants) (Adamson 2015; Cornelius 2016; Krupitsky 2012; Moak 2003; Pettinati 2001a);
- conducted in an inpatient setting (2 studies; 59 participants) (Krupitsky 1993 arm A; McLean 1986);
- in which participants were actively drinking at the beginning of the trial (4 studies; 263 participants) (Adamson 2015; Cornelius 2016; Moak 2003; Pettinati 2001a);
- with participants who were not actively drinking at the beginning of the trial (4 studies; 110 participants) (Krupitsky 1993 arm A; Krupitsky 2012; McLean 1986; Roy 1998);
- with primary depression (4 studies; 267 participants) (Adamson 2015; Krupitsky 1993 arm A; Moak 2003; Roy 1998); and
- with psychotherapy (6 studies; 305 participants) (Adamson 2015; Cornelius 2016; Krupitsky 2012; McLean 1986; Moak 2003; Pettinati 2001a). Analyses not shown.

Differences between baseline and final score (interviewer-rated scales)

The studies used different interviewer-rated scales, therefore, we used SMDs.

All studies

The analysis found no difference between antidepressants and placebo, with no evidence of heterogeneity (5 studies; 447 participants; SMD 0.15, 95% CI -0.12 to 0.42; Analysis 1.3) (Butterworth 1971b; Cornelius 1997; Kranzler 2006 arm A; Kranzler 2006 arm B; Pettinati 2001a).

Different classes of antidepressants and single antidepressant

There were no differences between SSRIs and placebo (4 studies; 408 participants; Analysis 1.3) (Cornelius 1997; Kranzler 2006 arm A; Kranzler 2006 arm B; Pettinati 2001a), and sertraline and placebo (3 studies; 357 participants; Analysis 1.3) (Kranzler 2006 arm A; Kranzler 2006 arm B; Pettinati 2001a).

Confounder factors

There were no differences between antidepressants and placebo when other possible confounder factors were examined (high risk of bias, duration of study, typology of depression, typology of setting, being actively drinking at the beginning of the study, and receiving psychotherapy) (analyses not shown).

Differences between baseline and final score (self-administered scales)

The studies used different interviewer-rated scales, therefore, we used SMDs.

All studies

The analysis found no difference between antidepressants and placebo, with no evidence of heterogeneity (4 studies; 121 participants; SMD 0.20, 95% CI -0.16 to 0.56; Analysis 1.4) (Cornelius 1997; Cornelius 2016; McLean 1986; Pettinati 2001a).

Different classes of antidepressants and single antidepressants

There was no difference between SSRIs and placebo (2 studies; 80 participants; Analysis 1.4) (Cornelius 1997; Pettinati 2001a), and 5-HT_2 antagonists and placebo (2 studies; 41 participants; Analysis 1.4) (Cornelius 2016; McLean 1986).

Confounder factors

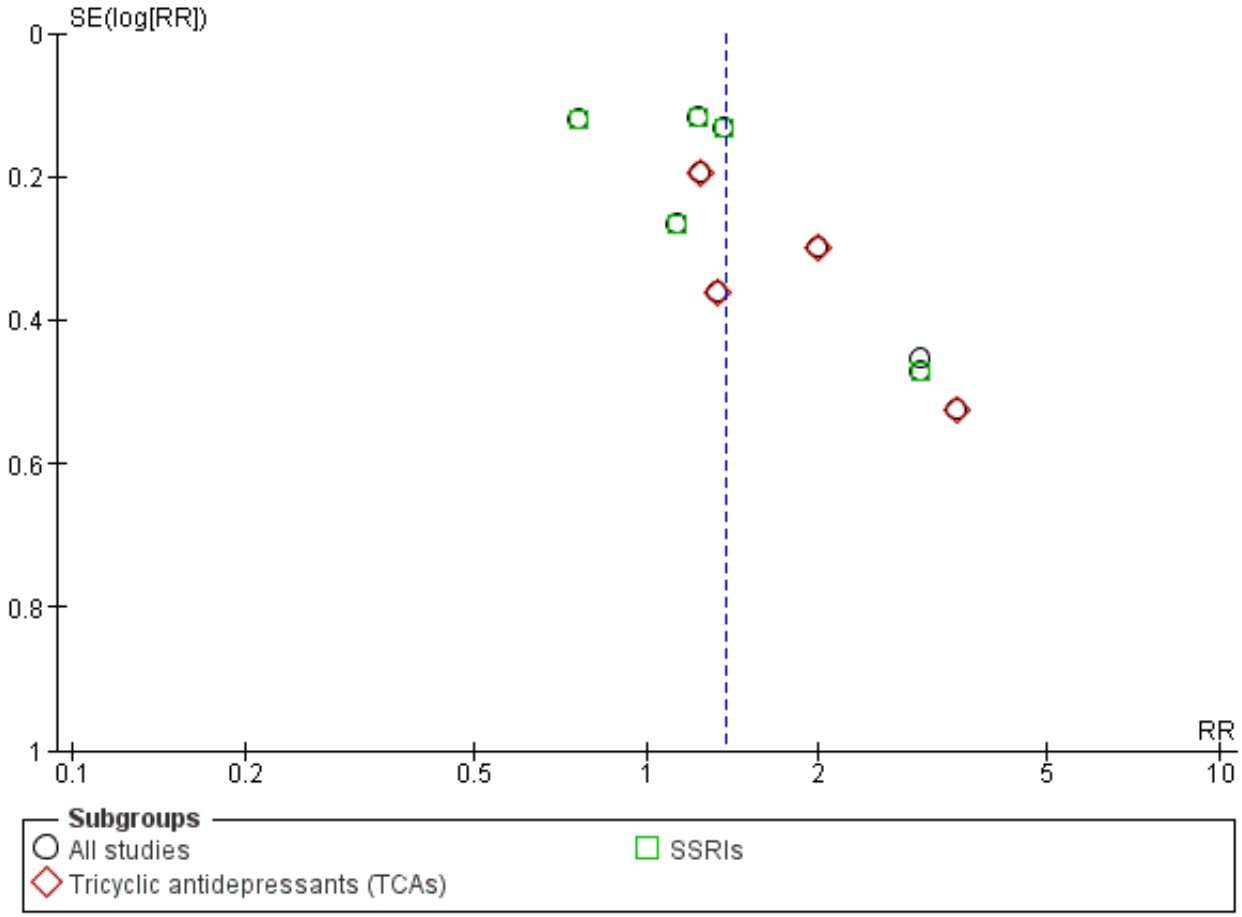
The analyses found no differences between antidepressants and placebo when possible confounder factors were examined (high risk of bias, duration of study, typology of depression, typology of setting, being actively drinking at the beginning of the study, and receiving psychotherapy) (analyses not shown).

Primary outcome: response to antidepressive treatment

All studies

The analysis found very low-quality evidence of a significantly higher number of responses among participants who received antidepressants than placebo (P = 0.01), with substantial evidence of heterogeneity (10 studies; 805 participants; RR 1.40, 95% CI 1.08 to 1.82; Tau^2 = 0.10; Chi^2 = 31.63, df = 9 (P = 0.0002); I^2 = 72%; Analysis 1.5; Summary of findings for the main comparison; Figure 5) (Butterworth 1971b; Gallant 1969 arm a; Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Roy 1998; Roy-Byrne 2000).

Figure 5. Funnel plot of comparison: 1 Antidepressants versus placebo: all studies, outcome: 1.5 Response to antidepressive treatment.



Different classes of antidepressants and single antidepressant

For the subgroup analyses, the analysis found a significantly higher number of responses among participants who received TCAs compared to placebo (P = 0.02), with no evidence of heterogeneity (4 studies; 212 participants; RR 1.60, 95% CI 1.09 to 2.34; Analysis 1.5; Figure 5) (Butterworth 1971b; Gallant 1969 arm a; Mason 1996; McGrath 1996). However, three of these four studies had a high risk of bias. There were no differences in the number of responses between SSRIs and placebo, with substantial evidence of heterogeneity (5 studies; 529 participants; RR 1.19, 95% CI 0.87 to 1.63; Tau^2 = 0.09; Chi^2 = 17.60, df = 4 (P = 0.001); I^2 = 77%; Analysis 1.5; Figure 5) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Roy 1998).

There was a significantly higher number of responses among participants who received imipramine (P = 0.02), with no evidence of heterogeneity (2 studies; 108 participants; RR 1.68, 95% CI 1.07 to 2.63; analysis not shown) (Butterworth 1971b; McGrath 1996). Both these studies had a high risk of bias. There was no difference between sertraline and placebo in the number of responses, with substantial evidence of heterogeneity (5 studies; 529 participants; RR 1.19, 95% CI 0.87 to 1.63; Tau^2 = 0.09; Chi^2 = 17.60, df = 4 (P

= 0.001); I^2 = 77%; Analysis 1.5) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Roy 1998).

Confounder factors

The analysis found a significantly higher number of responses among participants who received antidepressants among the studies: with a duration of four weeks or greater (P = 0.04), with significant evidence of heterogeneity (8 studies; 690 participants; RR 1.40, 95% CI 1.02 to 1.91; Tau^2 = 0.12; Chi^2 = 28.51, df = 7 (P = 0.0002); I^2 = 75%) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Roy 1998; Roy-Byrne 2000); and with primary depression (P = 0.007), with no evidence of heterogeneity (4 studies; 404 participants; RR 1.36, 95% CI 1.09 to 1.70) (Kranzler 2006 arm A; McGrath 1996; Moak 2003; Roy-Byrne 2000). One of these studies had a high risk of bias (McGrath 1996). However, the analysis found a significantly higher number of responses among participants who received antidepressants also after the exclusion of this study (P = 0.02), with no evidence of heterogeneity (3 studies; 335 participants; RR 1.40, 95% CI 1.05 to 1.87) (Kranzler 2006 arm A; Moak 2003; Roy-Byrne 2000).

There were no differences between antidepressants and placebo in the number of responses among the studies:

- without high risk of bias, with substantial evidence of heterogeneity (7 studies; 669 participants; RR 1.27, 95% CI 0.96 to 1.68; Tau^2 = 0.09; Chi^2 = 23.20, df = 6 (P = 0.0007); I^2 = 74%) (Gallant 1969 arm a; Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Roy 1998; Roy-Byrne 2000);
- conducted in an outpatient setting, with substantial evidence of heterogeneity (7 studies; 654 participants; RR 1.30, 95% CI 0.96 to 1.76; Tau^2 = 0.10; Chi^2 = 23.69, df = 6 (P = 0.0006); I^2 = 75%) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Roy-Byrne 2000);
- conducted an inpatient setting (2 studies; 115 participants; RR 1.48, 95% CI 0.94 to 2.32), with no evidence of heterogeneity (Butterworth 1971b; Gallant 1969 arm a);
- with a duration less than four weeks (P = 0.09), with no evidence of heterogeneity (2 studies; 115 participants; RR 1.48, 95% CI 0.94 to 2.32) (Butterworth 1971b; Gallant 1969 arm a); and
- in which participants received psychotherapy, with substantial evidence of heterogeneity (6 studies; 571 participants; RR 1.35, 95% CI 0.95 to 1.92; Tau^2 = 0.12; Chi^2 = 23.85, df = 5 (P = 0.0002); I^2 = 79%) (Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Roy-Byrne 2000);
- in which participants were actively drinking at the beginning of the trial (5 studies; 543 participants; RR 1.23, 95% CI 0.88 to 1.72) (Kranzler 2006 arm A; Kranzler 2006 arm B; McGrath 1996; Moak 2003; Roy-Byrne 2000); and
- in which participants were not actively drinking at the beginning of the trial (2 studies; 111 participants; RR 1.81, 95% CI 0.60 to 5.45) (Gual 2003; Mason 1996). Analyses not shown.

Primary outcome: full remission of depression

All studies

The analysis found no significant difference in the number of remissions between antidepressants and placebo, with a substantial evidence of heterogeneity (4 studies; 372 participants; RR 1.19, 95% CI 0.77 to 1.83; Tau^2 = 0.12; Chi^2 = 8.82, df = 3 (P = 0.03); I^2 = 66%; Analysis 1.6) (Adamson 2015; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000).

Different classes of antidepressants and single antidepressant

There was no difference in the number of remissions between SSRIs and placebo, with no evidence of heterogeneity (3 studies; 308 participants; RR 1.00, 95% CI 0.74 to 1.36; Tau^2 = 0.03; Chi^2 = 3.10, df = 2 (P = 0.21); I^2 = 35%; Analysis 1.6) (Adamson 2015; Pettinati 2010 arm A; Pettinati 2010 arm B).

There was no difference in the number of remissions between sertraline and placebo, with no evidence of heterogeneity (2 studies; 170 participants; RR 1.18, 95% CI 0.83 to 1.67; Tau^2 = 0.00; Chi^2 = 1.07, df = 1 (P = 0.30); I^2 = 7%; analysis not shown) (Pettinati 2010 arm A; Pettinati 2010 arm B).

Confounder factors

All the studies (4 studies; 372 participants; RR 1.19, 95% CI 0.77 to 1.83; Tau^2 = 0.12; Chi^2 = 8.82, df = 3 (P = 0.03); I^2 = 66%; Analysis 1.6) were without high risk of bias, with a duration of four weeks or greater, conducted in an outpatient setting, with primary depression, with participants who were not actively drinking at the beginning of the trial, and with psychotherapy (Adamson 2015; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000).

Primary outcome: consumption of alcohol

Abstinent days (%)

All studies

There was low-quality evidence that the rate of abstinent days did not differ between antidepressants and placebo (9 studies; 821 participants; MD 1.34%, 95% CI -1.66% to 4.34%; Analysis 1.7; Summary of findings for the main comparison) (Adamson 2015; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; McGrath 1996; Moak 2003; Pettinati 2001a).

For the five studies where the SDs were not available (Cornelius 1997; Gual 2003; Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a), we imputed SDs using the mean value of SD calculated from the other four studies (Adamson 2015; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003). Sensitivity analysis, excluding studies without SDs, showed no evidence of difference between antidepressants and placebo (MD -1.37 abstinent days, 95% CI -3.96 to 1.21).

Different classes of antidepressants and single antidepressant

There were no differences in the rate of abstinent days between SSRIs and placebo (7 studies; 711 participants; analysis not shown) (Adamson 2015; Cornelius 1997; Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Pettinati 2001a), and sertraline and placebo (5 studies; 522 participants; analysis not shown) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Pettinati 2001a).

Confounder factors

The rate of abstinent days did not differ between antidepressants and placebo when possible confounder factors were examined. Analysis not shown.

Abstinent participants

All studies

The analysis found moderate-quality evidence of a higher number of abstinents among participants who received antidepressants than placebo (P = 0.002), with no evidence of heterogeneity (7 studies; 424 participants; RR 1.71, 95% CI 1.22 to 2.39; Analysis 1.8; Summary of findings for the main comparison) (Cornelius 1997; Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000).

Different classes of antidepressants and single antidepressant

The analyses found a higher number of abstinents among participants who received SSRIs (P = 0.04), with no evidence of heterogeneity (4 studies; 250 participants; RR 1.66, 95% CI 1.02 to 2.68; Analysis 1.8) (Cornelius 1997; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B). There were no differences in the number of abstinents between 5-HT_2 antagonists and placebo (2 studies; 105 participants; Analysis 1.8) (Hernandez-Avila 2004; Roy-Byrne 2000).

There were no differences in the number of abstinents between sertraline and placebo (3 studies; 199 participants; analysis not shown) (Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B), and nefazodone and placebo (2 studies; 105 participants; analysis not shown) (Hernandez-Avila 2004; Roy-Byrne 2000).

Confounder factors

The analyses found a higher number of abstinents among participants treated with antidepressants among the studies:

- without high risk of bias (P = 0.005), with no evidence of heterogeneity (6 studies; 355 participants; RR 1.69, 95% CI 1.18 to 2.43) (Cornelius 1997; Hernandez-Avila 2004; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000);
- with a duration of four weeks or greater (P = 0.002), with no evidence of heterogeneity (7 studies; 424 participants; RR 1.71, 95% CI 1.22 to 2.39) (Cornelius 1997; Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000);
- with primary depression (P = 0.002), with no evidence of heterogeneity (5 studies; 354 participants; RR 1.78, 95% CI 1.24 to 2.55) (Cornelius 1997; McGrath 1996; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000);
- conducted in an outpatient setting (P = 0.003), with no evidence of heterogeneity (6 studies; 373 participants; RR 1.70, 95% CI 1.20 to 2.41) (Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000);
- with participants who were actively drinking at the beginning of the trial (P = 0.002), with no evidence of heterogeneity (7 studies; 424 participants; RR 1.71, 95% CI 1.22 to 2.39) (Cornelius 1997; Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000); and
- with psychotherapy (P = 0.002), with no evidence of heterogeneity (7 studies; 424 participants; RR 1.71, 95% CI 1.22 to 2.39) (Cornelius 1997; Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000). Analyses not shown.

Drinking days (per week)

All studies

The analysis found no difference between antidepressants and placebo, with no evidence of heterogeneity (2 studies; 55 participants; MD -1.15 days/week, 95% CI -2.35 to 0.05; Analysis 1.9) (Cornelius 2016; Hernandez-Avila 2004).

Different classes of antidepressants and single antidepressant

The analysis found no difference between 5-HT_2 antagonists and placebo, with no evidence of heterogeneity (2 studies; 55 participants; MD -1.15 days/week, 95% CI -2.35 to 0.05) (Cornelius 2016; Hernandez-Avila 2004).

Confounder factors

There were no differences between antidepressants and placebo in the number of drinking days per week when possible confounder factors were examined (analyses not shown).

Drinks (per drinking day)

All studies

The analysis found moderate-quality evidence of a significantly lower number of drinks per drinking days among participants who received antidepressants compared to placebo (P = 0.0009), with no evidence of heterogeneity (7 studies; 451 participants; MD -1.13 drinks/drinking day, 95% CI -1.79 to -0.46; Analysis 1.10; Summary of findings for the main comparison) (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003; Roy-Byrne 2000).

Different classes of antidepressants and single antidepressant

The analysis found a significantly lower number of drinks per drinking days among participants who received SSRIs (P = 0.02) (3 studies; 271 participants; MD -1.42 drinks/drinking day, 95% CI -2.58 to -0.26; Analysis 1.10) (Adamson 2015; Cornelius 1997; Moak 2003), and 5-HT_2 antagonists (P = 0.03) (3 studies; 111 participants; MD -1.06 drinks/drinking day, 95% CI -2.00 to -0.11; Analysis 1.10) (Cornelius 2016; Hernandez-Avila 2004; Roy-Byrne 2000). The number of drinks per drinking days did not differ between nefazodone and placebo, with no evidence of heterogeneity (2 studies; 97 participants; MD -1.14 drinks/drinking day, 95% CI -2.30 to 0.03; analysis not shown) (Hernandez-Avila 2004; Roy-Byrne 2000).

Confounder factors

The analysis found a significantly lower number of drinks per drinking days among participants treated with antidepressants among the studies:

- without high risk of bias (P = 0.0007), with no evidence of heterogeneity (6 studies; 382 participants; MD -1.21 drinks/drinking day, 95% CI -1.91 to -0.51) (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; Moak 2003; Roy-Byrne 2000);
- with a duration of four weeks or longer (P = 0.006), with no evidence of heterogeneity (6 studies; 400 participants; MD -0.97 drinks/drinking day, 95% CI -1.66 to -0.28) (Adamson 2015; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003; Roy-Byrne 2000);

- with primary depression (P = 0.005), with no evidence of heterogeneity (5 studies; 396 participants; MD -1.20 drinks/drinking day, 95% CI -2.03 to -0.36) (Adamson 2015; Cornelius 1997; McGrath 1996; Moak 2003; Roy-Byrne 2000);
- conducted in an outpatient setting (P = 0.006), with no evidence of heterogeneity (6 studies; 400 participants; MD -0.97 drinks/drinking day, 95% CI -1.66 to -0.28) (Adamson 2015; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003; Roy-Byrne 2000);
- with participants who were actively drinking at the beginning of the trial (P = 0.009), with no evidence of heterogeneity (7 studies; 451 participants; MD -1.13 drinks/drinking day, 95% CI -1.79 to -0.46) (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003; Roy-Byrne 2000); and
- with psychotherapy (P = 0.002), with no evidence of heterogeneity (6 studies; 395 participants; MD -1.12 drinks/drinking day, 95% CI -1.83 to -0.41) (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003). Analyses not shown.

Drinks (per week)

All studies

The analysis found no difference between antidepressants and placebo, with no evidence of heterogeneity (2 studies; 55 participants; MD -5.06 drinks/week, 95% CI -12.30 to 2.18; Analysis 1.11) (Cornelius 2016; Hernandez-Avila 2004).

Different classes of antidepressants and single antidepressant

The analysis found no difference between 5-HT_2 antagonists and placebo, with no evidence of heterogeneity (2 studies; 55 participants; Analysis 1.11) (Cornelius 2016; Hernandez-Avila 2004).

Confounder factors

There were no differences between antidepressants and placebo in the number of drinks per week when possible confounder factors were examined (analyses not shown).

Heavy drinking days (per week)

All studies

The analysis found no difference between antidepressants and placebo, with substantial evidence of heterogeneity (5 studies; 313 participants; MD -0.33 heavy drinking days/week, 95% CI -0.85 to 0.20; $Tau^2 = 0.25$; $Chi^2 = 15.22$, df = 4 (P = 0.004); $I^2 = 74\%$; Analysis 1.12) (Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996). Because the SDs were not available for three studies, we used the mean of the SDs of the other studies.

Different classes of antidepressants and single antidepressant

The analysis found no difference between SSRIs and placebo (2 studies; 189 participants; MD -0.41 heavy drinking days/week, 95% CI -1.09 to 0.27; Analysis 1.12) (Adamson 2015; Cornelius 1997), and 5-HT_2 antagonists and placebo (2 studies; 55 participants; MD -0.43 heavy drinking days/week, 95% CI -2.09 to 1.22; Analysis 1.12) (Cornelius 2016; Hernandez-Avila 2004).

Confounder factors

There were no differences between antidepressants and placebo when possible confounder factors were examined (analyses not shown).

Heavy drinkers

All studies

The analysis found no difference between antidepressants and placebo in the number of heavy drinkers, with substantial evidence of heterogeneity (7 studies; 459 participants; RR 0.78, 95% CI 0.57 to 1.07; $Tau^2 = 0.09$; $Chi^2 = 15.49$, df = 6 (P = 0.02); $I^2 = 61\%$; Analysis 1.13) (Gual 2003; Krupitsky 2012; Mason 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998).

Different classes of antidepressants and single antidepressant

The analysis found no difference in the number of heavy drinkers between SSRIs and placebo (6 studies; 431 participants; RR 0.87, 95% CI 0.69 to 1.11; Analysis 1.13) (Gual 2003; Krupitsky 2012; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998), and sertraline and placebo (5 studies; 371 participants; RR 0.94, 95% CI 0.78 to 1.13; analysis not shown) (Gual 2003; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998).

Confounder factors

There were no differences between antidepressants and placebo when possible confounder factors were examined (analyses not shown).

Time to first relapse (days)

All studies

The analysis found no difference between antidepressants and placebo in the time to the first relapse, with substantial evidence of heterogeneity (6 studies; 348 participants; MD 2.54 days, 95% CI -8.79 to 13.87; $Tau^2 = 102.26$; $Chi^2 = 13.58$, df = 5 (P = 0.02); $I^2 = 63\%$; Analysis 1.14) (Cornelius 1997; Gual 2003; Krupitsky 2012; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B).

Different classes of antidepressants and single antidepressant

The analysis found no difference between SSRIs and placebo (6 studies; 348 participants; MD 2.54 days, 95% CI -8.79 to 13.87; Analysis 1.14) (Cornelius 1997; Gual 2003; Krupitsky 2012; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B), and sertraline and placebo (4 studies; 282 participants; MD 0.70, 95% CI -12.67 to 14.08; analysis not shown) (Gual 2003; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B).

Confounder factors

There were no differences between antidepressants and placebo when the possible confounder factors were examined (analyses not shown).

Primary outcome: liver enzyme levels

GGT

All studies

There was no evidence of a difference between antidepressants and placebo (2 studies; 56 participants; MD -8.39 U/L, 95% CI -26.47 to 9.68; Analysis 1.15) (Hernandez-Avila 2004; Krupitsky 2012).

Different classes of antidepressants and single antidepressant

Final levels of GGT were not available for more than one study for any analysis.

Confounder factors

There were no differences between antidepressants and placebo in the final levels of GGT when the possible confounder factors were examined (analyses not shown).

Global response (depression and alcohol consumption)

All studies

The analysis found a higher number of global responses among participants treated with antidepressants than placebo (P = 0.003), with no evidence of heterogeneity (3 studies; 152 participants; RR 2.37, 95% CI 1.34 to 4.19; Analysis 1.16) (Krupitsky 2012; McGrath 1996; Nunes 1993). However, all the three studies had a high risk of bias.

Different classes of antidepressants and single antidepressant

There was a higher number of global responses among participants treated with TCAs compared to placebo (P = 0.03) (2 studies; 92 participants; RR 2.09, 95% CI 1.09 to 4.02; Analysis 1.16) (McGrath 1996; Nunes 1993), and imipramine compared to placebo (P = 0.03) (2 studies; 92 participants; RR 2.09, 95% CI 1.09 to 4.02; analysis not shown) (McGrath 1996; Nunes 1993). However, both these studies had a high risk of bias.

Confounder factors

The analyses found a higher number of global responses among participants treated with antidepressants compared to placebo among the studies:

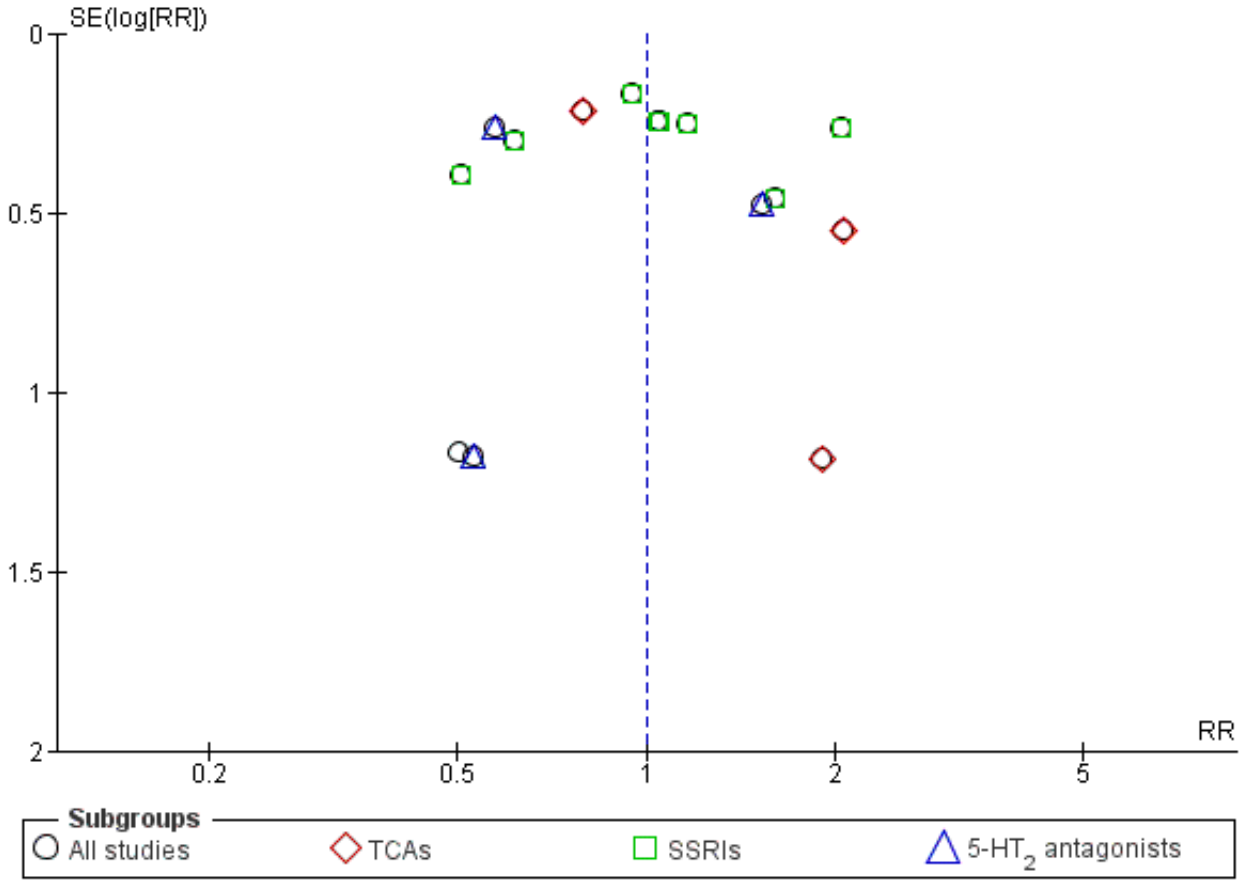
- with a duration of four weeks or greater (P = 0.003), with no evidence of heterogeneity (3 studies; 152 participants; RR 2.37, 95% CI 1.34 to 4.19) (Krupitsky 2012; McGrath 1996; Nunes 1993);
- with primary depression (P = 0.03), with no evidence of heterogeneity (2 studies; 92 participants; RR 2.09, 95% CI 1.09 to 4.02) (McGrath 1996; Nunes 1993);
- conducted in an outpatient setting (P = 0.003), with no evidence of heterogeneity (3 studies; 152 participants; RR 2.37, 95% CI 1.34 to 4.19) (Krupitsky 2012; McGrath 1996; Nunes 1993);
- with participants who were not actively drinking at the beginning of the trial (P = 0.003), with no evidence of heterogeneity (3 studies; 152 participants; RR 2.37, 95% CI 1.34 to 4.19) (Krupitsky 2012; McGrath 1996; Nunes 1993);
- with psychotherapy (P = 0.003), with no evidence of heterogeneity (3 studies; 152 participants; RR 2.37, 95% CI 1.34 to 4.19) (Krupitsky 2012; McGrath 1996; Nunes 1993). Analyses not shown. However, all the three studies had a high risk of bias.

Primary outcome: acceptability (all-cause dropouts)

All studies

The analysis found low-quality of evidence of no difference in all-cause dropouts between antidepressants and placebo, with no evidence of heterogeneity (17 studies; 1159 participants; RR 0.98, 95% CI 0.79 to 1.22; Tau^2 = 0.07; Chi^2 = 23.80, df = 14 (P = 0.05); I^2 = 41%; Analysis 1.17; Summary of findings for the main comparison; Figure 6) (Altamura 1990; Butterworth 1971b; Cornelius 2016; Gallant 1969 arm a; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000).

Figure 6. Funnel plot of comparison: 1 Antidepressants versus placebo: all studies, outcome: 1.17 Acceptability: dropouts.



Different classes of antidepressants and single antidepressant

There were no differences in the number of dropouts between:

- TCAs and placebo (4 studies; 216 participants; RR 1.21, 95% CI 0.48 to 3.06) (Butterworth 1971b; Gallant 1969 arm a; Mason 1996; McGrath 1996);
- SSRIs and placebo (8 studies; 759 participants; RR 1.04, 95% CI 0.79 to 1.36) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998);
- 5-HT_2 antagonists and placebo (4 studies; 154 participants; RR 0.79, 95% CI 0.38 to 1.64; Analysis 1.17; Figure 6) (Cornelius 2016; Hernandez-Avila 2004; McLean 1986; Roy-Byrne 2000);
- imipramine and placebo (2 studies; 112 participants; RR 2.03, 95% CI 0.76 to 5.41) (Butterworth 1971b; McGrath 1996);
- sertraline and placebo (7 studies; 699 participants; RR 1.00, 95% CI 0.76 to 1.33) (Gual 2003; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998); and
- nefazodone and placebo (2 studies; 105 participants; RR 0.86, 95% CI 0.33 to 2.24) (Hernandez-Avila 2004; Roy-Byrne 2000) (not all analyses shown).

Confounder factors

There were no differences between antidepressants and placebo when possible confounder factors were examined (high risk of bias, setting, duration of study, typology of depression, and use of psychotherapy; analyses not shown).

Primary outcome: tolerability of treatment

Withdrawal for medical reasons

All studies

The analysis found low-quality of evidence of no difference in the number of withdrawals for medical reasons between antidepressants and placebo (10 studies; 947 participants; RR 1.15, 95% CI 0.65 to 2.04; Analysis 1.18; Summary of findings for the main comparison) (Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Krupitsky 2012; Mason 1996; McGrath 1996; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000).

Different classes of antidepressants and single antidepressant

There were no differences in the number of withdrawals for medical reasons between SSRIs and placebo (7 studies; 786 participants; RR 1.10, 95% CI 0.52 to 2.32; Analysis 1.18) (Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Krupitsky 2012; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998), TCAs and placebo (2 studies; 97 participants; RR 0.91, 95% CI 0.10 to 8.41; Analysis 1.18) (Mason

1996; McGrath 1996), and sertraline and placebo (4 studies; 537 participants; RR 0.90, 95% CI 0.35 to 2.34; analysis not shown) (Kranzler 2006 arm A; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998).

Confounder factors

There were no differences between antidepressants and placebo when possible confounder factors were examined. Analyses not shown.

Total adverse events

All studies

The analysis found no difference in the total number of adverse events between antidepressants and placebo, with substantial evidence of heterogeneity (5 studies; 644 participants; RR 1.18, 95% CI 0.97 to 1.44; $Tau^2 = 0.02$; $Chi^2 = 13.57$, df = 4 (P = 0.009); $I^2 = 71\%$; Analysis 1.18) (Adamson 2015; Butterworth 1971b; Gallant 1969 arm a; Kranzler 2006 arm A; Krupitsky 2012).

Different classes of antidepressants and single antidepressant

There were no differences between SSRIs and placebo (3 studies; 529 participants; RR 1.06, 95% CI 0.92 to 1.23; Analysis 1.18) (Adamson 2015; Kranzler 2006 arm A; Krupitsky 2012), whereas there was a higher number of total adverse events (P = 0.009) among the studies in which participants received TCAs, with no evidence of heterogeneity (2 studies; 115 participants; RR 1.66, 95% CI 1.13 to 2.42; Analysis 1.18) (Butterworth 1971b; Gallant 1969 arm a). However, one of these studies had a high risk of bias (Butterworth 1971b).

Confounder factors

There was a higher number of total adverse events among participants treated with antidepressants for studies with a duration less than four weeks (P = 0.009) (2 studies; 115 participants; RR 1.66, 95% CI 1.13 to 2.42; analysis not shown) (Butterworth 1971b; Gallant 1969 arm a), and conducted in an inpatient setting (P = 0.009) (2 studies; 115 participants; RR 1.66, 95% CI 1.13 to 2.42; analysis not shown) (Butterworth 1971b; Gallant 1969 arm a). However, one of these studies had a high risk of bias (Butterworth 1971b). There were no differences between antidepressants and placebo when the other possible confounder factors were examined.

Other observations

All studies

Seven single adverse events were investigated by more than one study: dry mouth, insomnia, headache, dizziness, diarrhoea, nausea, and constipation. There was a higher number of episodes of insomnia among participants who received antidepressants compared to those who received placebo (P = 0.04) (4 studies; 564 participants; RR 1.69, 95% CI 1.02 to 2.77; Analysis 1.18) (Adamson 2015; Butterworth 1971b; Kranzler 2006 arm A; Roy-Byrne 2000). There was no difference between antidepressants and placebo for the other adverse events.

Different classes of antidepressants and single antidepressant

The analyses found a higher number of episodes of insomnia among participants treated with SSRIs (P = 0.04) (2 studies; 469 participants; RR 1.75, 95% CI 1.04 to 2.96; Analysis 1.18) (Adamson 2015; Kranzler 2006 arm A). Neither study had a high risk of bias.

There was no difference between antidepressants and placebo in the occurrence of headache for SSRIs (2 studies; 414 participants; Analysis 1.18) (Gual 2003; Kranzler 2006 arm A), or sertraline (2 studies; 414 participants; analysis not shown) (Gual 2003; Kranzler 2006 arm A).

The analyses found no differences between SSRIs and placebo in the occurrence of nausea (2 studies; 221 participants; Analysis 1.18) (Adamson 2015; Gual 2003). The other adverse events were not reported by more than one study of each class of antidepressants.

Confounder factors

The numbers of episodes of insomnia and dry mouth did not differ between antidepressants and placebo when possible confounder factors were examined (analysis not shown).

Total serious adverse events

All studies

The analysis found no difference in the number of total serious adverse events between antidepressants and placebo, with no evidence of heterogeneity (7 studies; 774 participants; RR 1.22, 95% CI 0.80 to 1.86; Analysis 1.18) (Adamson 2015; Butterworth 1971b; Cornelius 2016; Kranzler 2006 arm A; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B).

Different classes of antidepressants and single antidepressant

The analyses found no differences between antidepressants and placebo in total serious adverse events for SSRIs (5 studies; 721 participants; Analysis 1.18) (Adamson 2015; Kranzler 2006 arm A; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B), or sertraline (4 studies; 583 participants; analysis not shown) (Kranzler 2006 arm A; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B).

Confounder factors

There were no differences between antidepressants and placebo when the role of all the possible confounder factors was investigated (analyses not shown).

Single serious adverse event

All studies

The analysis found no difference between antidepressants and placebo regarding the two single serious adverse events investigated by more than one study: worsening of clinical condition because of relapse and depression (Analysis 1.18).

Different classes of antidepressants and single antidepressant

The analysis found no difference when the studies were analyzed according to the different classes of antidepressants and when the role of all the possible confounder factors was investigated (analyses not shown).

Primary outcome: suicide and suicidal attempts

All studies

The analysis found no difference between antidepressants and placebo, with no evidence of heterogeneity (4 studies; 602 participants; RR 1.33, 95% CI 0.23 to 7.61; Analysis 1.19) (Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Moak 2003). None of these studies had a high risk of bias.

Different classes of antidepressants and single antidepressant

The analyses found no difference in the number of suicide attempts between antidepressants and placebo for SSRIs (4 studies; 602 participants; Analysis 1.19) (Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Moak 2003), or sertraline (2 studies; 413 participants; analysis not shown) (Kranzler 2006 arm A; Moak 2003).

Confounder factors

There were no differences between antidepressants and placebo when confounder factors were examined (analyses not shown).

Secondary outcome: craving

All studies

The analysis found no significant difference between antidepressants and placebo (2 studies; 29 participants; MD 1.00 cravings for alcohol, 95% CI -3.27 to 5.27; Analysis 1.20) (Cornelius 2016; Krupitsky 2012).

Different classes of antidepressants and single antidepressant

Measures on craving for alcohol were not available for more than one study for any analysis.

Confounder factors

The analyses found no significant differences between antidepressants and placebo among the studies conducted in an outpatient setting and with psychotherapy (2 studies; 29 participants; analysis not shown) (Cornelius 2016; Krupitsky 2012).

Secondary outcome: severity of alcohol dependence

Because different scales were used, we used SMDs (see Appendix 8; Appendix 9).

All studies

The analysis found no significant difference between antidepressants and placebo (2 studies; 168 participants; SMD -0.14, 95% CI -0.44 to 0.17; Analysis 1.21) (Adamson 2015; Hernandez-Avila 2004).

Different classes of antidepressants and single antidepressant

Measures on severity of alcohol dependence were not available for more than one study for any analysis.

Confounder factors

Both the two studies (168 participants; Adamson 2015; Hernandez-Avila 2004) were without high risk of bias, conducted in an outpatient setting, with a duration of four weeks or greater, in which participants were actively drinking at the beginning of the trial, and with psychotherapy.

Secondary outcome: psychiatric symptoms/psychological distress

All studies

Final score of anxiety severity using an interviewer-rated scale was not available for more than one study. The analysis found a significantly lower value among participants using a self-administered scale (P = 0.002), with no evidence of heterogeneity (3 studies; 97 participants; MD -6.31 points, 95% CI -10.33 to -2.28; Chi^2 = 0.18, df = 2 (P = 0.91); I^2 = 0%; Analysis 1.22) (Hernandez-Avila 2004; Krupitsky 1993 arm A; Krupitsky 2012). However, two of these studies had a high risk of bias (Krupitsky 1993 arm A; Krupitsky 2012).

Different classes of antidepressants and single antidepressant

Data were not available for more than one study for any analysis.

Confounder factors

The analyses found a significantly lower value among participants who received antidepressants than placebo (P = 0.02) among the studies conducted in an outpatient setting, with psychotherapy, with a duration of four weeks or greater, with no evidence of heterogeneity (2 studies; 56 participants; MD -5.78, 95% CI -10.50 to -1.06; Chi^2 = 0.01, df = 1 (P = 0.94); I^2 = 0%; analysis not shown) (Hernandez-Avila 2004; Krupitsky 2012), and in which participants were not actively drinking at the beginning of the trial, with no evidence of heterogeneity (2 studies; 56 participants; MD -6.73, 95% CI -12.48 to -0.98; Chi^2 = 0.14, df = 1 (P = 0.71); I^2 = 0%; analysis not shown) (Krupitsky 1993 arm A; Krupitsky 2012).

Antidepressants versus other medications

Data were not available for more than one study for any analysis.

Antidepressants versus psychotherapy

Depression severity: final score

The analysis found no difference between antidepressants and psychotherapy, with no evidence of heterogeneity (2 studies; 60 participants; MD -2.61 points, 95% CI -6.92 to 1.70; Analysis 2.1) (Liappas 2005 arm A; Liappas 2005 arm B).

Global assessment: final score

Participants who received antidepressants achieved lower final scores (P = 0.01) than participants who received psychotherapy, with no evidence of heterogeneity (2 studies; 60 participants; MD 5.92 points, 95% CI 1.30 to 10.54; Analysis 2.2) (Liappas 2005 arm A; Liappas 2005 arm B). Both studies had a high risk of bias.

Acceptability: all-causes dropouts

The analysis found no difference between antidepressants and psychotherapy, with no evidence of heterogeneity (2 studies; 68 participants; RR 1.43, 95% CI 0.31 to 6.54; Analysis 2.3) (Liappas 2005 arm A; Liappas 2005 arm B).

DISCUSSION

Summary of main results

A total of 33 trials (2242 participants) met the inclusion criteria: among them, 22 studies (1438 participants) compared an antidepressant to placebo; five (621 participants) compared one antidepressant to another; and four (228 participants) compared the efficacy of an antidepressant to another medication. Two studies (60 participants) compared the efficacy of an antidepressant to psychotherapy.

The antidepressants considered in the studies were: amitriptyline (five studies); citalopram (one study); desimipramine (one study); doxepin (three studies); escitalopram (one study), fluoxetine (one study); fluvoxamine (one study); imipramine (three studies); mianserine (one study); mirtazapine (four studies); nefazodone

(two studies); paroxetine (one study); sertraline (eight studies); tianeptine (two studies); venlafaxine (two studies); and vilofaxine (one study).

Comparing antidepressants to placebo, we found low-quality evidence that antidepressants reduced the severity of depression evaluated using a continuous outcome (i.e. final score in interviewer-rated scales) and very low-evidence using a dichotomous outcome (i.e. response). We found no difference between antidepressants and placebo excluding studies with high risk of bias. In addition, we found no difference for other relevant outcomes such as the difference between baseline and final score.

Regarding alcohol consumption, we found moderate-quality evidence that antidepressants increased with respect to placebo, the number of participants abstaining during the trial and reduced the number of drinks per drinking day. However, we found no differences between antidepressants and placebo for other relevant outcomes such as the rate of abstinent days (low-quality evidence).

With regards to acceptability and tolerability, we found low-quality evidence that antidepressants did not increase the rate of dropouts or withdrawals for medical reasons when compared with placebo.

Considering confounders/moderators, trials lasting more than four weeks or including only people with primary major depression showed no impact on the efficacy of antidepressants in reducing the severity of depression at the end of treatment and rate of response. The other confounders/moderators (typology of depression, setting, and psychotherapy) did not have a substantial impact on these results, which were often limited by the small number of included studies in the subgroup and confounders/moderators analyses.

There were few studies comparing one antidepressant versus another or antidepressants versus other interventions, and these had a small sample size and were heterogeneous in terms of the types of interventions that were compared, yielding results that were not informative.

Overall completeness and applicability of evidence

Besides the limits in external validity due to the general requirements of RCTs (strict inclusion criteria, highly homogeneous study groups, limitations in dose adjustment, etc.), the types of participants (adults with co-occurring depression and alcohol dependence) are quite representative of the general target population. Moreover, interventions (antidepressant dosages), settings, and outcomes investigated (dropouts, alcohol use, adverse events, depression severity changes) are important to patients, practitioners, and decision makers and are relevant to the context of current practice.

In contrast to other reviews in the field of addiction, for which a large majority of studies were conducted in the USA, more than one third of the studies included in this review were conducted in other countries. This is an important issue in terms of generalizability of the evidence, because different social contexts can influence depression severity and alcohol dependence and availability to enter a clinical trial; also, different clinical contexts can influence the selection of participants and the results of the treatment, acting as an effect modifier in the estimation of efficacy of treatment.

Quality of the evidence

For the evaluation of the quality of the evidence, we collected supplementary information from the authors of the primary studies, mainly because some features of the study design were omitted from trial reports or data on outcomes were lacking. Some outcome measures were obtained according to the *Cochrane Handbook for Systematic Reviews of Interventions* suggested procedures from available values (Higgins 2011). In one case (Analysis 1.7), missing SDs were imputed as the mean of SDs of the other studies included in the comparison. In this case, a sensitivity analysis was carried out to assess how the results were sensitive to changes.

Moreover, the assumption that missing data correspond to poor outcome was made choosing dropout as a primary outcome. Another approach, as the last observation carried forward was not followed since included studies with missing data did not provide multiple point data. In the end, availability of data on primary outcomes varied from 72.7% (16 of 22 RCTs) for dropouts to 9.5% (2 of 22 RCTs) for the GGT values.

The poor reporting of study design was mainly for the methods used for generating random sequences and allocation concealment, with more than two-thirds of trials at unclear risk for selection bias. Moreover, 25% of the studies had a high risk of attrition and reporting bias. Finally, about half of the studies were at high or unclear risk of performance bias and almost all at unclear risk of detection bias.

Overall, the quality of evidence was moderate for people abstinent during the trial and for the number of drinks per drinking day; low for the severity of depression measured at the end of the trial, for the rate of abstinent days, dropouts, and adverse events; and very low for the ascertainment of the response to the treatment.

Potential biases in the review process

We did not find any unpublished studies despite a significant effort in contacting all the first authors of the included studies and the search of conference proceedings.

The possibility of publication bias was inspected by funnel plot only for the comparison 'Antidepressants versus placebo' and for the outcomes, severity of depression at the end of treatment (Figure 4), rate of responses (Figure 5), and dropouts (Figure 6), because in the other comparisons and for the other outcomes there were too few studies to make the funnel plot informative. One of the three funnel plots (dropouts) showed asymmetry suggesting publication bias in favour of studies with positive results (Figure 6).

We acknowledge that the funnel plot should be seen as a generic mean of displaying small-study effects, so that asymmetry could be due to publication bias, but also to other reasons such as greater risk of bias of smaller studies, inclusion of a more restrictive and thus responsive population, or merely by the play of chance. The majority of the studies included in this review had a small sample size (fewer than 100 participants). GRADE guidelines suggest that authors of systematic reviews should suspect publication bias when studies are uniformly small (Guyatt 2011).

Agreements and disagreements with other studies or reviews

Four previous non-Cochrane systematic reviews evaluating pooled data with meta-analyses have been identified (Foulds 2015; Iovieno 2011; Nunes 2004; Torrens 2005). These reviews were carried out on the basis of pre-established criteria for searching literature, selecting studies, and assessing their risk of bias. The first review evaluated the efficacy of depression treatment in people with substance-use disorders, but eight studies specifically investigated the efficacy of antidepressants in people with co-occurring alcohol dependence and depression (Nunes 2004). This review concluded that antidepressants exert a modest beneficial effect for people with co-occurring depression and substance-use disorders, including a positive impact on alcohol consumption.

The second meta-analysis investigated the efficacy of antidepressants in people with substance-use disorder with and without depression (Torrens 2005). Among the selected trials, nine studies specifically investigated the efficacy of antidepressants in people with co-occurring alcohol dependence and depression. The results of the meta-analysis failed to demonstrate any impact of antidepressants on alcohol consumption or a significant advantage for the use of SSRIs for the treatment of depression while giving indication for a possible effect of other antidepressants (Torrens 2005).

The third meta-analysis evaluated the efficacy of antidepressants in participants with substance-use disorder with depression or dysthymic disorder (Iovieno 2011). The results of the meta-analysis (11 trials) showed that antidepressants are more efficacious than placebo in this population. This review did not consider the impact of antidepressants on alcohol consumption.

The fourth meta-analysis investigated possible differences in response to a treatment for depression in alcohol-dependent participants according to the different typology of depression, divided into independent and alcohol-induced depression (Foulds 2015). This study selected 22 clinical trials of which 13 evaluated the efficacy of antidepressants compared to placebo in people with alcohol dependence and depression. The meta-analysis was conducted on 11 trials. The results showed that, globally, treatment of depression in alcohol-dependent people is associated with a large early improvement in depression severity, even when depression is independent from drinking, with a stronger effect in independent depression than in alcohol-induced depression (Foulds 2015). In this review, the effect of antidepressants on alcohol consumption was not considered.

The first three reviews were not specifically designed for evaluating the efficacy and safety of antidepressants for alcohol-dependent people. The fourth review adopted very selective inclusion criteria (studies reporting data over at least eight weeks; studies reporting a change in depression scales). All the reviews did not apply stringent Cochrane criteria for systematic reviews and did not consider dropouts and adverse effects as a primary outcome.

Compared to the previous reviews, our review adopted Cochrane criteria, included relevant variables among the primary outcomes such as severity depression, alcohol consumption, dropout rate, and adverse events. Unfortunately, the results obtained, despite based on more than 30 RCTs and 2000 participants, did not resolve the uncertainty coming from the previous reviews. According to our results, compared to placebo, antidepressants exert some positive effects both on depression and alcohol dependence. However, these effects may only have modest impact on both depression and alcohol-related outcomes. Considering depression severity, the positive effects were limited to only some outcomes (i.e. depression severity evaluated with interviewer-rated scales at the end of trial and response to treatment) and were no longer significant when studies at high risk of bias were excluded. Similarly, the positive effects observed considering potential confounders (i.e. for depression severity, duration of treatment and setting; for response to treatment, classes of antidepressants, and duration of treatment) were no longer significant when studies at high risk of bias were excluded. Only for primary depression, the positive effects were still present after the exclusion of studies at high risk of bias.

The positive effects also had a modest impact on alcohol consumption. Indeed, antidepressants improve only some outcomes (i.e. the number of abstinent participants and the number of drinks per drinking days) and not others (e.g. the rate of abstinent days). However, the positive effects shown by antidepressants were still evident when studies at high risk of bias are excluded both in the entire sample of participants and when they are divided into subgroups according potential confounders (outpatient setting, duration of treatment greater than four weeks, primary depression, receiving psychotherapy, and being actively drinking at the begging of treatment) and different classes of antidepressants (i.e. SSRIs).

AUTHORS' CONCLUSIONS

Implications for practice

We found low-quality evidence supporting the clinical use of antidepressants in the treatment of people with co-occurring depression and alcohol dependence. Low-quality evidence suggests that antidepressants have positive effects on certain outcomes related to depression (severity of depression at the end of the trial and response to treatment) and moderate-quality evidence in certain outcomes related to alcohol use (number of abstinent participants during the trial and number of drinks per drinking day). However, we found no differences in other relevant outcomes, such as the difference between the baseline and final score for depression severity and rate of abstinent days for alcohol consumption. Moreover, the positive findings for antidepressants on the outcomes related to depression are no longer significant when studies with high risk of bias are excluded. In contrast, low-quality evidence shows that antidepressants have good acceptability and tolerability, with no significant differences compared to placebo in all-cause dropouts, withdrawals for medical reasons, and total adverse events.

According to our results, in people with co-occurring depression and alcohol dependence, antidepressants may be useful for the treatment of depression, alcohol dependence, or both disorders, although the clinical relevance may be modest. Results are also limited by the large number of studies showing high or unclear risk of bias and by the low number of studies comparing one antidepressant to another or antidepressants to other medications. In people with co-occurring depression and alcohol dependence, the risk of developing adverse effects appears to be minimal, especially for the newer classes of antidepressants (such as selective serotonin reuptake inhibitors).

Implications for research

Further research is required to strengthen evidence on the efficacy of antidepressants in the treatment of people with co-occurring depression and alcohol dependence. In implementing new trials on the topic, specific attention should be paid to the main methodological challenges associated with addiction research, particularly the rate of dropouts and related handling of missing data, the validation of self-reported measures by objective measures, the choice of outcomes and related measures to allow comparison of results between studies, and, more generally, the stricter adherence to methodological standards of reporting, as outlined in the CONSORT statement (Moher 2001).

Looking at the literature on the management of depression in alcohol-dependent people, factors that influence the research on the efficacy of pharmacological interventions include the uncertainty of diagnosis of depression in people affected by alcohol dependence or substance-use disorder (or both) (Nunes 2004; Torrens 2005; Nunes 2006), the timeframe necessary for antidepressants to have full effect, and the inadequate reporting of associated psychosocial interventions. Regarding these issues, the adoption of strict operationalized criteria should be encouraged.

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*Authors of primary studies not mentioned in this section were not contacted, as all relevant data and information were available from the trial publication, or they were unable to provide requested data or information.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adamson 2015

Methods	Randomized, double-blind, placebo-controlled trial
Participants	138 depressed people with alcohol dependence (56 men and 82 women; mean (± SD) age 43.6 ± 9.1 years). Inclusion criteria: • aged 17-65 years • current DSM-IV diagnoses of alcohol dependence and depression • MADRS score > 20 Exclusion criteria: • past regular intravenous drug use for > 2 weeks • recreational use of any opioid drugs in the previous 4 weeks or a current requirement for ongoing opioid use • psychosis, including psychotic delirium complicating alcohol or other drug withdrawal • mania or hypomania • significant current suicidality or homicidality • current severe psychiatric symptoms requiring hospitalization, • unstable physical disease • use of disulfiram, naltrexone, antidepressant, or mood stabilizing medication in past 4 weeks • serum AST, ALT, or GGT greater than 3 × the upper limit of laboratory reference range, or a bilirubin level > upper limit of reference range • pregnancy, breastfeeding, or unwillingness to use a reliable method of contraception in women of childbearing age • current or pending imprisonment Participants with bipolar disorder were excluded.
Interventions	Drugs: • citalopram (up to 60 mg/day) + naltrexone (up to 100 mg/day) (73 participants; 29 men and 44 women) • placebo + naltrexone (up to 100 mg/day) (65 participants; 27 men and 38 women) Psychotherapy: manualized clinical case management was delivered by experienced addiction clinicians. Scheduled duration of treatment: 12 weeks Sites: 7 addiction clinics spanning urban, provincial, and rural catchments in Australia. Setting: outpatients

Adamson 2015 *(Continued)*

	Route of administration: orally Starting dose: • citalopram: 20 mg/day in week 1; if tolerated, dose then increased to 40 mg/day. After 6 weeks, dose could be further increased to 60 mg/day if participants remained depressed • naltrexone: 25 mg daily for 1 week, then increased to 50 mg in participants without significant adverse effects. Dose could be further increased to 75 mg or 100 mg after 6 weeks Pattern of dose reduction: information not available
Outcomes	Depression: • final MADRS score • final SCL-90 score • remission Alcohol dependence: • rate of abstinent days • number of heavy drinking days per week (obtained from the rate of heavy drinking days) • number of drinks per drinking day • final LDQ score Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (% of participants): 76.1% • duration (years): 19.3 • MADRS score (mean ± SD): 31.0 ± 5.8 Alcohol dependence: • number of drinks per drinking day (mean ± SD): 14.3 ± 8.0 • duration (years): 13.8 • being actively drinking: participants were not required to be abstinent Other psychiatric comorbidity: 47.1% of participants had current anxiety disorder. Other substance-use disorders: 14.5% of participants had current substance dependence. **Other characteristics of study** Other pharmacological treatment offered: all participants received naltrexone. Funding sources: study funded by Health Research Council of New Zealand grant HRC 07/138. Declaration of interest: authors declared no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using a computer-generated random number table.

Adamson 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Treatment allocation was conducted by an administrative staff member independent of study investigators or research clinicians, and the allocation sequence record was stored securely.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators, doctors, participants, and any other staff members taking part in the experiment were unaware which of the groups any particular participant belonged to.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed using appropriate methods.
Selective reporting (reporting bias)	Unclear risk	Numbers of dropouts per group were missing.

Altamura 1990

Methods	Randomized, placebo-controlled, double-blind trial
Participants	30 people with alcohol dependence with dysthymia (24 men and 6 women; mean (± SD) age: 44.5 ± 2.6 years). Inclusion criteria: • alcohol dependence and dysthymia according to DSM-III-R • HRSD score ≥ 18 Exclusion criteria: • diagnosis of cirrhosis • substance-use disorders by other substances • relevant internal or neurological conditions Participants with bipolar disorder: information not available.
Interventions	Drugs: • viloxazine (400 mg/day, in 4 daily administrations; 15 participants; information on number of men and women not available) • placebo (15 participants; information on number of men and women not available) Psychotherapy: information not available Scheduled duration of treatment: 12 weeks Site: 1 centre, Department of Clinical Psychiatry, Policlinico, Milan, Italy Setting: inpatient setting for first 4 weeks, then outpatients for following 8 weeks.

Altamura 1990 *(Continued)*

	Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score (obtained from a figure) Alcohol dependence: information not available Dropouts Adverse effects: information not available
Notes	**Baseline characteristics of participants** Depression: • primary depression: "Patients were not depressed but affected by dysthymic disorder" • duration: information not available • HRSD score (mean ± SD): viloxazine = 26.7 ± 2.8; placebo = 25.6 ± 1.7 Alcohol dependence: • severity: information not available • duration of alcohol consumption (mean ± SD): 10.2 ± 1.3 years • being actively drinking: information not available • length of abstinence: information not available Other psychiatric comorbidity: information not available Other substance-use disorders: participants with other substance-use disorders were excluded. **Other characteristics of study** Other pharmacological treatment offered: information not available Funding sources: information not available Declaration of interest: information not available **Other information** Standard errors were converted into SDs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated but no further details provided.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement.

Altamura 1990 *(Continued)*

Blinding of outcome assessment (detection bias) objective	Low risk	No information on blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Method to account for missing data not described. Intention-to-treat approach not reported. No high numbers of dropouts or unbalanced between groups.
Selective reporting (reporting bias)	High risk	DBI and DOTES scores are reported in 2 figures (figures 3 and 4 of the publication) in which the titles of the y axis do not correspond to those reported in the legends and in the text, and the positions of the points do not correspond to the values indicated in the y axes. Accordingly, these results were not included in the present meta-analysis.

Altintoprak 2008

Methods	Double-blind, randomized, comparative trial
Participants	44 depressed people with alcohol dependence (number of men and women: information not available; mean age: information not available). Sociodemographic characteristics available only for 36 participants (20 mirtazapine, 16 amitriptyline). Inclusion criteria: • aged 18-65 years • current DSM-IV diagnoses of alcohol dependence and depressive disorder • HDRS score ≥ 14 after detoxification Exclusion criteria: • serious physical illness • for women, lack of protection against pregnancy, pregnancy, or breastfeeding • other major psychiatric disorder on the DSM-IV axis-I other than depressive disorder • history of a psychiatric problem other than depressive disorder • organic brain diseases • history of hypersensitivity to mirtazapine or amitriptyline • other drug dependence and abuse, excluding nicotine and caffeine • consumption of alcohol during study Participants with bipolar disorder were excluded.
Interventions	Drugs: • mirtazapine (30-60 mg/day; 24 participants) • amitriptyline (100-150 mg/day; 20 participants) Psychotherapy: information not available. Scheduled duration of treatment: 8 weeks. Site: Ege University School of Medicine Hospital, Specialized Addiction Unit, Izmir, Turkey Setting: inpatient

Altintoprak 2008 *(Continued)*

Route of administration: orally

Starting dose:

- mirtazapine: 15 mg/day (increased to 30 mg/day at the third day; at end of first week, dose was increased to 45-60 mg/day if severity of symptoms persisted)
- amitriptyline 50 mg/day (increased to 100 mg/day at the third day; at end of first week, dose was increased to 125-150 mg/day if severity of symptoms persisted)

Pattern of dose reduction: information not available

Outcomes	Depression: • final HRSD score Alcohol dependence: data not available Alcohol craving: • final score in a questionnaire prepared by authors Dropouts: data not available Adverse effects: • evaluated using the UKU scale Bodyweight: • final value Anxiety: • final STAI score
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 34.1% • duration: information not available • HRSD score (mean ± SD): mirtazapine = 24.0 ± 4.4; amitriptyline = 23.7 ± 4.8 Alcohol dependence: • MAST score (mean ± SD): 38.9 ± 6.1 • duration (mean ± SD): 12.1 ± 3.9 years • being actively drinking: people who consumed alcohol during study were excluded from study. • length of abstinence: 2 weeks Anxiety: • STAI score (mean ± SD): mirtazapine = 51.8 ± 3.9; amitriptyline = 53.4 ± 4.5. Global assessment: information not available. Weight (mean ± SD): • mirtazapine = 75.9 ± 16.2 kg; amitriptyline = 71.4 ± 10.9 kg Other psychiatric comorbidity: participants with other psychiatric disorders were excluded. Other substance use disorders: participants with other substance use disorders were excluded. **Other characteristics of study**

Altintoprak 2008 *(Continued)*

Other pharmacological treatment: no other pharmacological treatment was allowed.

Funding sources: not available.

Declaration of interest: not available.

Other information

After their inclusion in study, participants were admitted at a specialized department for alcohol detoxification on an inpatient basis. Alcohol consumption was prohibited during hospitalization and people who consumed alcohol during study were excluded from study. At end of alcohol detoxification treatment (approximately 10-14 days), people were included in study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated. No further details provided.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind stated. Medication and placebo prepared to appear identical ("Both the clinicians and patients were blind to the treatment. Drugs were given in identical-looking opaque capsules").
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat approach not used ("Dropouts were not included in the analysis due to missing data"). People who consumed alcohol during study were excluded by study.
Selective reporting (reporting bias)	High risk	People who consumed alcohol during study were excluded by study.

Butterworth 1971a

Methods	Randomized, double-blind, comparative trial
Participants	39 people with alcohol dependence (all men; mean age: information not available) with a significant degree of anxious-depressive symptomatology. Inclusion criteria: • aged 20-55 years • significant degree of anxiety and depression as determined by psychiatric interview • current diagnosis of alcohol dependence Exclusion criteria:

Butterworth 1971a *(Continued)*

- physical brain
- liver illnesses
- psychotic disorder

Participants with bipolar disorder: information not available

Interventions	Drugs: • doxepin (75 mg/day; 20 participants, all men; mean age: 45 years) • diazepam (15 mg/day; 19 participants, all men; mean age: 41 years) Psychotherapy: information not available Scheduled duration of treatment: 3 weeks Site: Alcoholism Treatment Service of East Louisiana State Hospital, Mandeville, LA, USA Setting: inpatients Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression: • final BPRS score • final ZUNG score • response Alcohol dependence: data not available Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration: information not available • BPRS score (mean): doxepin = 76.3; diazepam = 73.8 • ZUNG score (mean): doxepin = 47.8; diazepam = 37.9 Alcohol dependence: • severity: information not available • being actively drinking: participants not actively drinking Other psychiatric comorbidity: information not available Other substance-use disorders: information not available **Other characteristics of study** Other pharmacological treatment: other concomitant therapy not allowed Funding source: medications were supplied by Laboratories of Pfizer Inc. Declaration of interest: information not available

Butterworth 1971a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated. No further details provided.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind stated. Medications prepared to appear identical. Evaluations conducted by 2 independent investigators and the results pooled.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	No information on dropouts provided. Methods applied to account for missing data not described. Intention-to-treat approach not reported.
Selective reporting (reporting bias)	High risk	No information on dropouts provided. Methods applied to account for missing data not described. Intention-to-treat approach not reported.

Butterworth 1971b

Methods	Randomized, placebo-controlled, double-blind trial
Participants	40 depressed people with alcohol dependence (all men; mean age: majority aged 31-50 years) Inclusion criteria: • alcohol dependence requiring involuntarily admission for detoxification • diagnoses of depression according to clinical impression • LDRS score ≥ 12 Exclusion criteria: • hepatic disease • organic brain damage • psychosis Participants with bipolar disorder: information not available
Interventions	Drugs: • imipramine (75-200 mg/day; 20 participants) • placebo (20 participants) Psychotherapy: none

Butterworth 1971b *(Continued)*

	Scheduled duration of treatment: 3 weeks Site: Alcoholic Treatment Service, East Louisiana State Hospital, Jackson, LA, USA Setting: inpatients for first 3-4 days for treatment of alcohol withdrawal, then 3 weeks for trial Route of administration: orally Starting dose: • 75 mg/day • increased to maximum 200 mg/day according to individual requirements • reduced if indicated by adverse effects Pattern of dose reduction: information not available
Outcomes	Depression: • difference between basal and final LRDS score • response Alcohol dependence: data not available Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration: information not available • after detoxification and washout, LDRS score (mean ± SD): imipramine = 16.0 ± 3.1; placebo = 15.6 ± 3.3. Alcohol dependence: • duration: for 24 participants = 1-5 years; for 16 participants ≥ 10 years; • severity: all participants required involuntarily admission for detoxification, many participants had been hospitalized repeatedly for detoxification, in some instances as many as 30 times; • being actively drinking: participants were abstinent; • length of abstinence: 0.5 weeks 3-4 days for the treatment of alcohol withdrawal). Other psychiatric comorbidity: information not available. Other substance-use disorders: information not available. **Other characteristics of study** Other pharmacological treatment offered: participants received pharmacological treatment to control the acute symptoms of alcohol withdrawal for 3-4 days. Funding sources: information not available Declaration of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated. No further details provided.

Butterworth 1971b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated. Medication and placebo prepared to appear identical. No specific reference made to blinding of participants and personnel.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Methods applied to account for missing data not described. Intention-to-treat approach not reported. People who left study were replaced by other people ("One patients taking imipramine left the hospital ... and global evaluation were omitted. Two additional patients left without permission just after entering the trial, and were therefore replaced in the study. One had received six doses of imipramine and the other one placebo").
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement.

Cocchi 1997

Methods	Randomized comparative trial
Participants	122 depressed people with alcohol dependence (95 men and 27 women; mean age: 42 years) Inclusion criteria: • DSM-IV diagnosis F10-24 • ZUNG score > 49 Exclusion criteria: information not available Participants with bipolar disorder: information not available
Interventions	Drugs: • paroxetine (20 mg/day; 61 participants; 49 men and 12 women; age (mean ± SD) = 42.1 ± 11.5 years) • amitriptyline (25 mg/day; 61 participants; 46 men and 15 women; age (mean ± SD) = 42.2 ± 10.7 years) Psychotherapy: information not available Scheduled duration of treatment: 3-4 weeks Site: Alcohol Unit, casa di Cura Villa Silvia per malattie nervose e mentali, Senigallia, Italy Setting: inpatients Route of administration: orally Starting dose: information not available

Cocchi 1997 *(Continued)*

	Pattern of dose reduction: information not available
Outcomes	Depression • final ZUNG score • response (according to ZUNG) • remission (according to ZUNG) Alcohol dependence: data not available Dropouts: data not available Adverse effects: data not available
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration: information not available • ZUNG score (mean ± SD): paroxetine = 68.8 ± 9.0; amitriptyline = 63.3 ± 6.0 Alcohol dependence: data not available Other psychiatric comorbidity: information not available Other substance use disorders: information not available **Other characteristics of study** Other pharmacological treatment: information not available Funding sources: information not available Declaration of interest: information not available **Other information** Data on response and remission were excluded because evaluated using a self-administered scale.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated. No further details provided.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on the design (double-blind or open trial), on the preparation and appearance of medications, and on blinding of participants and personnel.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on study design (double-blind or open trial).

Cocchi 1997 *(Continued)*

Blinding of outcome assessment (detection bias) subjective	High risk	No information on study design (double-blind or open trial).
Incomplete outcome data (attrition bias) All outcomes	High risk	Methods applied to account for missing data. Intention-to-treat approach not reported. No high number of dropouts or unbalanced between groups.
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement.

Cornelius 1997

Methods	Randomized, double-blind, placebo-controlled trial
Participants	51 depressed people with alcohol dependence (26 men and 25 women; age (mean ± SD) = 34.8 ± 10.2 years) Inclusion criteria: • current DSM-III-R diagnoses of depression and alcohol dependence Exclusion criteria: • diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or non-alcohol substance dependence • hyperthyroidism or hypothyroidism • clinically significant medical diseases • pregnancy • mental retardation or cognitive impairment • use of antipsychotic or antidepressant medication in the previous month Participants with bipolar disorder were excluded.
Interventions	Drugs: • fluoxetine (20 mg/day; 25 participants) • placebo (26 participants) Psychotherapy: • weekly supportive psychotherapy sessions • weekly meetings with an attending psychiatrist with expertise in treating people with dual-disorder • attendance at Alcoholics Anonymous was encouraged. Scheduled duration of treatment: 12 weeks Site: Western Psychiatric Institute and Clinic of the University of Pittsburgh, Pittsburgh, USA Setting: inpatients for first 2 weeks of abstinence, then outpatients Route of administration: orally Starting dose: • 20 mg/day • increased to 40 mg/day after 2 weeks if substantial residual depressive symptoms persisted

Cornelius 1997 *(Continued)*

	Pattern of dose reduction: information not available
Outcomes	Depression: • difference between baseline and final HRSD score • difference between baseline and final BDI score Alcohol dependence: • rate of abstinent days (obtained from cumulative number of drinking days) • number of abstinent participants • number of drinks per drinking day • number of heavy drinking days per week (obtained from the cumulative number of heavy drinking days) • time to first relapse (obtained from the number of weeks until first relapse) Global assessment: • severity (difference between baseline and final GAS score) Dropouts: information not available Adverse effects: information not available
Notes	**Baseline characteristics of participants** Depression: • primary depression: 100% • duration: information not available • after detoxification and washout, HRSD score (mean ± SD): fluoxetine = 19.2 ± 8.2; placebo = 17.9 ± 8.1 • number of diagnostic criteria (mean ± SD): fluoxetine = 6.7 ± 1.1; placebo = 6.8 ± 1.1 • current suicide ideation: fluoxetine = 92.0%; placebo = 88.5% Alcohol dependence: • number of diagnostic criteria (mean ± SD): fluoxetine = 5.5 ± 1.6; placebo = 5.9 ± 1.8; range: 3.9-7.7 • duration: information not available • being actively drinking: participants were actively drinking • length of abstinence: 0 • number of drinking days in past 90 days (mean ± SD): fluoxetine = 54.5 ± 29.2; placebo = 45.2 ± 28.9 • number of days drinking to drunkenness in past 90 days (mean ± SD): fluoxetine = 40.1 ± 27.7; placebo = 32.0 ± 26.4 Other psychiatric comorbidity: participants with other mental disorders were excluded. Other substance-use disorders: participants with substance-use disorders were excluded. Abuse of other substances was not an exclusionary criterion, provided that alcohol was the main substance of abuse. **Other characteristics of study** Other pharmacological treatment: other pharmacological treatments were not allowed. Funding sources: work was supported by the National Institute on Alcohol Abuse and Alcoholism (grants AA09127 and AA10523), and by the Mental Health Clinical Research Center, Rockville, MD (grant MH30915). Declarations of interest: information not available

Risk of bias

Cornelius 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization balanced for gender and race. It was not reported whether a computer-generated list was used.
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement. Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Medications were administered in identical opaque capsules. Substantial blood levels of fluoxetine were observed in more than 99% of participants assigned to fluoxetine. Not reported if blood analyses were made also to participants who received placebo.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis and last point carried forward analysis applied.
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement.

Cornelius 2016

Methods	Randomized, double-blind, placebo-controlled trial
Participants	14 depressed people with alcohol dependence (10 men and 4 women; mean age = 41.3 years) Inclusion criteria: • aged 18-55 years • current DSM-IV diagnoses of depression and alcohol dependence • eligible for outpatient treatment Exclusion criteria: • aged < 18 years or over 55 years • presence of psychotic symptoms or a diagnosis involving psychosis • receiving psychotropic medication in the prior month • current DSM diagnosis of dependence or abuse on substances other than alcohol, cannabis, nicotine, or caffeine • current significant medical or neurological condition • suicidal ideation in the last 3 months, or lifetime suicidal attempt • positive pregnancy test or breastfeeding • inability or unwillingness to use contraceptive methods • inability to read or understand study forms • pending incarceration • current participation in another research study

Cornelius 2016 *(Continued)*

	Participants with bipolar disorder: information not available
Interventions	Drugs: • mirtazapine (30 mg/day; 7 participants; 4 men and 3 women) • placebo (7 participants; 6 men and 1 woman) Psychotherapy: • brief MET at each assessment Scheduled duration of treatment: 12 weeks Site: University of Pittsburgh, Western Psychiatric Institute and Clinic, Pittsburgh, USA Setting: outpatients Route of administration: orally Starting dose: • 15 mg/day for the first 2 weeks • then 30 mg/day for 12 weeks Pattern of dose reduction: information not available
Outcomes	Depression: • final BDI score • difference between baseline and final BDI score Alcohol dependence: • number of drinking days per week • number of drinks per drinking days • number of drinks per week • number of heavy drinking days per week Craving for alcohol: • final OCDS score • difference between baseline and final OCDS score Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration: information not available • BDI score (mean ± SD): mirtazapine = 27.6 ± 7.7; placebo = 26.1 ± 11.7 Alcohol dependence: • severity: information not available • duration: information not available • number of drinks per drinking day (mean ± SD): 6.6 ± 2.0 • being actively drinking: participants were not abstinent Other psychiatric comorbidity: participants with other mental disorders were excluded.

Cornelius 2016 *(Continued)*

	Other substance use disorders: participants with substance use disorders were excluded. **Other characteristics of study** Other pharmacological treatment: participants did not receive other pharmacological treatments. Funding sources: study received grants from the National Institute on Alcohol Abuse and Alcoholism (R21 AA022123, R21 AA022863, R01 AA013370, R01 AA015173, K24 AA15320) and from the National Institute on Drug Abuse (R01 DA019142, P50 DA05605, K02 DA017822). Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement of low or high risk.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medications were identical in appearance (identical-looking opaque capsules).
Blinding of outcome assessment (detection bias) objective	Low risk	Medications were identical in appearance (identical-looking opaque capsules).
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat approach reported.
Selective reporting (reporting bias)	Low risk	No dropouts

Gallant 1969 arm a

Methods	Randomized, double-blind, placebo-controlled trial
Participants	76 people with alcohol dependence (all men; mean age = 42 years) in association with a predominant chronic anxiety or depressive reaction. Inclusion criteria: information not available Exclusion criteria: • psychotic disorders Participants with bipolar disorder: information not available
Interventions	Drugs:

Gallant 1969 arm a *(Continued)*

- doxepin (150 mg/day, in 3 daily administrations; 24 participants; all men)
- doxepin (75 mg/day, in 3 daily administrations; 23 participants; all men)
- placebo (29 participants; all men)

Psychotherapy: information not available

Scheduled duration of treatment: 3 weeks

Site: Alcoholism Treatment Service of Southeast Louisiana Hospital, Mandeville, LA, USA

Setting: inpatients

Route of administration: orally

Starting dose: information not available

Pattern of dose reduction: information not available

Outcomes	Depression: • response Alcohol dependence: data not available Dropouts Adverse effects
Notes	**Baseline characteristics of participants included in** Gallant 1969 arm a; Gallant 1969 arm b Depression: • primary depression: information not available • duration: information not available • severity: information not available Alcohol dependence: • severity: information not available • being actively drinking: information not available • duration: information not available Other psychiatric comorbidity: participants with other mental disorders were included. Other substance use disorders: information not available **Other characteristics of study** Other pharmacological treatment offered: information not available Funding source: the project was partially supported by PHS Grant MH-03701-08, Psychopharmacology Research Branch, NIMH. Declarations of interest: information not available **Other information** In the original study, 100 participants were divided into 4 groups: • doxepin 150 mg/day (24 participants) • doxepin 75 mg/day (23 participants) • diazepam 15 mg/day (24 participants) • placebo (29 participants)

Gallant 1969 arm a *(Continued)*

In the present meta-analysis, participants were divided into 2 substudies:

- Gallant 1969 arm a (76 participants), in which the 2 groups with different doses of doxepin were combined into a single group and compared to placebo group
- Gallant 1969 arm b (71 participants), in which the 2 groups with different doses of doxepin were combined into a single group and compared to diazepam group

The first arm (Gallant 1969 arm a) was included in the 'Effects of interventions: Antidepressants versus placebo' comparison and the second arm (Gallant 1969 arm b) in the 'Effects of interventions: Antidepressants versus other medications' comparison.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement of low or high risk.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medications were identical in appearance and were coded in accordance with double-blind procedure to ensure that all personal involved in project remained blind as to which group any given participant belonged.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Methods applied to account for missing data not described. Intention-to-treat approach not reported. However, there were no dropouts.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. However, there were no dropouts.

Gallant 1969 arm b

Methods	Randomized, double-blind, placebo-controlled trial
Participants	71 people with alcohol dependence (all men; mean age: 42 years) in association with a predominant chronic anxiety or depressive reaction (diagnosis of depression was uncertain). Inclusion criteria: information not available Exclusion criteria: • psychotic disorders Participants with bipolar disorder: information not available
Interventions	Drugs:

Gallant 1969 arm b *(Continued)*

- doxepin (150 mg/day, in 3 daily administrations; 24 participants; all men)
- doxepin (75 mg/day, in 3 daily administrations; 23 participants; all men)
- diazepam (24 participants; all men)

Psychotherapy: information not available

Scheduled duration of treatment: 3 weeks

Site: Alcoholism Treatment Service of Southeast Louisiana Hospital, Mandeville, LA, USA

Setting: inpatients

Route of administration: orally

Starting dose: information not available

Pattern of dose reduction: information not available

Outcomes

Depression:

- response

Alcohol dependence: data not available (probably because of inpatient setting).

Dropouts

Adverse effects

Notes

Baseline characteristics of participants included in Gallant 1969 arm a; Gallant 1969 arm b

Depression:

- primary depression: information not available
- duration: information not available
- severity: information not available

Alcohol dependence:

- severity: information not available
- being actively drinking: information not available
- duration: information not available

Other psychiatric comorbidity: participants with other mental disorders were included.

Other substance use disorders: information not available

Other characteristics of study

Other pharmacological treatment offered: information not available

Funding source: the project was partially supported by PHS Grant MH-03701-08, Psychopharmacology Research Branch, NIMH.

Declarations of interest: information not available

Other information

In the original study, 100 patients were divided into 4 groups:

- doxepin 150 mg/day (24 participants)
- doxepin 75 mg/day (23 participants)
- diazepam 15 mg/day (24 participants)
- placebo (29 participants)

Gallant 1969 arm b *(Continued)*

In the present meta-analysis, participants were divided into 2 substudies:

- Gallant 1969 arm a (76 participants), in which the 2 groups with different doses of doxepin were combined into a single group and compared to placebo group
- Gallant 1969 arm b (71 participants), in which the 2 groups with different doses of doxepin were combined into a single group and compared to diazepam group

The first arm (Gallant 1969 arm a) was included in the 'Effects of interventions: Antidepressants versus placebo' comparison and the second arm (Gallant 1969 arm b) in the 'Effects of interventions: Antidepressants versus other medications' comparison.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medications were identical in appearance and were coded in accordance with double-blind procedure to ensure that all personal involved in project remained blind as to which group any given participant belonged.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Methods applied to account for missing data not described. Intention-to-treat approach not reported. However, there were no dropouts.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Gual 2003

Methods	Randomized, double-blind, placebo-controlled trial
Participants	83 depressed people with alcohol dependence (44 men and 39 women; mean age = 47 years) Inclusion criteria: • age ≥ 18 years • current DSM-IV and ICD-10 diagnoses of alcohol dependence and depression or dysthymia Exclusion criteria: • women who were pregnant, breastfeeding, or who were of childbearing potential and were not using reliable contraception or who wished to become pregnant during study or within 1 month after study • psychiatric disorders apart from alcohol dependence and depressive symptoms

Gual 2003 *(Continued)*

- moderate or severe liver disease including active cirrhosis or acute hepatitis
- high suicide risk
- requiring therapy with additional psychotropic drugs, ECT, or intensive psychotherapy during study
- history of convulsive disorders, cerebral organic disease, or laxative misuse within the 6 months prior to receiving test drug
- had received therapy with depot neuroleptics during the 6 months prior to their inclusion in study
- requiring medical treatment
- history of failure on sertraline or any other serotonin reuptake selective inhibitor, either alone or combined with another therapy
- people in whom sertraline therapy was contraindicated
- other severe organic diseases

Participants with bipolar disorder were excluded.

Interventions	Drugs: • sertraline (50–150 mg/day; 44 participants) • placebo (39 participants) Psychotherapy: information not available Scheduled duration of treatment: 24 weeks Site: Alcohol Unit of the Hospital 'Clínico y Provincial' in Barcelona, Spain Setting: outpatients Route of administration: orally Starting dose: 50 mg/day Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score (data obtained from a figure) • final MADRS score (data obtained from a figure) • response • remission Alcohol dependence: • rate of abstinent days • number of heavy drinkers • time to first relapse Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration: about 3 years for men; about 1 year for women • MADRS score (mean ± SD): sertraline = 22 ± 7; placebo = 23 ± 8 • HRSD score (mean ± SD): sertraline = 14 ± 6, placebo = 13 ± 4 Alcohol dependence:

Gual 2003 *(Continued)*

- severity: information not available
- duration: about 16 years
- being actively drinking: participants had to be "abstinent for at least 2 weeks following detoxification" and "to have a negative drug and alcohol urine screen at inclusion"
- length of abstinence: ≥ 2 weeks

Other psychiatric comorbidity: people with other mental disorders were excluded.

Other substance-use disorders: people with substance-use disorders were excluded.

Other characteristics of study

Other pharmacological treatment: other pharmacological treatments were not allowed.

Funding source: information not available

Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation stated. The investigator did not have access to the randomization code.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching packets containing placebo were provided for all possible sertraline dose progressions, so that titration could be performed double blind. Medication was dispensed in bottles with MEMS caps, which contain an electronic monitoring device that records the date and time of bottle cap openings (Aprex Corp, San Diego, CA).
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat method utilized in all statistical analyses.
Selective reporting (reporting bias)	Low risk	For alcohol consumption data, participants with missing assessments at last observation were treated as non-abstinent. For depression scale scores, missing data were handled on the principle of last observation carried forward.

Habrat 2006

Methods	Randomized, double-blind, comparative trial
Participants	286 depressed people with alcohol dependence (222 men and 64 women; mean age: information not available). Inclusion criteria:

Habrat 2006 *(Continued)*

	• aged 21-65 years • ICD-10 diagnoses of alcohol dependence or alcohol abuse and depression or bipolar disorder • HRSD score ≥ 16 Exclusion criteria: • any condition potentially dangerous, e.g. suicidal thoughts, psychotic depression, or pregnancy • needs of treatment for other diseases • treatments in near past with drugs that interfere with drugs in research or influence investigated therapy • lack of conscious agreement • depression resistant to pharmacotherapy Participants with bipolar disorder were included.
Interventions	Drugs: • tianeptine (37.5 mg/day; 146 participants; 109 men and 37 women; age: information not available) • fluvoxamine (100 mg/day; 140 participants; 113 men and 27 women; age: information not available) Psychotherapy: information not available Scheduled duration of treatment: 6 weeks (responders were proposed to continue the same treatment up to 12 weeks). Site: Department of Substance Use Prevention and Treatment, Institute of Psychiatry and Neurology, Warsaw, Poland Setting: outpatients Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score • response Alcohol dependence: data not available Craving for alcohol: • final OCDS score Anxiety: • final HRSA score Dropout Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 12.2% • duration: information not available • HRSD score (mean ± SD): tianeptine = 22.2 ± 4.9; fluvoxamine = 21.8 ± 4.2 Alcohol dependence:

Habrat 2006 *(Continued)*

- alcohol dependence = 89.3%; alcohol abuse = 10.7%
- severity: information not available
- duration: information not available
- being actively drinking: participants had to be abstinent
- length of abstinence: ≥ 2 weeks

Craving for alcohol:

- OCDS score (mean ± SD): tianeptine = 18.2 ± 7.3; fluvoxamine = 18.1 ± 7.7

Anxiety:

- HRSA score (mean ± SD): tianeptine = 19.2 ± 6.2; fluvoxamine = 19.5 ± 6.9

Other psychiatric comorbidity: information not available

Other substance use disorders: information not available

Other characteristics of study

Other pharmacological treatment: other pharmacological treatments were not allowed.

Funding source: information not available

Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured. Both drugs were blinded to participants.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only full analysis set were evaluated by the present meta-analysis.
Selective reporting (reporting bias)	Low risk	Only full analysis set were evaluated by the present meta-analysis.

Hernandez-Avila 2004

Methods	Randomized, double-blind, placebo-controlled trial
Participants	41 depressed people with alcohol dependence (20 men and 21 women; age (mean ± SD): 42.9 ± 8.6 years) Inclusion criteria: • current DSM-IV diagnoses of alcohol dependence and depression • HRSD score ≥ 17 with a score ≥ 1 on item 1 • aged 21-65 years Exclusion criteria: • history of major medical or psychiatric problems other than major depression or an anxiety disorder • clinically significant baseline laboratory abnormalities or a positive pregnancy test • current DSM-IV diagnosis of drug dependence other than for alcohol or nicotine • positive urine drug screen • being treated with disulfiram or naltrexone or with any psychotropic drug • being at serious suicide risk Participants with bipolar disorder were excluded.
Interventions	Drugs: • nefazodone (200-600 mg/day; 21 participants; 10 men and 11 women; age (mean ± SD): 43.1 ± 9.0 years) • placebo (20 participants; 10 men and 10 women; age (mean ± SD): 42.7 ± 8.4 years) Psychotherapy: • participants received manual-guided supportive psychotherapy at each study visit Scheduled duration of treatment: 10 weeks Site: Alcohol Research Center, Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT, USA Setting: outpatients Route of administration: orally Starting dose: • 100 mg twice daily • then titrated up to a maximum dose of 300 mg twice daily Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score Alcohol dependence: • rate of abstinent days (obtained from weekly drinking days) • number of abstinent participants • number of drinking days per week • number of drinks per week • number of heavy drinking days per week • final DrinC score • final GGT levels

Hernandez-Avila 2004 *(Continued)*

Anxiety:

- final STAI score

Sleep quality:

- final PSQI score

Dropouts

Adverse effects

Notes

Baseline characteristics of participants

Depression:

- primary depression: information not available
- duration: information not available
- HRSD score (mean ± SD): nefazodone = 16.3 ± 2.3; placebo = 17.3 ± 2.0

Alcohol dependence:

- drinks per drinking days (mean ± SD): nefazodone = 6.4 ± 6.5; placebo = 8.4 ± 5.2
- duration: information not available
- being actively drinking: participants were not abstinent alcohol (their consumption had to be a mean ≥ 18 drinks per week for men or 14 drinks per week for women; heavy drinking (≥ 5 drinks for men and ≥ 4 drinks for women) on at least 1 day/week during the month preceding screening)
- length of abstinence at entry: 0 weeks

Anxiety:

- STAI score (mean ± SD): nefazodone = 51.1 ± 9.9; placebo = 47.9 ± 9.4

Quality of sleep

- PSQI score (mean ± SD): nefazodone = 22.2 ± 4.5; placebo = 22.1 ± 3.9

Other psychiatric comorbidity: participants with other mental disorders were included.

Other substance use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding sources: study supported by NIH Grants P50-AA03510, K24-AA13736, and M01-RR06192 and the Bristol-Myers Squibb Co.

Declarations of interest: information not available

Other information

After a baseline assessment, participants entered a 1-week single-blind placebo treatment, followed by random assignment to nefazodone or placebo groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment groups used an urn randomization procedure, which balanced group assignment on sex, age, educational level, percentage of heavy drinking days, and severity of depressive symptoms at the time of the initial assessment.

Hernandez-Avila 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Method of concealment not reported but unlikely that selection bias was introduced.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) objective	Low risk	No information provided on blinding of assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information provided on blinding of assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Mixed model analysis used to examine variables measured at each visit during study. This procedure allows the inclusion of all cases (41 participants) by estimating individual trajectories even when other data points are missing because of participant attrition.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.

Kranzler 2006 arm A

Methods	Randomized, double-blind, placebo-controlled trial
Participants	189 depressed people with alcohol dependence (123 men; 66 women; age (mean ± SD): placebo = 44.0 ± 8.0 years; sertraline = 41.7 ± 9.4 years) Inclusion criteria: • aged 21-65 years • current DSM-IV diagnoses of alcohol dependence and depression (modified: to meet DSM-IV criteria for depression, except that symptoms could have occurred during a period of heavy alcohol use) • HRSD score ≥ 17 Exclusion criteria: • pregnant, nursing, or of childbearing potential not using an effective method of contraception • clinically significant co-occurring psychiatric or medical diagnoses, including dependence on any psychoactive substance other than alcohol or nicotine during the preceding year • current treatment with disulfiram, naltrexone, or psychotropic medication • serum aminotransferase levels or other measures of hepatic function that were > 250% of normal • significant suicidal risk Participants with bipolar disorder were excluded.
Interventions	Drugs: • sertraline (up to 200 mg/day; 89 participants) • placebo (100 participants) Psychotherapy: at each study visit, participants received supportive therapy delivered according to a manual developed specifically for study consisting in:

Kranzler 2006 arm A *(Continued)*

- general support for abstinence
- promotion of compliance
- monitoring of medication adverse effects

Scheduled duration of treatment: for up to 10 weeks

Sites: 13 investigative sites in USA

Setting: outpatients

Route of administration: orally

Starting dose: 50 mg/day

Pattern of dose reduction:

- participants who achieved a satisfactory therapeutic response and who wished to continue treatment beyond the end of week 10 were continued double-blind on the same medication they were taking at the end of week 10 for an additional 14-week period;
- participants who did not continue in the extension study were tapered off medication by reducing the daily dose by one capsule every 2 to 3 days until the medication was completely discontinued.

Outcomes

Depression:

- final HRSD score (obtained from a figure)
- difference between baseline and final HRSD score
- response

Alcohol dependence:

- rate of abstinent days (obtained from a figure)

Dropout

Adverse effects

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 100%
- duration: information not available
- number of DSM-IV criteria (mean ± SD): sertraline = 6.7 ± 1.0; placebo = 6.8 ± 1.2
- HRSD score (mean ± SD): sertraline = 20.3 ± 2.8; placebo = 20.9 ± 4.0

Alcohol dependence:

- number of DSM-IV criteria (mean ± SD): sertraline = 5.6 ± 0.9; placebo = 5.5 ± 0.9
- number of drinks per week (mean ± SD): sertraline = 45.9 ± 32.2; placebo = 63.1 ± 44.4
- duration (mean ± SD): sertraline = 11.9 ± 9.0 years; placebo = 11.9 ± 9.9 years
- being actively drinking: participants had to have drunk a mean of 18 drinks weekly for men or 14 drinks weekly for women and at least 1 heavy drinking day per week during the month before screening
- length of abstinence: at least 4 days with no heavy drinking and no more than 16 days of abstinence

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Kranzler 2006 arm A *(Continued)*

Funding source: supported by Pfizer Pharmaceuticals. Manuscript preparation supported by NIH grant K24 AA13736.

Declarations of interest: information not available.

Other information

In the original study, 328 participants were divided into the 2 groups on whether initially elevated HRSD score declined with cessation of heavy drinking:

- HRSD score ≥ 17 (189 participants);
- HRSD score ≤ 16 (139 participants).

In the present meta-analysis, participants were divided into 2 substudies:

- Kranzler 2006 arm A (189 participants with HRSD scores ≥ 17);
- Kranzler 2006 arm B (139 participants which HRSD scores ≤ 16).

Both the substudies (Kranzler 2006 arm A; Kranzler 2006 arm B) were included in the 'Effects of interventions: Antidepressants versus placebo' comparison. Unfortunately, the original study did not report the adverse events for the single substudies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization schedule.
Allocation concealment (selection bias)	Unclear risk	Assignment to medication group was done according to a computer-generated randomization schedule for groups A and B, with the medication groups within each stratum balanced for recent outpatient/inpatient status. Despite random assignment, participants who received placebo were older, reported more drinks per week during the pretreatment period, and had higher CGI depression scores at baseline.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses used an intention-to-treat approach.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported. However, some of them were reported only as a % reduction (e.g. BDI score).

Kranzler 2006 arm B

Methods	Randomized, double-blind, placebo-controlled trial
Participants	139 depressed people with alcohol dependence (86 men and 53 women; age (mean ± SD): placebo = 42.9 ± 9.2 years; sertraline = 41.8 ± 9.4 years) Inclusion criteria: • aged 21-65 years • current DSM-IV diagnoses of alcohol dependence and depression (modified: to meet DSM-IV criteria for depression, except that symptoms could have occurred during a period of heavy alcohol use) • HRSD score ≤ 16 with cessation of heavy drinking Exclusion criteria: • pregnant, nursing, or women of childbearing potential not using an effective method of contraception • clinically significant co-occurring psychiatric or medical diagnoses • including dependence on any psychoactive substance other than alcohol or nicotine during the preceding year • current treatment with disulfiram, naltrexone, or psychotropic medication • serum aminotransferase levels or other measures of hepatic function > 250% of normal • significant suicidal risk Participants with bipolar disorder were excluded.
Interventions	Drugs: • sertraline (up to 200 mg/day; 70 participants) • placebo (69 participants) Psychotherapy: At each study visit, participants received supportive therapy delivered according to a manual developed specifically for study consisting of: • general support for abstinence; • promotion of compliance; • monitoring of medication adverse effects. Scheduled duration of treatment: up to 10 weeks Sites: 13 investigative sites in the USA Setting: outpatients Route of administration: orally Starting dose: 50 mg/day Pattern of dose reduction: • participants who achieved a satisfactory therapeutic response and who wished to continue treatment beyond the end of week 10 were continued double-blind on the same medication they were taking at the end of week 10 for an additional 14-week period; • participants who did not continue in the extension study were tapered off medication by reducing the daily dose by 1 capsule every 2 or 3 days until the medication was completely discontinued.
Outcomes	Depression: • final HRSD score (obtained from a figure) • difference between baseline and final HRSD score • response

Kranzler 2006 arm B *(Continued)*

Alcohol dependence:

- rate of abstinent days (obtained from a figure)

Dropout

Adverse effects

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 0%
- duration: information not available
- number of DSM-IV criteria (mean ± SD): sertraline = 5.3 ± 1.3; placebo = 5.4 ± 1.1
- HRSD score (mean ± SD): sertraline = 12.6 ± 2.8; placebo = 12.5 ± 2.9

Alcohol dependence:

- number of DSM-IV criteria (mean ± SD): sertraline = 4.6 ± 1.2; placebo = 4.5 ± 1.0
- number of drinks per week (mean ± SD): sertraline = 54.4 ± 40.5; placebo = 46.8 ± 27.9
- duration (mean ± SD): sertraline = 10.7 ± 8.1 years; placebo = 11.1 ± 8.5 years
- being actively drinking: participants had to have drunk a mean of 18 drinks weekly for men or 14 drinks weekly for women and at least 1 heavy drinking day per week during the month before screening
- length of abstinence: at least 4 days with no heavy drinking and no more than 16 days of abstinence

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: study supported by Pfizer Pharmaceuticals. Manuscript preparation supported by NIH grant K24 AA13736.

Declarations of interest: information not available

Other information

In the original study, 328 participants were divided into the 2 groups on whether initially elevated HRSD score declined with cessation of heavy drinking:

- HRSD score ≥ 17 (189 participants);
- HRSD score ≤ 16 (139 participants).

In the present meta-analysis, participants were divided into 2 substudies:

- Kranzler 2006 arm A (189 participants with HRSD scores ≥ 17);
- Kranzler 2006 arm B (139 participants which HRSD scores ≤ 16).

Both the substudies (Kranzler 2006 arm A; Kranzler 2006 arm B) were included in the 'Effects of interventions: Antidepressants versus placebo' comparison. Unfortunately, the original study did not report the adverse events for the single substudies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization schedule reported.

Kranzler 2006 arm B *(Continued)*

Allocation concealment (selection bias)	Unclear risk	The method of concealment was not described. Despite random assignment, participants who received placebo were older, reported more drinks per week during the pretreatment period, and had higher CGI depression scores at baseline.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses used an intention-to-treat approach. Weekly comparisons including only participants for whom data were available from that visit, whereas end of study analyses used last observation carried forward analysis.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported. However, some of them were reported only as a % reduction (e.g. BDI score).

Krupitsky 1993 arm A

Methods	Randomized, placebo-controlled trial
Participants	41 people with alcohol dependence (number of men and women not available; mean age = 36-37 years) with non-severe affective disorders Inclusion criteria: information not available Exclusion criteria: information not available Participants with bipolar disorder: information not available
Interventions	Drugs: • amitriptyline (dose: 75 mg/day; 18 participants; number of men and women not available; age (mean ± SD): 36.3 ± 1.9 years) • placebo (23 participants; number of men and women not available; age (mean ± SD): 37.3 ± 1.7 years) Psychotherapy: information not available Scheduled duration of treatment: 3 weeks Site: Russia Setting: inpatients Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression:

Krupitsky 1993 arm A *(Continued)*

- final ZUNG score
- final MMPI score

Alcohol dependence: no information provided

Anxiety:

- final STAI score
- final MMPI score

Dropouts: data not available

Adverse effects: information not provided

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 100%
- duration: information not available
- ZUNG score (mean ± SD): amitriptyline = 55.6 ± 1.2; placebo = 55.3 ± 1.0
- MMPI score (mean ± SD): amitriptyline = 82.1 ± 1.5; placebo = 81.3 ± 3.9

Alcohol dependence:

- severity: information not available
- duration: information not available
- participants were abstinent for at least 3-4 weeks

Anxiety:

- STAI score (mean ± SD): amitriptyline = 51.9 ± 2.6; placebo = 52.5 ± 2.9
- MMPI score (mean ± SD): amitriptyline = 25.5 ± 1.9; placebo = 28.0 ± 2.0

Other psychiatric comorbidity: information not available

Other substance use disorders: information not available

Other characteristics of study

Other pharmacological treatment offered: other treatments were not administrated during study

Funding sources: information not available.

Other information

In the original study, 90 people with alcohol dependence were randomly divided into 4 groups:

- baclofen (37.5 mg/day, 29 participants)
- diazepam (15 mg/day; 20 participants)
- amitriptyline (75 mg/day, 18 participants)
- placebo (23 participants)

In the present meta-analysis, study was divided into 2 substudies:

- Krupitsky 1993 arm A, which included the group 'amitriptyline' and the group 'placebo'
- Krupitsky 1993 arm B, which included the group 'amitriptyline' and the group 'diazepam'

The first substudy (Krupitsky 1993 arm A) was included in the 'Effects of interventions: Antidepressants versus placebo' comparison and the second substudy (Krupitsky 1993 arm B) in the 'Antidepressants versus other medications' comparison

Krupitsky 1993 arm A *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported if it was a double- or single-blind study.
Blinding of outcome assessment (detection bias) objective	Low risk	Not reported if it was a double- or single-blind study.
Blinding of outcome assessment (detection bias) subjective	High risk	Not reported if it was a double- or single-blind study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of dropouts not reported.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Krupitsky 1993 arm B

Methods	Randomized, controlled trial
Participants	38 people with alcohol dependence (number of men and women not available; mean age = 36-37 years) with affective disorders not severe Inclusion criteria: information not available Exclusion criteria: information not available Participants with bipolar disorder: information not available
Interventions	Drugs: • amitriptyline (75 mg/day; 18 participants; number of men and women not available; age (mean ± SD): 36.3 ± 1.9 years) • diazepam (15 mg/day; 20 participants; number of men and women not available; age (mean ± SD): 38.3 ± 1.8 years) Psychotherapy: information not available Scheduled duration of treatment: 3 weeks Site: Russia Setting: inpatients

Krupitsky 1993 arm B *(Continued)*

Route of administration: orally

Starting dose: information not available

Pattern of dose reduction: information not available

Outcomes

Depression:

- final ZUNG score
- final MMPI score

Alcohol dependence: no information provided

Anxiety:

- final STAI score
- final MMPI score

Dropouts: data not available

Adverse effects: data not available

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 100%
- duration: information not available
- ZUNG score (mean ± SD): amitriptyline = 55.6 ± 1.2; diazepam = 54.2 ± 0.6
- MMPI score (mean ± SD): amitriptyline = 82.1 ± 1.5; diazepam =81.1 ± 3.3

Alcohol dependence:

- severity: information not available
- duration: information not available
- being actively drinking: participants were abstinent for at least 3-4 weeks

Anxiety:

- STAI score (mean ± SD): amitriptyline = 51.9 ± 2.6; diazepam = 51.8 ± 1.5
- MMPI score (mean ± SD): amitriptyline = 25.5 ± 1.9; diazepam = 27.0 ± 1.7

Other psychiatric comorbidity: information not available

Other substance use disorders: information not available

Other characteristics of study

Other pharmacological treatment offered: other treatments were not administrated during study

Funding sources: information not available

Other information

In the original study, 90 people with alcohol dependence were randomly divided into 4 groups:

- baclofen (37.5 mg/day, 29 participants)
- diazepam (15 mg/day; 20 participants)
- amitriptyline (75 mg/day, 18 participants)
- placebo (23 participants)

In the present meta-analysis, study was divided into 2 substudies:

- Krupitsky 1993 arm A, which included the group 'amitriptyline' and the group 'placebo'

Krupitsky 1993 arm B *(Continued)*

- Krupitsky 1993 arm B, which included the group 'amitriptyline' and the group 'diazepam'

The first substudy (Krupitsky 1993 arm A) was included in the 'Effects of interventions: Antidepressants versus placebo' comparison and the second substudy (Krupitsky 1993 arm B) in the 'Antidepressants versus other medications' comparison.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported if it was a double- or single-blind study.
Blinding of outcome assessment (detection bias) objective	Low risk	Not reported if it was a double- or single-blind study.
Blinding of outcome assessment (detection bias) subjective	High risk	Not reported if it was a double- or single-blind study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of dropouts not reported.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Krupitsky 2012

Methods	Randomized, double-blind, placebo-controlled trial
Participants	60 depressed people with alcohol dependence (47 men and 13 women; age (mean ± SD): escitalopram = 43.9 ± 1.1 years; placebo = 40.9 ± 1.3 years). Inclusion criteria: • current ICD-10 diagnoses of alcohol dependence and affective disorders (a depression episode, a moderate depression episode, or a recurrent depression disorder) • HRSD score: 7-23 Exclusion criteria: • substance dependence besides alcohol or nicotine dependence • bipolar-affective disorder, schizophrenia, or other psychotic or organic mental disorders • other psychotropic drug • severe medical illnesses • pregnancy

Krupitsky 2012 *(Continued)*

	Participants with bipolar disorder were excluded.
Interventions	Drugs: • escitalopram (10 mg/day; 29 participants; 22 men and 7 women) • placebo (31 participants, 25 men and 6 women) Psychotherapy: • medical management which included elements of cognitive behavioural psychotherapy, once a week Scheduled duration of treatment: 13 weeks Site: a single-site at the Department of Narcology (Addiction Psychiatry) of the Bekhterev PsychoNeurological Research Institute, St Petersburg, Russia Setting: outpatients Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score • final MADRS score • final ZUNG score Alcohol dependence: • heavy drinkers • time to first relapse • final GGT levels Craving for alcohol: • final PACS score • final OCDS score • final VAS score Global response: • response • final GAF score Anxiety: • final HRSA score • final STAI score Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): information not available • duration: information not available • severity: mild or moderate depression

Krupitsky 2012 *(Continued)*

Alcohol dependence:

- duration (mean ± SD): escitalopram = 11.5 ± 1.5 years; placebo = 9.5 ± 1.4 years
- being actively drinking: participants had to be abstinent at least 7 days and had a negative alcohol test on expired air
- length of abstinence: 1 week

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: information not available.

Declarations of interest: information not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by means of generation random numbers in Excel.
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical appearance.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators, doctors, participants, and any other staff members taking part in the experiment were unaware which of the groups any particular person belonged to.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Methods: participants who relapsed to heavy drinking were excluded from study. Results: the relatively small number of alcohol consumption days in the groups was due to participants who relapsed being excluded from trial.
Selective reporting (reporting bias)	High risk	Methods: participants who relapsed to heavy drinking were excluded from study. Results: the relatively small number of alcohol consumption days in the groups was due to participants who relapsed being excluded from trial.

Liappas 2005 arm A

Methods	Randomized, single-blind, comparative trial

Liappas 2005 arm A *(Continued)*

Participants	30 people with alcohol dependence of an original group constituted by 60 participants (41 men and 19 women; mean age: 47 years) Inclusion criteria: • current DSM-IV diagnosis of alcohol abuse or alcohol dependence • aged 18-70 years Exclusion criteria: • DSM-IV diagnosis of primary depression; secondary depression was not an exclusion criterion • serious physical illness • other pre- or coexisting major psychiatric disorder, i.e. any psychotic disorder and bipolar disorder • other drug abuse, excluding nicotine Participants with bipolar disorder were excluded.
Interventions	Treatment: • mirtazapine (30-60 mg/day, in 1-2 divided doses per day; 20 participants; 13 men and 7 women) and psychotherapy • only psychotherapy (10 participants) Psychotherapy: cognitive behavioural psychotherapy administered in individual sessions and family interventions, twice a week Scheduled duration of treatment: 3 weeks Site: Drug and Alcohol Addiction Clinic, Athens University Psychiatric Clinic, Eginition Hospital, Athens, Greece Setting: inpatients for 1 week, then residential treatment Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score Alcohol dependence: no information available Anxiety: • final HRSA score Global assessment: • final GAS score Dropouts Adverse effects: data not available
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 0% • duration: information not available

Liappas 2005 arm A *(Continued)*

- HRSD score (mean ± SD): mirtazepine = 37.9 ± 7.8; controls = 39

Alcohol dependence:

- drinks per drinking days (mean ± SD): mirtazepine = 27.6 ± 18.5; controls = 22.1,
- duration (mean ± SD): mirtazepine = 15 years; controls = 14 years,
- being actively drinking: participants were detoxicated before treatment,
- length of abstinence: 1 week

Anxiety:

- HRSA score (mean ± SD): mirtazapine = 33.2 ± 12.6; controls = 33.

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance-use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: information not available

Declarations of interest: information not available

Other information

In the original study, 60 participants were included into 4 groups:

- only psychotherapy (20 participants)
- mirtazapine plus psychotherapy (20 participants)
- venlafaxine plus psychotherapy (20 participants)

Participants but not clinicians were blind to group status

In the present meta-analysis, we divided the control group (only psychotherapy) into 2 smaller groups, and compared these 2 smaller groups to the 2 antidepressants, using 3 subgroups:

- Liappas 2005 arm A ('Effects of interventions: Antidepressants versus psychotherapy') included 10 participants of the group 'only psychotherapy' and the group 'mirtazapine plus psychotherapy'
- Liappas 2005 arm B ('Effects of interventions: Antidepressants versus psychotherapy') included 10 participants of the group 'only psychotherapy' and the group 'venlafaxine plus psychotherapy'
- Liappas 2005 arm C ('Effects of interventions: Antidepressants versus another antidepressant') included the group 'mirtazapine plus psychotherapy' and the group 'venlafaxine plus psychotherapy'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random sequence generation was used ("At the end of the first week, individuals were randomly/electronically allocated to one of the three groups").
Allocation concealment (selection bias)	Low risk	Computer sequence of allocation used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study ("Patients but not clinicians were blind to group status").

Liappas 2005 arm A *(Continued)*

Blinding of outcome assessment (detection bias) objective	Low risk	Single-blind study ("Patients but not clinicians were blind to group status").
Blinding of outcome assessment (detection bias) subjective	High risk	Single-blind study ("Patients but not clinicians were blind to group status").
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts were not included in the analysis due to missing data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Liappas 2005 arm B

Methods	Randomized, single-blind, comparative trial
Participants	30 people with alcohol dependence of an original group constituted by 60 participants (41 men and 19 women; mean age: 47 years) Inclusion criteria: • current DSM-IV diagnosis of alcohol abuse or alcohol dependence • aged 18-70 years Exclusion criteria: • DSM-IV diagnosis of primary depression; secondary depression was not an exclusion criterion • serious physical illness • other pre- or coexisting major psychiatric disorder, i.e. any psychotic disorder and bipolar disorder • other drug abuse, excluding nicotine Participants with bipolar disorder were excluded.
Interventions	Treatment: • venlafaxine (150-300 mg/day, in 1-2 divided doses per day; 20 participants; 13 men and 7 women) and psychotherapy • only psychotherapy (10 participants) Psychotherapy: cognitive behavioural psychotherapy was administered in individual sessions and family interventions, twice a week Scheduled duration of treatment: 3 weeks Site: Drug and Alcohol Addiction Clinic, Athens University Psychiatric Clinic, Eginition Hospital, Athens, Greece Setting: inpatients for 1 week, then residential treatment Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression:

Liappas 2005 arm B *(Continued)*

- final HRSD score

Alcohol dependence: no information available

Anxiety:

- final HRSA score

Global assessment:

- final GAS score

Dropouts

Adverse effects: data not available

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 0%
- duration: information not available
- HRSD score (mean ± SD): venlafaxine = 41.9 ± 4.5; controls = 39

Alcohol dependence:

- drinks per drinking days (mean ± SD): venlafaxine = 18.4 ± 6.2; controls = 22.1
- duration (mean ± SD): venlafaxine = 17 years; controls = 14 years
- being actively drinking: participants were detoxicated before treatment
- length of abstinence: 1 week

Anxiety:

- HRSA score (mean ± SD): venlafaxine = 36.6 ± 5.4; controls = 33

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance-use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: information not available

Declarations of interest: information not available

Other information

In the original study, 60 participants were included into 4 groups:

- only psychotherapy (20 participants)
- mirtazapine plus psychotherapy (20 participants)
- venlafaxine plus psychotherapy (20 participants)

Participants but not clinicians were blind to group status

In the present meta-analysis, we divided the control group (only psychotherapy) into 2 smaller groups, and compared these 2 smaller groups to the 2 antidepressants, using 3 subgroups:

- Liappas 2005 arm A ('Effects of interventions: Antidepressants versus psychotherapy') included 10 participants of the group 'only psychotherapy' and the group 'mirtazapine plus psychotherapy'
- Liappas 2005 arm B ('Effects of interventions: Antidepressants versus psychotherapy') included 10 participants of the group 'only psychotherapy' and the group 'venlafaxine plus psychotherapy'

Liappas 2005 arm B *(Continued)*

- Liappas 2005 arm C ('Effects of interventions: Antidepressants versus vs another antidepressant') included the group 'mirtazapine plus psychotherapy' and the group 'venlafaxine plus psychotherapy'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random sequence generation reported ("At the end of the first week, individuals were randomly/electronically allocated to one of the three groups")
Allocation concealment (selection bias)	Low risk	Computer sequence of allocation reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study ("Patients but not clinicians were blind to group status").
Blinding of outcome assessment (detection bias) objective	Low risk	Single-blind study ("Patients but not clinicians were blind to group status").
Blinding of outcome assessment (detection bias) subjective	High risk	Single-blind study ("Patients but not clinicians were blind to group status").
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts were not included in the analysis due to missing data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Liappas 2005 arm C

Methods	Randomized, single-blind, comparative trial
Participants	40 people with alcohol dependence of an original group constituted by 60 participants (41 men and 19 women; mean age: 47 years) Inclusion criteria: • current DSM-IV diagnosis of alcohol abuse or alcohol dependence • aged 18-70 years Exclusion criteria: • DSM-IV diagnosis of primary depression; secondary depression was not an exclusion criterion • serious physical illness • other pre- or coexisting major psychiatric disorder, i.e. any psychotic disorder and bipolar disorder • other drug abuse, excluding nicotine Participants with bipolar disorder were excluded.
Interventions	Drugs:

Liappas 2005 arm C *(Continued)*

- mirtazapine (30-60 mg/day, in 1-2 divided doses per day, 20 participants; 13 men and 7 women) and psychotherapy
- venlafaxine (150-300 mg/day, in 1-2 divided doses per day; 20 participants; 13 men and 7 women) and psychotherapy

Psychotherapy: cognitive behavioural psychotherapy was administered in individual sessions and family interventions, twice a week.

Scheduled duration of treatment: 3 weeks

Site: Drug and Alcohol Addiction Clinic, Athens University Psychiatric Clinic, Eginition Hospital, Athens, Greece

Setting: inpatients for 1 week, then residential treatment

Route of administration: orally

Starting dose: information not available

Pattern of dose reduction: information not available

Outcomes	Depression: • final HRSD score Alcohol dependence: no information available Anxiety: • final HRSA score Global assessment: • final GAS score Dropouts Adverse effects: data not available
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 0% • duration: information not available • HRSD score (mean ± SD): mirtazepine = 37.9 ± 7.8; venlafaxine = 41.9 ± 4.5 Alcohol dependence: • drinks per drinking days: mirtazepine = 27.6 ± 18.5; venlafaxine = 18.4 ± 6.2 • duration: venlafaxine = 17 years; controls = 14 years • being actively drinking: participants were detoxicated before treatment • length of abstinence: 1 week Anxiety: • HRSA score (mean ± SD): mirtazapine: 33.2 ± 12.6; venlafaxine = 36.6 ± 5.4 Other psychiatric comorbidity: participants with other mental disorders were excluded. Other substance use disorders: participants with substance use disorders were excluded. **Other characteristics of study** Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Liappas 2005 arm C *(Continued)*

Funding source: information not available

Declarations of interest: information not available

Other information

In the original study, 60 participants were included into 4 groups:

- only psychotherapy (20 participants)
- mirtazapine plus psychotherapy (20 participants)
- venlafaxine plus psychotherapy (20 participants)

Participants but not clinicians were blind to group status.

In the present meta-analysis, we divided the control group (only psychotherapy) into 2 smaller groups, and compared these 2 smaller groups to the 2 antidepressants, using 3 subgroups:

- Liappas 2005 arm A ('Effects of interventions: Antidepressants versus psychotherapy') included 10 participants of the group 'only psychotherapy' and the group 'mirtazapine plus psychotherapy'
- Liappas 2005 arm B ('Effects of interventions: Antidepressants versus psychotherapy') included 10 participants of the group 'only psychotherapy' and the group 'venlafaxine plus psychotherapy'
- Liappas 2005 arm C ('Effects of interventions: Antidepressants versus another antidepressant') included the group 'mirtazapine plus psychotherapy' and the group 'venlafaxine plus psychotherapy'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random sequence generation reported ("At the end of the first week, individuals were randomly/electronically allocated to one of the three groups")
Allocation concealment (selection bias)	Low risk	Computer sequence of allocation reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study, and the outcomes are likely to be influenced by lack of blinding ("Patients but not clinicians were blind to group status").
Blinding of outcome assessment (detection bias) objective	Low risk	Single-blind study, and the outcomes are likely to be influenced by lack of blinding ("Patients but not clinicians were blind to group status").
Blinding of outcome assessment (detection bias) subjective	High risk	Single-blind study, and the outcomes are likely to be influenced by lack of blinding ("Patients but not clinicians were blind to group status").
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts were not included in the analysis due to missing data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Lôo 1988

Methods	Randomized, double-blind, comparative trial
Participants	129 people with alcohol dependence with depression or dysthymic disorder (111 men and 18 women; mean age: approximately 38 years) Inclusion criteria: • DSM-III diagnoses of alcohol dependence or alcohol abuse and depression or dysthymia • MADRS score ≥ 20 Exclusion criteria: • persistent alcohol intoxication at time of trial • presence of psychotic traits • recent antidepressant or neuroleptic treatment • serious somatic illness • pregnancy or absence of contraception in a woman of childbearing potential Participants with bipolar disorder: information not available
Interventions	Drugs: • tianeptine (37.5 mg/day; 64 participants; 57 men and 7 women; age (mean ± SD): 37.9 ± 1.0 years) • amitriptyline (75.0 mg/day; 65 participants; 54 men and 11 women) Psychotherapy: information not available Scheduled duration of treatment: 4-8 weeks (depending on the centre concerned) Sites: 7 centres, in France Setting: unclear Route of administration: orally Starting dose: tianeptine = 37.5 mg/day; amitriptyline = 75.0 mg/day Pattern of dose reduction: information not available
Outcomes	Depression: • final MADRS score (obtained from a figure) • final SCL-90 (obtained from a figure) • response Alcohol dependence: data not available Anxiety: • final HRSA score (obtained from a figure) Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 100% • duration: information not available • MADRS score (mean ± SD): tianeptine = 30.0 ± 0.8; amitriptyline = 29.3 ± 0.8

Lôo 1988 *(Continued)*

Alcohol dependence:

- duration: information not available
- severity: information not available
- being actively drinking: participants were withdrawn from alcohol 2-5 weeks before inclusion

Other psychiatric comorbidity: information not available

Other substance use disorders: information not available

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were allowed.

Funding source: information not available

Declarations of interest: information not available

Other information

In the original study, the duration of the trial was 4-8 weeks depending on the centre concerned. In the present meta-analysis, only data of 4 weeks were analyzed.

Before the onset of the trial, participants received a pretreatment with a placebo for 3-10 days to screen out placebo-responder participants. After this period, participants received tianeptine or amitriptyline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated. Medication and placebo prepared to appear identical. No specific reference made to blinding of participants and personnel.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis not used. However, the numbers of dropouts were low (10/64, 12/65) and were not unbalanced between groups.
Selective reporting (reporting bias)	High risk	Several data were missing (final MADRS score for amitriptyline, adverse effects, and alcohol consumption).

Mason 1996

Methods	Randomized, double-blind, placebo-controlled trial
Participants	28 depressed people with alcohol dependence (24 men and 4 women; mean age = desimipramine: 36.0 ± 22 years; placebo = 41.0 ± 15.5 years) Inclusion criteria: • current DSM-III-R diagnoses of alcohol dependence and depression • secondary depression • aged 18-65 years Exclusion criteria: • primary depression • instable medical illnesses • pregnancy • psychosis • suicidal ideation • cognitively impairment • dependence on any substance except alcohol or nicotine Participants with bipolar disorder: information not available
Interventions	Drugs: • desimipramine (200 mg/day; 15 participants; 13 men and 2 women) • placebo (13 participants; 11 men and 2 women) Psychotherapy: participants were encouraged to participate in Alcoholics Anonymous and any other psychosocial treatments. Scheduled duration of treatment: 6 months Sites: Department of the New York (NY) Hospital-Cornell Medical Center, and the University of Miami (FL), School of Medicine, USA Setting: outpatients Route of administration: orally Starting dose: medication was prescribed in divided doses for the first week, then changed to bedtime dosing Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score • difference between baseline and final HRSD score • response Alcohol dependence: • number of heavy drinkers (obtained from a figure) Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression:

Mason 1996 *(Continued)*

- primary depression (rate of participants): 0%
- HRSD score (mean ± SD): desimipramine = 20.5 ± 9.7; placebo = 19.0 ± 11.0
- family history of depression: desimipramine = 41%; placebo = 83%

Alcohol dependence:

- ADS score (mean ± SD): desimipramine = 23.5 ± 10.5; placebo = 23.0 ± 13.0
- duration: information not available
- being actively drinking: participants had to be abstinent (maximum = 3 months; minimum = 1 week)
- number of drinks per drinking days (mean ± SD): desimipramine = 15.0 ± 15.0; placebo = 13.0 ± 6.7
- family history of alcohol dependence: desimipramine = 66%; placebo = 66%

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: grants from the National Institute on Alcohol Abuse and Alcoholism (AA06866 and AA08111)

Declarations of interest: information not available

Other information

Final HRSD score and difference between baseline and final HRSD score were excluded because they were expressed as medians and interquartile ranges.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind stated and blinding of key study personnel ensured by sentences of the evaluation of plasma desipramine concentration. "Plasma desipramine concentration was assessed and results were reviewed by a physician not involved in patient ratings to verify compliance and make dose recommendations. Equivalent dosing instructions were given by the nonblinded physician to blinded therapists for placebo-treated patients to preserve the double-blind study design."
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention to treat was not used. Participants who relapsed, who demonstrated non-compliance, or who did not improve were removed from study.

Mason 1996 *(Continued)*

Selective reporting (reporting bias)	High risk	Participants who relapsed, who demonstrated non-compliance, or who did not improve were removed from study.

McGrath 1996

Methods	Randomized, double-blind, placebo-controlled trial
Participants	69 depressed people with alcohol dependence (34 men and 35 women; age (mean ± SD): imipramine = 37.4 ± 6.7 years; placebo = information not available (report stated "10.6 ± 9.1")). Inclusion criteria: • current DSM-III-R diagnoses of depression (or dysthymia, or depressive disorder not otherwise specified) and alcohol dependence (or abuse) • primary depression • aged 18-65 years Exclusion criteria: • history of mania, psychosis, seizure disorder, severe current physical dependence on alcohol requiring inpatient detoxification, abstinence of 2 weeks' duration at baseline, or for current serious and unstable physical illnesses • dependence on another substance, apart from nicotine, within the last 6 months • women not using adequate contraception Participants with bipolar disorder were excluded.
Interventions	Drugs: • imipramine (50-300 mg/day; 36 participants; 19 men and 17 women) • placebo (33 participants; 15 men and 18 women) Psychotherapy: • weekly individual relapse prevention counselling sessions; • attendance at Alcoholics Anonymous was strongly encouraged. Scheduled duration of treatment: 12 weeks Site: Depression Evaluation Service, New York State Psychiatric Institute, New York, NY, USA Setting: outpatients Route of administration: orally Starting dose: • 50 mg/day • increased by 50 mg every 3-5 days to a maximum dose of 300 mg Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score • response Alcohol dependence: • rate of abstinent days (obtained from the rate of drinking days)

McGrath 1996 *(Continued)*

- number of abstinent participants
- number of drinks per drinking days
- number of heavy drinking days per week (obtained from the rate of heavy drinking days)

Global response

Dropouts

Adverse effects: data not available

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 100%
- duration: information not available
- HRSD score (mean ± SD): imipramine = 15.4 ± 5.2; placebo = 14.3 ± 5.2

Alcohol dependence:

- age of onset (mean ± SD): imipramine = 28.6 ± 15.2 years; placebo = 25.7 ± 9.2 years
- being actively drinking: participants excluded if their abstinence ≥ 2 weeks
- number of drinks per drinking days (mean ± SD): imipramine = 9.1 ± 6.5; placebo = 11.4 ± 13.7

Other psychiatric comorbidity: history of hypomania was not exclusionary.

Other substance-use disorders: history of current abuse of other substances was not exclusionary, provided that alcohol was clearly the main substance of abuse.

Other characteristics of study

Other pharmacological treatment offered: information not available

Funding source: grants from the National Institute on Alcohol Abuse and Alcoholism (AA9539), the state of New York, and the Mental Health Clinical Research Center (NIMH 30906). Medications were supplied by Ciba-Geigy Corp.

Declarations of interest: information not available

Other information

Eligible participants were given single-blind placebo for 1 week. Participants whose depression was not rated 'much improved' or 'very much improved' on the improvement item of the CGI scale for depression were randomized to receive placebo or imipramine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Double-blind stated and medications prepared to appear identical. No specific reference made to blinding of participants and personnel. Plasma dosage of imipramine performed but no information on blinding of personnel provided.

McGrath 1996 *(Continued)*

Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses used. "Ratings from the last observation were carried forward for those subjects who did not complete all 12 weeks of treatment. Intention-to-treat analyses included all randomized patients and carried last observation forward for dropouts and those who completed less than 12 weeks."
Selective reporting (reporting bias)	High risk	Treatment outcomes were reported only for completers.

McLean 1986

Methods	Randomized, double-blind, placebo-controlled trial
Participants	35 people with alcohol dependence (number of men and women: not available; mean age: information not available) Inclusion criteria: • people with alcohol dependence with inability to restrict alcohol consumption, alcohol craving, and tolerance • most of the features of alcohol dependence described in Edwards 1976 • score in a self-rating scale derived by HRSD ≥ 17 within 4 days of detoxification with benzodiazepines Exclusion criteria: • pregnant or lactating women • psychosis, or a severe organic or mental disease Participants with bipolar disorder: information not available
Interventions	Drugs: • mianserin (60 mg/day; 17 participants) • placebo (18 participants) Psychotherapy: • group meetings • individual counselling • relaxation • occupational therapy Scheduled duration of treatment: 4 weeks Site: Alcoholism Treatment Unit, Mapperley Hospital, Nottingham, UK Setting: inpatients Route of administration: orally

McLean 1986 *(Continued)*

	Starting dose: • 30 mg/day for 7 days • then 60 mg/day for the next 3 weeks Pattern of dose reduction: • after 4 weeks of treatment, drug was withdrawn
Outcomes	Depression: • final score in a self-rating scale derived by HRSD • difference between final and initial score in a self-rating scale derived by HRSD • response (evaluated using a self-rating scale derived by HRSD) Alcohol dependence: data not available Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration: information not available • score in a self-rating scale derived by HRSD (mean ± SD): 27 ± 6.1 Alcohol dependence: • severity: information not available • being actively drinking: participants were rated within 4 days of admission • length of abstinence: information not available. Other psychiatric comorbidity: sociopathic personality disorder was present in 6 participants; 3 were considered to have significant anxiety; there were no diagnoses of schizophrenia or psychotic illness. Other substance-use disorders: information not available **Other characteristics of study** Other pharmacological treatment offered: • disulfiram (18 participants) • chlordiazepoxide (10 participants) • benzodiazepines (8 participants) Funding source: Bencard. Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation stated. No further details provided.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.

McLean 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated. No information on blinding of participants and personnel and on the appearance of medications.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis not used. However, the number of dropouts was low and balanced between groups.
Selective reporting (reporting bias)	High risk	Data of participants who dropped out of study were not included in results.

Moak 2003

Methods	Randomized, placebo-controlled trial
Participants	82 depressed people with alcohol dependence (50 men and 32 women; age (mean ± SD): sertraline = 41 ± 11 years; placebo = 42 ± 10 years) Inclusion criteria: • current DSM-III-R diagnoses of depression or dysthymic disorder and alcohol dependence or abuse • HRSD ≥ 17, both at screening and at the end of 1 week of single-blind placebo • minimum of 40 standard drinks during month before study entry Exclusion criteria: • any current psychoactive substance dependence other than nicotine • psychoactive substance abuse in month before study entry other than marijuana • current panic disorder or post-traumatic stress disorder • lifetime history of bipolar affective or psychotic disorder • evidence of treatment-resistant depression • significant current suicidal ideation or plan, homicidal ideation, unstable medical illness, or history of a seizure disorder Participants with bipolar disorder were excluded.
Interventions	Drugs: • sertraline (up to 200 mg/day; 38 participants) • placebo (44 participants) Psychotherapy: • weekly individual CBT according to Project MATCH guidelines Scheduled duration of treatment: 12 weeks Site: Alcohol Research Center, Center for Drug and Alcohol Programs, Charleston, SC, USA

Moak 2003 *(Continued)*

	Setting: outpatients Route of administration: orally Starting dose: 50 mg/day Pattern of dose reduction: titrated back down 50 mg over 7-day period
Outcomes	Depression: • final HRSD score • final BDI score • response (calculated from significant depression) Alcohol dependence: • rate of abstinent days • number of drinks per drinking days • number of heavy drinkers (calculated from a figure on % without relapse) Dropout Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 85.4% • duration: information not available • HRSD score (mean ± SD): sertraline = 19.4 ± 2.6; placebo = 18.8 ± 2.4 Alcohol dependence: • number of drinks per drinking days (mean ± SD): sertraline = 11.3 ± 5.2; placebo = 10.5 ± 4.5 • duration (mean ± SD): sertraline = 10.9 ± 8.0 years; placebo = 12.0 ± 8.6 years • being actively drinking: participants had to have drunk a minimum of 40 standard drinks during the month before • length of abstinence: not available Other psychiatric comorbidity: participants with other mental disorders were excluded. Other substance use disorders: participants with substance use disorders were excluded. **Other characteristics of study** Other pharmacological treatment offered: other pharmacological treatments were not allowed. Funding source: National Institute on Alcohol Abuse and Alcoholism (grant AA10476). Pfizer supplied study drug and matched placebo. Declarations of interest: information not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Urn randomization used.

Moak 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of concealment not provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, placebo-controlled medication design applied. Medications dispensed in identically tablets. No further details provided on blinding of participants and personnel.
Blinding of outcome assessment (detection bias) objective	Low risk	No information provided on blinding of assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information provided on blinding of assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

Muhonen 2008

Methods	Randomized, double-blind, comparative trial
Participants	80 depressed people with alcohol dependence (44 men and 36 women; age (mean ± SD): memantine = 47.5 ± 8.3 years; escitalopram = 47.9 ± 8.3 years) Inclusion criteria: • aged 26-65 years • current DSM-IV diagnoses of alcohol dependence and depression Exclusion criteria: • other substance use dependence • schizophrenia or other psychotic disorder and bipolar I and II disorder • acute risk of suicide • pregnant or breastfeeding • severe untreated somatic problem or a serious liver dysfunction • mental disability Participants with bipolar disorder were excluded.
Interventions	Drugs: • escitalopram (20 mg/day; 40 participants) • memantine (20 mg/day; 40 participants) Psychotherapy: no psychosocial intervention was offered. Scheduled duration of treatment: 26 weeks (6 months) Sites: 3 centres, Helsinki, Finland, and Europe. Setting: outpatients

Muhonen 2008 *(Continued)*

	Route of administration: orally Starting dose: • 5 mg/day • increased at weekly intervals by 5 mg/day to 20 mg/day for both drugs. Pattern of dose reduction: information not available
Outcomes	Depression: • final MADRS score • final BDI score • response (participants reporting that their depression was reduced) Alcohol dependence: • number of abstinent participants Anxiety: • final HRSA score • final BAI score Cognitive functioning: • final MMSE score • final score in a retrieval wordlist Quality of life: • final VAS score • final SOFAS score Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • duration (mean ± SD): memantine = 1.9 ± 2.5 years; escitalopram = 3.9 ± 5.6 years • MADRS score (mean ± SD): memantine = 25.8 ± 4.4; escitalopram = 26.8 ± 4.1 Alcohol dependence: • AUDIT score (mean ± SD): memantine = 27.4 ± 7.1; escitalopram = 28.4 ± 6.4 • number of heavy drinking days per week (mean ± SD): memantine = 2.9 ± 1.1; escitalopram = 3.1 ± 1.0 • duration: participants had a history of heavy drinking for at least 10 years • being actively drinking (rate of participants): memantine = 43.6%; escitalopram = 42.5% • length of abstinence: abstinence not required but encouraged Other psychiatric comorbidity: participants with other mental disorders were excluded. Other substance use disorders: participants with substance use disorders were excluded. **Other characteristics of study** Other pharmacological treatment offered: other medications prescribed by the patient's physician were allowed, except other antidepressants.

Muhonen 2008 *(Continued)*

Funding source: National Public Health Institute, the Finnish Foundation for Alcohol Research and Helsinki Health Center Research. Study medication provided by Lundbeck Oy Ab, Turku, Finland

Declaration of interest: no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All participants meeting the inclusion criteria were randomly assigned by an independent person to escitalopram or memantine groups using a 1:1 ratio and random permuted blocks (Vassar Statistics randomizing algorithm).
Allocation concealment (selection bias)	Low risk	Randomization was concealed until study database was locked on by an independent clinical study monitor.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication was double-dummy packed: participant took 2 tablets every time, 1 of which was the active medicine and 1 was an identical placebo for the second medication. The medication was labelled and controlled by an independent supplier.
Blinding of outcome assessment (detection bias) objective	Low risk	Outcome analysis was performed by an independent source.
Blinding of outcome assessment (detection bias) subjective	Low risk	Outcome analysis was performed by an independent source.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used.
Selective reporting (reporting bias)	Low risk	Data of all randomized participants were reported except for 1 participant due to an interrupted interview.

Nunes 1993

Methods	Randomized, double-blind, placebo-controlled trial
Participants	26 depressed people with alcohol dependence (number of men and women: data not available; mean age: data not available) Inclusion criteria: • current DSM-III-R diagnoses of depressive disorders (or dysthymia, or depressive disorder not otherwise specified) and alcohol dependence (or abuse) Exclusion criteria: information not available Participants with bipolar disorder: information not available
Interventions	Drugs: • imipramine (dose: information not available; 13 participants) • or placebo (10 participants) Psychotherapy: information not available

Nunes 1993 *(Continued)*

	Scheduled duration of treatment: 6 months Site: Depression Evaluation Service, New York State Psychiatric Institute, New York, NY, USA Setting: outpatients Route of administration: orally Starting dose: • participants completed a previous open label study in which received a mean dose of 263 mg/day Pattern of dose reduction: information not available
Outcomes	Depression: data not available Alcohol dependence: data not available Global response Dropouts: data not available Adverse effects: data not available
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 100% • duration: information not available • CGI score: 'much improved' or 'very much improved' after 1-week of single-blind placebo treatment Alcohol dependence: • severity: information not available • being actively drinking: participants were abstinent • length of abstinence: approximately 12 weeks Other psychiatric comorbidity: information not available. Other substance use disorders: information not available. **Other characteristics of study** Other pharmacological treatment offered: information not available. Funding sources: supported in part by training grant MH-15144 from NIMH, grants AA-07688 and AA-08030 from the National Institute on Alcohol Abuse and Alcoholism, and Scientist Development Award for Clinicians DA-00154 from the National Institute on Drug Abuse. CIBA/Geigy provided imipramine and matching placebo. Declarations of interest: information not available **Other information** Only data of the double-blind trial were included in the present meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information insufficient to permit judgement.

Nunes 1993 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement.
Selective reporting (reporting bias)	High risk	Not all of study's prespecified outcomes were reported.

Pettinati 2001a

Methods	Randomized, double-blind, placebo-controlled trial
Participants	29 depressed people with alcohol dependence (number of men and women: data not available; mean age: data not available) Inclusion criteria: • aged ≥ 18 years • DSM-III-R diagnoses of depression and alcohol dependence Exclusion criteria: • current substance dependence other than alcohol or nicotine • serious or unstable physical illness • bipolar illness, dementia, or psychosis • need for other psychotropic medications Participants with bipolar disorder were excluded.
Interventions	Drugs: • sertraline (up to 200 mg/day; 12 participants) • placebo (17 participants) Psychotherapy: weekly individual cognitive-behavioural therapy Scheduled duration of treatment: 14 weeks Sites: University of Pennsylvania and the Carrier Foundation, USA Setting: outpatients Starting dose: 50 mg/day

Pettinati 2001a *(Continued)*

	Pattern of dose reduction: tapering during the last 2 weeks of treatment
Outcomes	Depression: • final HRSD score • final BDI score Alcohol dependence: • rate of abstinent days (obtained from the rate of drinking days) • number of abstinent participants • time to first relapse Dropouts: information not available Adverse effects: information not available
Notes	**Baseline characteristics of participants** Depression: • primary depression: information not available • severity: information not available • duration: information not available Alcohol dependence: • severity: information not available • duration: information not available • being actively drinking: participants had to be actively drinking in the past 30 days, seeking treatment for alcohol problems Other psychiatric comorbidity: participants with other mental disorders were excluded. Other substance use disorders: participants with substance use disorders were excluded. **Other characteristics of study** Other pharmacological treatment offered: other pharmacological treatments were not allowed. Funding source: National Institute on Alcohol Abuse and Alcoholism (R01-AA09544 and KO2-AA00239) and by Veteran Affairs Medical Center. Pfizer Inc. provided sertraline and matching placebo. Declarations of interest: information not available **Other information** In the original study participants were divided into 2 groups: • never depressed (47 participants) • with lifetime depression (53 participants; 26 men and 27 women; age (mean ± SD): sertraline = 42.3 ± 9.3 years; placebo = 43.8 ± 10.9 years) Participants with lifetime depression were then divided into 2 subgroups: • with current depression (29 participants) • with only lifetime diagnosis of depression (24 participants) In the meta-analysis, we included only participants with current depression. Unfortunately, dropouts and adverse events were not provided for each subgroup.
Risk of bias	

Pettinati 2001a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation referred to 1 randomization schedule for both sites.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated and medications prepared to appear identical. No specific reference made to blinding of participants and personnel.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

Pettinati 2010 arm A

Methods	Randomized, double-blind, placebo-controlled trial
Participants	79 depressed people with alcohol dependence (49 men and 30 women; age (mean ± SD): sertraline = 43.9 ± 11.5 years; placebo = 43.4 ± 8.9 years) Inclusion criteria: • current DSM-IV diagnoses of depression and alcohol dependence • HRSD score ≥ 10 Exclusion criteria: • substance dependence besides alcohol or nicotine dependence • bipolar-affective disorder, schizophrenia, or other psychotic or organic mental disorders • regular use of antidepressants • requiring psychiatric medications other than an antidepressant • severe medical illness • pregnant or breastfeeding Participants with bipolar disorder were excluded.
Interventions	Drugs: • sertraline (200 mg/day; 40 participants) • placebo (39 participants) Psychotherapy: weekly individual CBT

Pettinati 2010 arm A *(Continued)*

	Scheduled duration of treatment: 14 weeks Site: University of Pennsylvania Treatment Research Center, USA Setting: outpatients Route of administration: orally Starting dose: 50 mg/day Pattern of dose reduction: • in week 14, sertraline was reduced to 100 mg/day; • medications were completed by the last treatment day.
Outcomes	Depression: • final HRSD score • remission Alcohol dependence: • number of abstinent participants • number of heavy drinkers (calculated from the figure on the rates of subjects without a heavy drinking day) • time to relapse Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 100% • duration: information not available • HRSD score (mean ± SD): sertraline = 23.4 ± 6.0; placebo = 22.9 ± 7.0 Alcohol dependence: • number of drinks per drinking days (mean ± SD): sertraline = 12.4 ± 5.6; placebo = 10.5 ± 5.9 • duration (mean ± SD): sertraline = 21.7 ± 10.6 years; placebo = 19.3 ± 10.1 years • being actively drinking: participants had to consume a mean of ≥12 alcoholic drinks per week and on ≥ 40% of the 90 days before treatment • length of abstinence: 3 days Other psychiatric comorbidity: participants with other mental disorders were excluded. Other substance use disorders: participants with substance use disorders were excluded. **Other characteristics of study** Other pharmacological treatment offered: other pharmacological treatments were not allowed. Funding source: National Institute on Alcohol Abuse and Alcoholism (grant R01-AA09544-10). Pfizer Inc., USA, Pharmaceutical Group provided sertraline and matching placebo. Declaration of interest: the authors declared the grants received. **Other information** In the original study participants were divided into 4 groups:

Pettinati 2010 arm A *(Continued)*

- sertraline (40 participants)
- naltrexone (49 participants)
- sertraline plus naltrexone (42 participants)
- double placebo (39 participants)

In the meta-analysis, data were analyzed and included in 2 substudies:

- Pettinati 2010 arm A including the groups 'sertraline' and 'placebo;'
- Pettinati 2010 arm B including the groups 'sertraline plus naltrexone' and 'naltrexone.'

Both the substudies (Pettinati 2010 arm A; Pettinati 2010 arm B) were included in the 'Effects of interventions: Antidepressants versus placebo' comparison.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Urn randomization reported.
Allocation concealment (selection bias)	Low risk	Urn randomization used to evenly distribute participants across groups using 4 pretreatment variables: gender, regular smoking, HRSD scores at time of randomization, and drinking frequency.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed using appropriate methods.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

Pettinati 2010 arm B

Methods	Randomized, double-blind, placebo-controlled trial
Participants	91 depressed people with alcohol dependence (57 men and 34 women; age (mean ± SD): sertraline plus naltrexone = 43.4 ± 10.2 years; naltrexone = 42.9 ± 8.1) Inclusion criteria: • current DSM-IV diagnoses of depression and alcohol dependence • HRSD score ≥ 10 Exclusion criteria:

Pettinati 2010 arm B *(Continued)*

- substance dependence besides alcohol or nicotine dependence
- bipolar-affective disorder, schizophrenia, or other psychotic or organic mental disorders
- regular use of antidepressants
- requiring psychiatric medications other than an antidepressant
- severe medical illness
- pregnant or breastfeeding

Participants with bipolar disorder were excluded.

Interventions	Drugs: • sertraline (200 mg/day) plus naltrexone (100 mg/day) (42 participants) • naltrexone (100 mg/day; 49 participants) Psychotherapy: weekly individual CBT Scheduled duration of treatment: 14 weeks Site: University of Pennsylvania Treatment Research Center, USA Setting: outpatients Route of administration: orally Starting doses: • naltrexone 50 mg/day for the first 4 days • naltrexone 100 mg/day for other 3 days • naltrexone 100 mg/day plus sertraline 50 mg/day added every third day to 200 mg/day Pattern of dose reduction: • in week 13, naltrexone was reduced to 50 mg/day and sertraline maintained at 200 mg/day; • in week 14, naltrexone was continued at 50 mg/day and sertraline reduced to 100 mg/day; • medications were completed by the last treatment day.
Outcomes	Depression: • final HRSD score • remission Alcohol dependence: • number of abstinent participants • number of heavy drinkers (calculated from the figure on the rates of subjects without a heavy drinking day) • time to relapse Dropouts Adverse effects
Notes	**Baseline characteristics of participants** Depression: • primary depression (rate of participants): 100% • duration: information not available • HRSD score (mean ± SD): sertraline plus naltrexone = 23.7 ± 6.7; naltrexone = 22.3 ± 5.7 Alcohol dependence:

Pettinati 2010 arm B *(Continued)*

- number of drinks per drinking days (mean ± SD): sertraline plus naltrexone = 12.8 ± 9.2; naltrexone = 13.6 ± 6.9
- duration (mean ± SD): sertraline plus naltrexone = 22.2 ± 10.5 years; naltrexone = 21.3 ± 8.3 years
- being actively drinking: participants had to consume a mean of ≥12 alcoholic drinks per week and on ≥ 40% of the 90 days before treatment
- length of abstinence: 3 days

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance use disorders: participants with substance use disorders were excluded.

Other characteristics of study

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: National Institute on Alcohol Abuse and Alcoholism (grant R01-AA09544-10). Pfizer Inc., USA, Pharmaceutical Group provided sertraline and matching placebo.

Declaration of interest: the authors declared the grants received.

Other information

In the original study participants were divided into 4 groups:

- sertraline (40 participants)
- naltrexone (49 participants)
- sertraline plus naltrexone (42 participants)
- double placebo (39 participants)

In the meta-analysis, data were analyzed and included in 2 substudies:

- Pettinati 2010 arm A including the groups 'sertraline' and 'placebo;'
- Pettinati 2010 arm B including the groups 'sertraline plus naltrexone' and 'naltrexone.'

Both the substudies (Pettinati 2010 arm A; Pettinati 2010 arm B) were included in the 'Effects of interventions: Antidepressants versus placebo' comparison.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Urn randomization.
Allocation concealment (selection bias)	Low risk	Urn randomization used to evenly distribute participants across groups using 4 pretreatment variables: gender, regular smoking, HRSD scores at the time of randomization, and drinking frequency.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.

Pettinati 2010 arm B *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed using appropriate methods.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

Roy 1998

Methods	Randomized, double-blind, placebo-controlled trial
Participants	36 depressed people with alcohol dependence (33 men and 3 women; age (mean ± SD): sertraline = 40.5 ± 7.7 years; placebo = 41.2 ± 5.6 years) Inclusion criteria: • current DSM-III-R diagnoses of depression and alcohol dependence Exclusion criteria: • schizophrenia, bipolar disorder, obsessive-compulsive disorder, dementia, other DSM-III-R major Axis I disorder • non-alcohol substance dependence, epilepsy, organic mental disorder, or significant medical disorder Participants with bipolar disorder were excluded.
Interventions	Drugs: • sertraline (100 mg/day; 18 participants) • placebo (18 participants) Psychotherapy: information not available Scheduled duration of treatment: 6 weeks Site: Alcoholic Rehabilitation Unit of the Veterans Administration Medical Center, East Orange, New Jersey, USA Setting: inpatients for the first 2 weeks then outpatients for 6 weeks Route of administration: orally Starting dose: information not available Pattern of dose reduction: information not available
Outcomes	Depression: • final HRSD score (calculated from a figure) • final BDI score (calculated from a figure) • response Alcohol dependence: information not available Dropouts Adverse effects: information not available.
Notes	**Baseline characteristics of participants**

Roy 1998 *(Continued)*

Depression:

- primary depression (rate of participants): 41.7%
- duration (mean ± SD): sertraline = 5.2 ± 5.3 months; placebo = 8.8 ± 9.0 months
- HRSD score (mean ± SD): sertraline = 25.3 ± 7.3; placebo = 20.2 ± 5.6

Alcohol dependence:

- severity: information not available
- duration (mean ± SD): sertraline = 16.3 ± 9.1 years; placebo = 19.4 ± 6.8 years
- being actively drinking: participants had to be abstinent at least 2 weeks
- length of abstinence (mean ± SD): sertraline = 4.8 ± 7.5 weeks; placebo = 4.7 ± 4.8 weeks

Other psychiatric comorbidity: participants with other mental disorders were excluded.

Other substance use disorders: participants with substance use disorders were excluded.

Abuse of other substances was not an exclusion.

Other characteristics of study

Other pharmacological treatment offered: participants who had received antidepressant medication in the previous month were excluded.

Funding source: information not available

Declarations of interest: information not available

Other information

Final HRSD and BDI scores and number of withdrawal for medical reasons were provided separately for participants with primary depression (arm A; 15 participants) and participants with secondary depression (arm B; 21 participants). For the other outcomes, data were provided for the entire sample of participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and key study personnel Information ensured but information insufficient to permit judgement.
Blinding of outcome assessment (detection bias) objective	Low risk	No information on the blinding of outcome assessors.
Blinding of outcome assessment (detection bias) subjective	Unclear risk	No information on the blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis referred to, but for participants who did not complete the study (dropouts), the last observation was not carried forward.

Roy 1998 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

Roy-Byrne 2000

Methods	Randomized, double-blind, placebo-controlled trial
Participants	64 depressed people with alcohol dependence (29 men and 35 women; age (mean ± SD): 40.2 ± 8.2 years) Inclusion criteria: • aged 18-55 years • current DSM-III-R diagnoses of depression and alcohol dependence Exclusion criteria: • intravenous drug use • other drug use more than once per week • schizophrenia and bipolar disorder • active suicidal ideation with a plan • recent history of delirium tremens or alcohol-withdrawal seizures • current treatment for depression or alcoholism • serious medical problems • treatment with medications that are contraindicated in combination with nefazodone • pregnancy • untreated hypothyroidism or hyperthyroidism • clinically significant live dysfunction, active cardiac or renal impairment • homelessness Participants with bipolar disorder were excluded.
Interventions	Drugs: • nefazodone (200-500 mg/day; 32 participants; 17 men and 15 women; age (mean ± SD): 40.9 ± 8.6 years) • placebo (32 participants; 12 men and 20 women; age (mean ± SD): 39.5 ± 7.9 years) Psychotherapy: cognitive-behavioural skills training and psychoeducational group for alcohol-dependence and depression led by an experienced therapist; group sessions lasted 1 hour once per week. Scheduled duration of treatment: 12 weeks Site: Harborview Medical Center Outpatient Psychiatry Clinic, University of Washington, Seattle, USA Setting: outpatients Route of administration: orally Starting dose: • 100 mg twice daily • additional 100 mg/day per week until 200 mg in the morning and 300 mg at night (500 mg total) Pattern of dose reduction: information not available
Outcomes	Depression:

Roy-Byrne 2000 *(Continued)*

- final HRSD score (obtained from a figure)
- response

Alcohol dependence:

- number of abstinent participants
- number of drinks per drinking day (obtained from a figure)

Dropouts

Adverse effects

Notes

Baseline characteristics of participants

Depression:

- primary depression (rate of participants): 100%
- duration: information not available
- HRSD score (mean ± SD): nefazodone = 23.1 ± 5.8; placebo = 24.8 ± 4.5

Alcohol dependence:

- number of drinks per drinking day (mean ± SD): nefazodone = 11.0 ± 10.5; placebo = 8.5 ± 10.1
- duration: information not available
- being actively drinking: participants were asked to decrease or discontinue their drinking before randomization, but only 9.5% stopped drinking
- length of abstinence: 0 weeks

Other psychiatric comorbidity: participants with other mental disorders were included.

Other substance use disorders: participants with substance use disorders were excluded.

Other pharmacological treatment offered: other pharmacological treatments were not allowed.

Funding source: supported in part by Bristol-Meyers Squibb.

Declarations of interest: information not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) objective	Low risk	Blinding of outcome assessment ensured.
Blinding of outcome assessment (detection bias) subjective	Low risk	Blinding of outcome assessment ensured.

Roy-Byrne 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed using appropriate methods.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

ADS: Alcohol Dependence Scale; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUDIT: Alcohol Use Disorders Identification Test; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BPRS: Brief Psychiatric Rating Scale; CBT: cognitive behavioural therapy; CGI: Clinical Global Impression scale; DBI: Drinking Behaviour Interview; DrInC: Drinker Inventory of Consequences scale; DOTES: Dosage Record and Treatment Emergent Symptoms Scale; DSM: Diagnostic and Statistic Manual of Mental Disorders; DSM-III-R: Diagnostic and Statistic Manual of Mental Disorders III - Revised; DSM-IV: Diagnostic and Statistic Manual of Mental Disorders - IV; ECT: electroconvulsive therapy; GAF: General Assessment of Functioning scale; GAS: Global Assessment Scale; GGT: γ-glutamyltransferase; HRSA: Hamilton Rating Scale for Anxiety; HRSD: Hamilton Rating Scale for Depression; ICD: International Classification of Diseases; LDQ: Leeds Dependence Questionnaire; LDRS: Lehmann Depression Rating Scale; MADRS: Montgomery and Åsberg Depression Rating Scale; MAST: Michigan Alcoholism Screening Test; MET: Motivational Enhancement Therapy; MMPI: Minnesota Multiphasic Personality Inventory; MMSE: Mini-Mental State Examination; OCDS: Obsessive-Compulsive Drinking Scale; PACS: Penn Alcohol Craving scale; PSQI: Pittsburgh Sleep Quality Index; SCL-90: Symptom Check List-90; SD: standard deviation; SOFAS: The Social and Occupational Functioning Assessment Scale; STAI: State Trait Anxiety Inventory; UKU: Udvalg for Kliniske Undersogelser Side Effect Rating Scale; VAS: Visual Analogue Scale; ZUNG: Zung Self-Assessment Depression Scale.

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

Study	Reason for exclusion
Anthenelli 2014	Type of participants not in the inclusion criteria: no depression
Arnow 2015	Type of participants not in the inclusion criteria: no alcohol dependence
Balaratnasingam 2011	Data of single group not available
Bandati 2013	Study design not in the inclusion criteria: no control group
Batki 2015	Type of participants and type of intervention not in the inclusion criteria: no depression, no use of antidepressant medications
Bowman 1966	Type of intervention not in the inclusion criteria: no antidepressant medications used
Brewer 2015	Type of participants and type of intervention not in the inclusion criteria: no depression, no alcohol dependence; no antidepressant medications used
Brown 2003	Study design not in the inclusion criteria: no control group
Brunelin 2014	Type of participants and type of intervention not in the inclusion criteria: no alcohol dependence; no antidepressant medications used
Charney 2015	Type of participants not in the inclusion criteria: only 22% of participants had depression (single data of these participants not available)
Charnoff 1967	Type of participants not in the inclusion criteria: no depression
Chick 2004b	Type of participants not in the inclusion criteria: no depression
Clark 2003	Study population not in the inclusion criteria: people aged < 18 years

Study	Reason for exclusion
Cornelius 1993	Study design not in the inclusion criteria: no control group
Cornelius 2011	Type of participants not in the inclusion criteria: people aged < 18 years
Cornelius 2012	Study design not in the inclusion criteria: no control group
Davis 2005	Study design not in the inclusion criteria: no control group
Desai 1999	Study design not in the inclusion criteria: no randomised trial
Douglas 1996	Study design not in the inclusion criteria: commentary on Mason 1996
Eriksson 2001	Type of participants not in the inclusion criteria: no alcohol dependence. Only 73% of recruited participants with alcohol dependence; data of these participants not reported.
Farren 1999	Study design not in the inclusion criteria: case report
Foulds 2016	Commentary
García-Portilla 2005	Study design not in the inclusion criteria: no control group
Glasner-Edwards 2007	Type of intervention not in the inclusion criteria: the name of the antidepressant medication used was not indicated
Gorelick 1992	Type of participants not in the inclusion criteria: no alcohol dependence
Grelotti 2014	Type of participants not in the inclusion criteria: no alcohol dependence
Han 2013	Study design not in the inclusion criteria: no control group for the antidepressant. Study compared the efficacy of aripripazole plus escitalopram to escitalopram in reducing the severity of depression and craving for alcohol in people with alcohol dependence and depression.
Hautzinger 2005	Type of participants not in the inclusion criteria: no depression
Ionescu 2011	Lack of information: number of patients for each group; time of collected data (1 month, 3 months, or 6 months?)
Ivanets 1998	Type of participants not in the inclusion criteria: no depression
Janiri 1996	Type of participants not in the inclusion criteria: no depression
Janiri 1997	Type of participants not in the inclusion criteria: no depression
Kalyoncu 2007	Study design not in the inclusion criteria: no control group
Kranzler 1995	Type of participants not in the inclusion criteria: no alcohol dependence. Only 14% of recruited participants with alcohol dependence; data of these participants not reported.
Kranzler 2011	Type of participants not in the inclusion criteria: no depression
Krupitsky 2013	Data on severity of depression, craving for alcohol, and consumption of alcohol were reported to be improved but not provided as score achieved in the different scales used
Krystal 2008	Type of intervention not in the inclusion criteria: the name of antidepressant medications was not indicated.

Study	Reason for exclusion
Labbate 2004	Study design not in the inclusion criteria. No control group for the antidepressant. Study compared the efficacy of sertraline in people with post-traumatic stress disorder and alcohol dependence with comorbid anxiety or depression to that in people with post-traumatic stress disorder and alcohol dependence but without comorbid anxiety or depression.
Lee 2012	Study design not in the inclusion criteria: no control group for the antidepressant. Study compared the efficacy of aripripazole plus escitalopram to escitalopram in reducing the severity of depression and craving for alcohol in people with alcohol dependence and depression.
Liappas 2004	Type of participants not in the inclusion criteria: no depression
Macher 1991	Study design not in the inclusion criteria: no control group
Malka 1992	Study design not in the inclusion criteria: no control group
Marey 1991	Study design not in the inclusion criteria: review
Mason 1999	Study design not in the inclusion criteria: no control group for the antidepressant. Study compared the efficacy of naltrexone plus sertraline to sertraline in reducing the severity of depression and alcohol consumption in people with alcohol dependence and depression.
Naranjo 1997	Study design not in the inclusion criteria: statistical elaboration of previous studies
Oslin 2005	Study design not in the inclusion criteria: no control group for the antidepressant. Study compared the efficacy of naltrexone plus sertraline to sertraline in reducing the severity of depression and alcohol consumption in people with alcohol dependence and depression.
Overall 1973	Type of participants not in the inclusion criteria: no depression
Powell 1995	Type of participants not in the inclusion criteria: no depression
Ruiz-Mellott 2005	Study design not in the inclusion criteria: no control group
Saatcioglu 2005	Study design not in the inclusion criteria: no control group
Salloum 2011	Study design not in the inclusion criteria: no control group
Salloum 2013	Study design not in the inclusion criteria: no control group
Schottenfeld 1989	Study design not in the inclusion criteria: no control group
Shaw 1975	Study design not in the inclusion criteria: no control group for the antidepressant. Study compared the efficacy of chlordiazepoxide plus imipramine to placebo.
Witte 2012	Study design not in the inclusion criteria: no control group for the antidepressant. Study compared the efficacy of acamprosate plus escitalopram to escitalopram in reducing the severity of depression and alcohol consumption in people with alcohol dependence and depression.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Petrakis 2013

Methods	Requested from the authors

Petrakis 2013 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	

Schifano 1993

Methods	Requested from the authors
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Antidepressants versus placebo: all studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression severity: final score (interviewer-rated scales)	14		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 All studies	14	1074	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.49, -0.04]
1.2 Selective serotonin reuptake inhibitors (SSRIs)	10	881	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.40, 0.07]
1.3 5-HT_2 antagonists	2	97	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.69, 0.11]
2 Depression severity: final score (self-administered scales)	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 All studies	8	373	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.64, 0.07]
2.2 SSRIs	5	300	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.69, 0.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 5-HT_2 antagonists	2	41	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.59, 0.64]
3 Depression severity: difference between basal and final score (interviewer-rated scales)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 All studies	5	447	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.12, 0.42]
3.2 SSRIs	4	408	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.18, 0.32]
4 Depression severity: difference between basal and final score (self-administered scales)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 All studies	4	121	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.16, 0.56]
4.2 SSRIs	2	80	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.16, 0.73]
4.3 5-HT_2 antagonists	2	41	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.59, 0.64]
5 Response to antidepressive treatment	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 All studies	10	805	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.08, 1.82]
5.2 Tricyclic antidepressants (TCAs)	4	212	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.09, 2.34]
5.3 SSRIs	5	529	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.87, 1.63]
6 Full remission of depression	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 All studies	4	372	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.77, 1.83]
6.2 SSRIs	3	308	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.74, 1.36]
7 Consumption of alcohol: abstinent days (%)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 All studies	9	821	Mean Difference (IV, Random, 95% CI)	1.34 [-1.66, 4.34]
7.2 SSRIs	7	711	Mean Difference (IV, Random, 95% CI)	-0.47 [-3.20, 2.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Consumption of alcohol: abstinent participants (number)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 All studies	7	424	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.22, 2.39]
8.2 SSRIs	4	250	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.02, 2.68]
8.3 5-HT_2 antagonists	2	105	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.77, 3.39]
9 Consumption of alcohol: drinking days (per week)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 All studies	2	55	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.35, 0.05]
9.2 5-HT_2 antagonists	2	55	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.35, 0.05]
10 Consumption of alcohol: drinks (per drinking days)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 All studies	7	451	Mean Difference (IV, Random, 95% CI)	-1.13 [-1.79, -0.46]
10.2 SSRIs	3	271	Mean Difference (IV, Random, 95% CI)	-1.42 [-2.58, -0.26]
10.3 5-HT_2 antagonists	3	111	Mean Difference (IV, Random, 95% CI)	-1.06 [-2.00, -0.11]
11 Consumption of alcohol: drinks (per week)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 All studies	2	55	Mean Difference (IV, Fixed, 95% CI)	-5.06 [-12.30, 2.18]
11.2 5-HT_2 antagonists	2	55	Mean Difference (IV, Fixed, 95% CI)	-5.06 [-12.30, 2.18]
12 Consumption of alcohol: heavy drinking days (per week)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 All studies	5	313	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.85, 0.20]
12.2 SSRIs	2	189	Mean Difference (IV, Random, 95% CI)	-0.41 [-1.09, 0.27]
12.3 5-HT_2 antagonists	2	55	Mean Difference (IV, Random, 95% CI)	-0.43 [-2.09, 1.22]
13 Consumption of alcohol: heavy drinkers (number)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 All studies	7	459	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.57, 1.07]

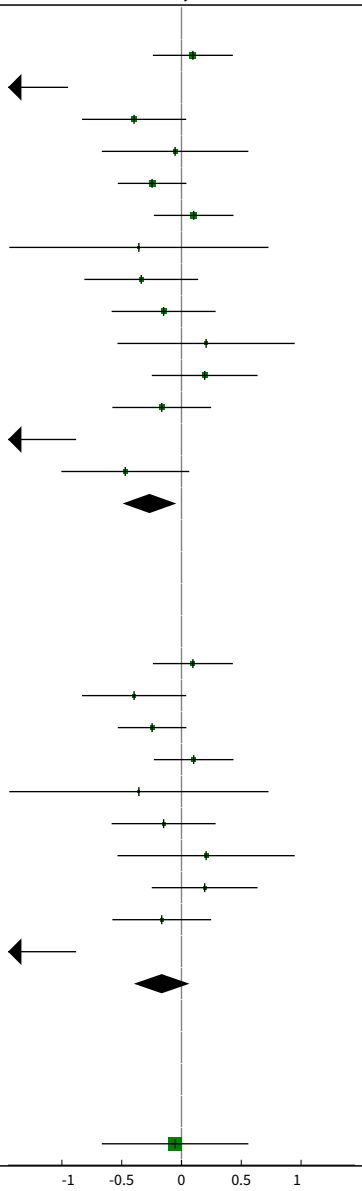
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 SSRIs	6	431	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.11]
13.3 5-HT_2 antagonists	2	99	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.68, 4.67]
14 Consumption of alcohol: time to first relapse (days)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 All studies	6	348	Mean Difference (IV, Random, 95% CI)	2.54 [-8.79, 13.87]
14.2 SSRIs	6	348	Mean Difference (IV, Random, 95% CI)	2.54 [-8.79, 13.87]
15 Liver enzyme levels: γ-glutamyltransferase (U/L)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 All studies	2	56	Mean Difference (IV, Random, 95% CI)	-8.39 [-26.47, 9.68]
16 Depression and alcohol: global response	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 All studies	3	152	Risk Ratio (M-H, Random, 95% CI)	2.37 [1.34, 4.19]
16.2 TCAs	2	92	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.09, 4.02]
17 Acceptability: dropouts	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 All studies	17	1159	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.79, 1.22]
17.2 TCAs	4	216	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.48, 3.06]
17.3 SSRIs	8	759	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.79, 1.36]
17.4 5-HT_2 antagonists	4	154	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.38, 1.64]
18 Tolerability of treatment: adverse events	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Withdrawal for medical reasons: all studies	10	947	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.65, 2.04]
18.2 Withdrawal for medical reasons: SSRIs	7	786	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.52, 2.32]
18.3 Withdrawal for medical reasons: TCAs	2	97	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.10, 8.41]
18.4 Total adverse events: all studies	5	644	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.97, 1.44]
18.5 Total adverse events: TCAs	2	115	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.13, 2.42]

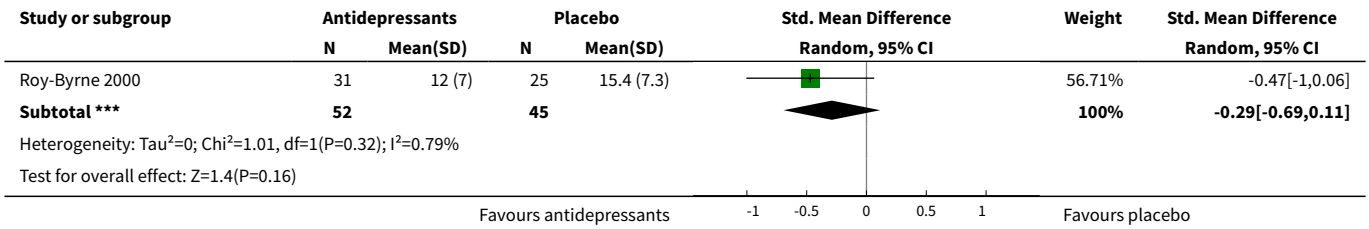
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.6 Total adverse events: SSRIs	3	529	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.92, 1.23]
18.7 Dry mouth: all studies	2	132	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.96, 3.81]
18.8 Insomnia: all studies	4	564	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.02, 2.77]
18.9 Insomnia: SSRIs	2	469	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.04, 2.96]
18.10 Headache: all studies	3	470	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.89, 1.64]
18.11 Headache: SSRIs	2	414	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.87, 1.61]
18.12 Dizziness: all studies	2	139	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.42, 6.73]
18.13 Diarrhoea: all studies	2	139	Risk Ratio (M-H, Random, 95% CI)	1.95 [0.37, 10.22]
18.14 Nausea: all studies	3	277	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.66, 3.23]
18.15 Nausea: SSRIs	2	221	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.62, 3.35]
18.16 Constipation: all studies	2	387	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.19, 15.64]
18.17 Total serious adverse events: all studies	7	774	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.80, 1.86]
18.18 Total serious adverse events: SSRIs	5	721	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.80, 1.86]
18.19 Worsening of clinical condition because of relapse: all studies	2	413	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.73, 10.87]
18.20 Worsening of clinical condition because of relapse: SSRIs	2	413	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.73, 10.87]
18.21 Depression: all studies	2	413	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.30, 17.69]
18.22 Depression: SSRIs	2	413	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.30, 17.69]
19 Suicide attempts	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 All studies	4	602	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.23, 7.61]
19.2 SSRIs	4	602	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.23, 7.61]
20 Secondary outcomes: craving	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 All studies	2	29	Mean Difference (IV, Fixed, 95% CI)	1.00 [-3.27, 5.27]
21 Secondary outcomes: severity of dependence	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 All studies	2	168	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.44, 0.17]
22 Secondary outcomes: severity of anxiety	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 All studies	3	97	Mean Difference (IV, Fixed, 95% CI)	-6.31 [-10.33, -2.28]

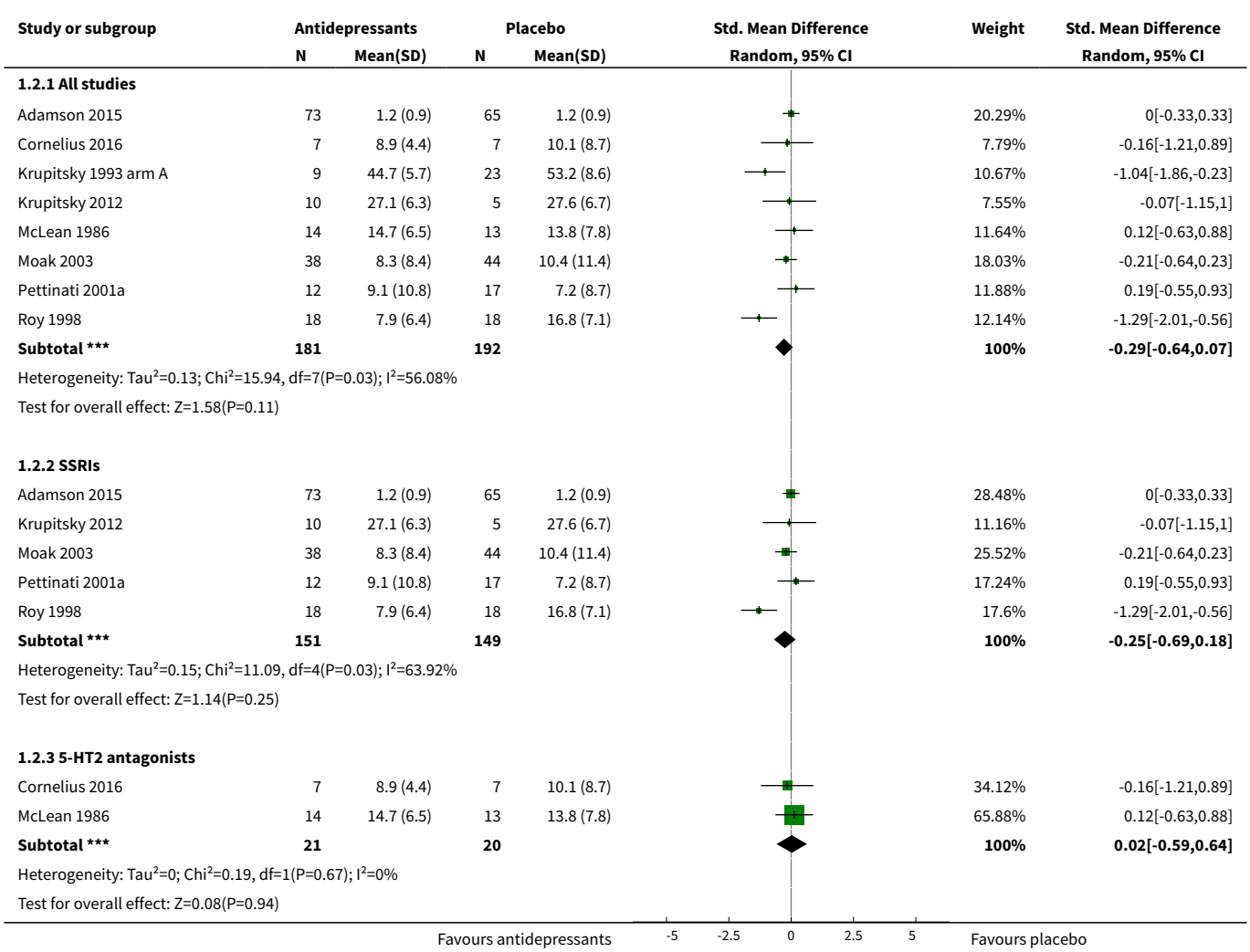
Analysis 1.1. Comparison 1 Antidepressants versus placebo: all studies, Outcome 1 Depression severity: final score (interviewer-rated scales).

Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.1.1 All studies							
Adamson 2015	73	12.8 (9.9)	65	11.8 (11)		9.37%	0.1[-0.24,0.43]
Altamura 1990	14	5 (8.2)	13	20.6 (7.9)		3.92%	-1.88[-2.81,-0.95]
Gual 2003	44	5 (5)	39	7 (5)		8.19%	-0.4[-0.83,0.04]
Hernandez-Avila 2004	21	7.1 (5.6)	20	7.4 (5.4)		6.3%	-0.05[-0.67,0.56]
Kranzler 2006 arm A	89	7.1 (5.7)	100	8.6 (6.4)		9.92%	-0.25[-0.53,0.04]
Kranzler 2006 arm B	70	5.2 (3.8)	69	4.8 (4)		9.39%	0.1[-0.23,0.43]
Krupitsky 2012	10	4.8 (3.2)	5	6 (3.1)		3.16%	-0.36[-1.44,0.73]
McGrath 1996	36	10.3 (7.2)	33	12.7 (6.9)		7.73%	-0.34[-0.81,0.14]
Moak 2003	38	7.8 (7)	44	8.8 (6.3)		8.2%	-0.15[-0.58,0.29]
Pettinati 2001a	12	8.8 (11.2)	17	6.8 (8)		5.18%	0.21[-0.54,0.95]
Pettinati 2010 arm A	40	11.7 (7.3)	39	10.2 (8)		8.12%	0.19[-0.25,0.64]
Pettinati 2010 arm B	42	6.9 (6.1)	49	8 (7)		8.46%	-0.17[-0.58,0.25]
Roy 1998	18	5.5 (5.5)	18	16.4 (7.3)		4.97%	-1.65[-2.42,-0.88]
Roy-Byrne 2000	31	12 (7)	25	15.4 (7.3)		7.09%	-0.47[-1,0.06]
Subtotal ***	**538**		**536**			**100%**	**-0.27[-0.49,-0.04]**
Heterogeneity: Tau²=0.11; Chi²=39.01, df=13(P=0); I²=66.68%							
Test for overall effect: Z=2.33(P=0.02)							
1.1.2 Selective serotonin reuptake inhibitors (SSRIs)							
Adamson 2015	73	12.8 (9.9)	65	11.8 (11)		12.97%	0.1[-0.24,0.43]
Gual 2003	44	5 (5)	39	7 (5)		10.93%	-0.4[-0.83,0.04]
Kranzler 2006 arm A	89	7.1 (5.7)	100	8.6 (6.4)		13.96%	-0.25[-0.53,0.04]
Kranzler 2006 arm B	70	5.2 (3.8)	69	4.8 (4)		13%	0.1[-0.23,0.43]
Krupitsky 2012	10	4.8 (3.2)	5	6 (3.1)		3.65%	-0.36[-1.44,0.73]
Moak 2003	38	7.8 (7)	44	8.8 (6.3)		10.94%	-0.15[-0.58,0.29]
Pettinati 2001a	12	8.8 (11.2)	17	6.8 (8)		6.33%	0.21[-0.54,0.95]
Pettinati 2010 arm A	40	11.7 (7.3)	39	10.2 (8)		10.8%	0.19[-0.25,0.64]
Pettinati 2010 arm B	42	6.9 (6.1)	49	8 (7)		11.37%	-0.17[-0.58,0.25]
Roy 1998	18	5.5 (5.5)	18	16.4 (7.3)		6.04%	-1.65[-2.42,-0.88]
Subtotal ***	**436**		**445**			**100%**	**-0.17[-0.4,0.07]**
Heterogeneity: Tau²=0.08; Chi²=23.74, df=9(P=0); I²=62.1%							
Test for overall effect: Z=1.4(P=0.16)							
1.1.3 5-HT2 antagonists							
Hernandez-Avila 2004	21	7.1 (5.6)	20	7.4 (5.4)		43.29%	-0.05[-0.67,0.56]



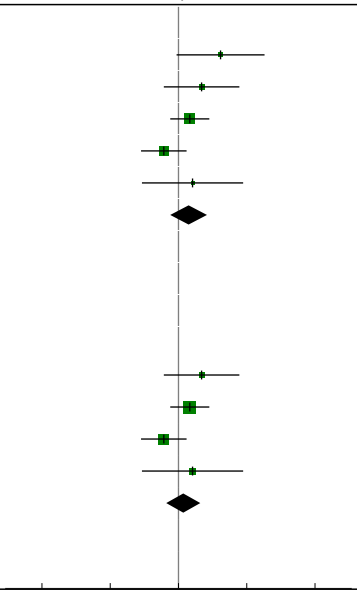


Analysis 1.2. Comparison 1 Antidepressants versus placebo: all studies, Outcome 2 Depression severity: final score (self-administered scales).



Analysis 1.3. Comparison 1 Antidepressants versus placebo: all studies, Outcome 3 Depression severity: difference between basal and final score (interviewer-rated scales).

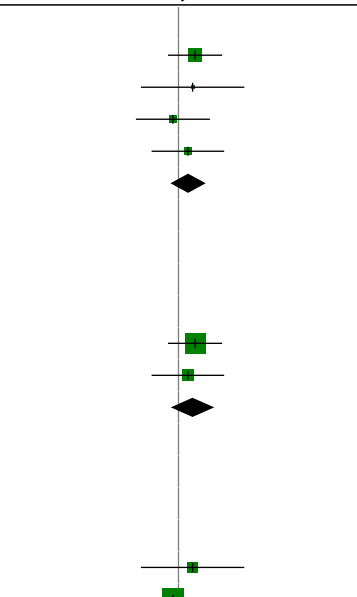
Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.3.1 All studies							
Butterworth 1971b	19	9.9 (4.5)	20	7.4 (3.4)		12.97%	0.62[-0.03,1.26]
Cornelius 1997	25	6 (9.6)	26	2 (13.3)		16.11%	0.34[-0.21,0.89]
Kranzler 2006 arm A	89	10.8 (6.5)	100	9.6 (7.8)		32.08%	0.17[-0.12,0.45]
Kranzler 2006 arm B	70	6 (5.4)	69	7.2 (5.7)		28.39%	-0.21[-0.55,0.12]
Pettinati 2001a	12	8.8 (11.2)	17	6.8 (8)		10.46%	0.21[-0.54,0.95]
Subtotal ***	**215**		**232**			**100%**	**0.15[-0.12,0.42]**
Heterogeneity: Tau^2=0.04; Chi^2=6.88, df=4(P=0.14); I^2=41.9%							
Test for overall effect: Z=1.08(P=0.28)							
1.3.2 SSRIs							
Cornelius 1997	25	6 (9.6)	26	2 (13.3)		16.39%	0.34[-0.21,0.89]
Kranzler 2006 arm A	89	10.8 (6.5)	100	9.6 (7.8)		39.98%	0.17[-0.12,0.45]
Kranzler 2006 arm B	70	6 (5.4)	69	7.2 (5.7)		33.64%	-0.21[-0.55,0.12]
Pettinati 2001a	12	8.8 (11.2)	17	6.8 (8)		9.99%	0.21[-0.54,0.95]
Subtotal ***	**196**		**212**			**100%**	**0.07[-0.18,0.32]**
Heterogeneity: Tau^2=0.02; Chi^2=4.26, df=3(P=0.23); I^2=29.54%							
Test for overall effect: Z=0.55(P=0.58)							



Favours placebo — Favours antidepressants

Analysis 1.4. Comparison 1 Antidepressants versus placebo: all studies, Outcome 4 Depression severity: difference between basal and final score (self-administered scales).

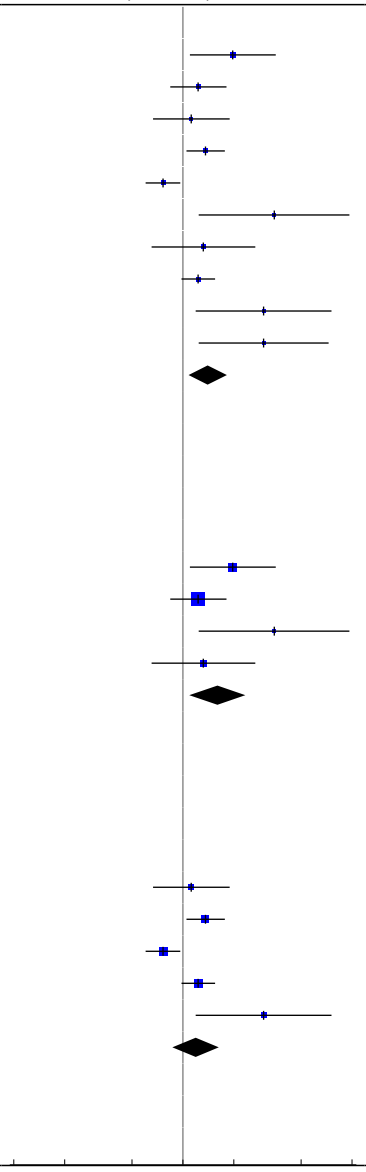
Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.4.1 All studies							
Cornelius 1997	25	6 (9.6)	26	2 (13.3)		42.22%	0.34[-0.21,0.89]
Cornelius 2016	7	18.7 (5.7)	7	16 (11)		11.61%	0.29[-0.77,1.34]
McLean 1986	14	11.2 (8.5)	13	12.1 (6.7)		22.63%	-0.11[-0.87,0.64]
Pettinati 2001a	12	9.1 (10.8)	17	7.2 (8.7)		23.54%	0.19[-0.55,0.93]
Subtotal ***	**58**		**63**			**100%**	**0.2[-0.16,0.56]**
Heterogeneity: Tau^2=0; Chi^2=0.93, df=3(P=0.82); I^2=0%							
Test for overall effect: Z=1.07(P=0.29)							
1.4.2 SSRIs							
Cornelius 1997	25	6 (9.6)	26	2 (13.3)		64.2%	0.34[-0.21,0.89]
Pettinati 2001a	12	9.1 (10.8)	17	7.2 (8.7)		35.8%	0.19[-0.55,0.93]
Subtotal ***	**37**		**43**			**100%**	**0.29[-0.16,0.73]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.76); I^2=0%							
Test for overall effect: Z=1.26(P=0.21)							
1.4.3 5-HT2 antagonists							
Cornelius 2016	7	18.7 (5.7)	7	16 (11)		33.9%	0.29[-0.77,1.34]
McLean 1986	14	11.2 (8.5)	13	12.1 (6.7)		66.1%	-0.11[-0.87,0.64]
Subtotal ***	**21**		**20**			**100%**	**0.02[-0.59,0.64]**
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%							
Test for overall effect: Z=0.07(P=0.94)							



Favours placebo — Favours antidepressants

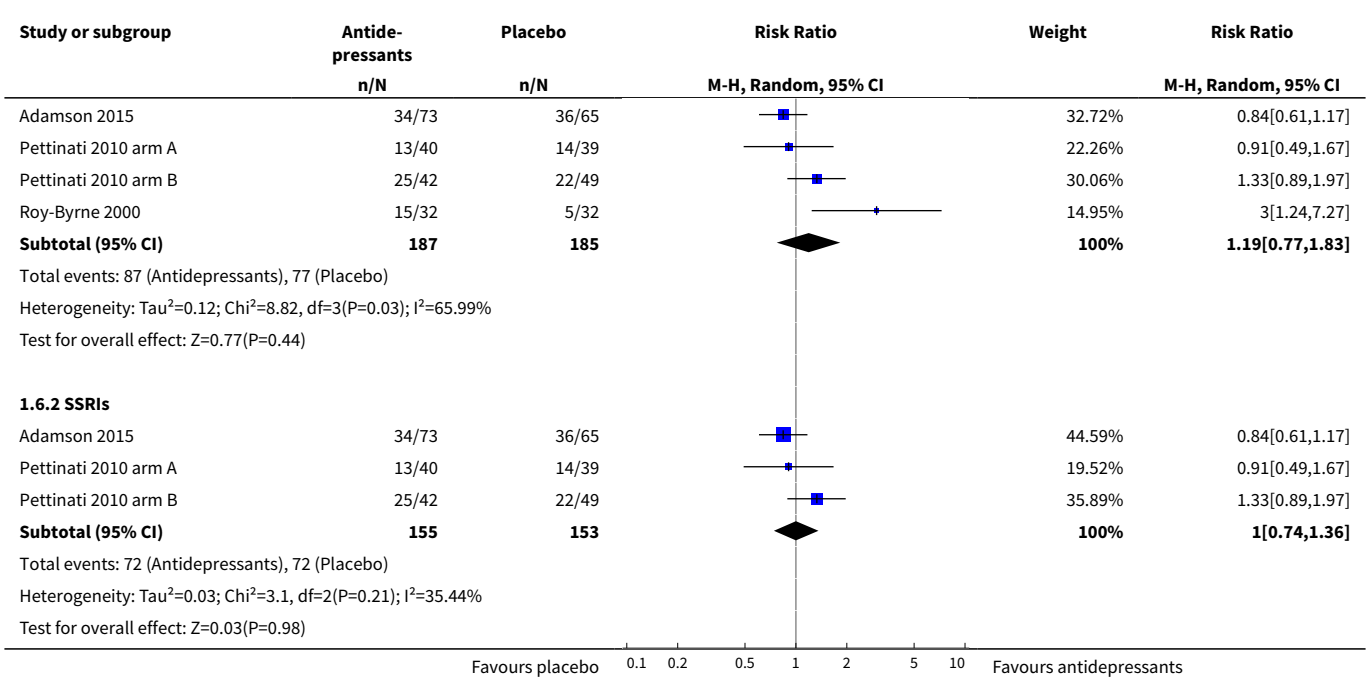
Analysis 1.5. Comparison 1 Antidepressants versus placebo: all studies, Outcome 5 Response to antidepressive treatment.

Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 All studies					
Butterworth 1971b	15/19	8/20		9.19%	1.97[1.1,3.54]
Gallant 1969 arm a	32/47	16/29		12.5%	1.23[0.84,1.81]
Gual 2003	19/44	15/39		10.14%	1.12[0.67,1.89]
Kranzler 2006 arm A	57/89	47/100		14.61%	1.36[1.05,1.77]
Kranzler 2006 arm B	41/70	53/69		14.99%	0.76[0.6,0.97]
Mason 1996	12/15	3/13		4.7%	3.47[1.24,9.65]
McGrath 1996	13/36	9/33		7.58%	1.32[0.65,2.68]
Moak 2003	33/38	31/44		15.12%	1.23[0.98,1.55]
Roy 1998	12/18	4/18		5.43%	3[1.19,7.56]
Roy-Byrne 2000	15/32	5/32		5.75%	3[1.24,7.27]
Subtotal (95% CI)	**408**	**397**		**100%**	**1.4[1.08,1.82]**
Total events: 249 (Antidepressants), 191 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=31.63, df=9(P=0); I^2=71.55%					
Test for overall effect: Z=2.55(P=0.01)					
1.5.2 Tricyclic antidepressants (TCAs)					
Butterworth 1971b	15/19	8/20		26.53%	1.97[1.1,3.54]
Gallant 1969 arm a	32/47	16/29		41.25%	1.23[0.84,1.81]
Mason 1996	12/15	3/13		11.6%	3.47[1.24,9.65]
McGrath 1996	13/36	9/33		20.62%	1.32[0.65,2.68]
Subtotal (95% CI)	**117**	**95**		**100%**	**1.6[1.09,2.34]**
Total events: 72 (Antidepressants), 36 (Placebo)					
Heterogeneity: Tau^2=0.05; Chi^2=4.66, df=3(P=0.2); I^2=35.56%					
Test for overall effect: Z=2.41(P=0.02)					
1.5.3 SSRIs					
Gual 2003	19/44	15/39		16.28%	1.12[0.67,1.89]
Kranzler 2006 arm A	57/89	47/100		24.55%	1.36[1.05,1.77]
Kranzler 2006 arm B	41/70	53/69		25.3%	0.76[0.6,0.97]
Moak 2003	33/38	31/44		25.54%	1.23[0.98,1.55]
Roy 1998	12/18	4/18		8.32%	3[1.19,7.56]
Subtotal (95% CI)	**259**	**270**		**100%**	**1.19[0.87,1.63]**
Total events: 162 (Antidepressants), 150 (Placebo)					
Heterogeneity: Tau^2=0.09; Chi^2=17.6, df=4(P=0); I^2=77.28%					
Test for overall effect: Z=1.07(P=0.29)					

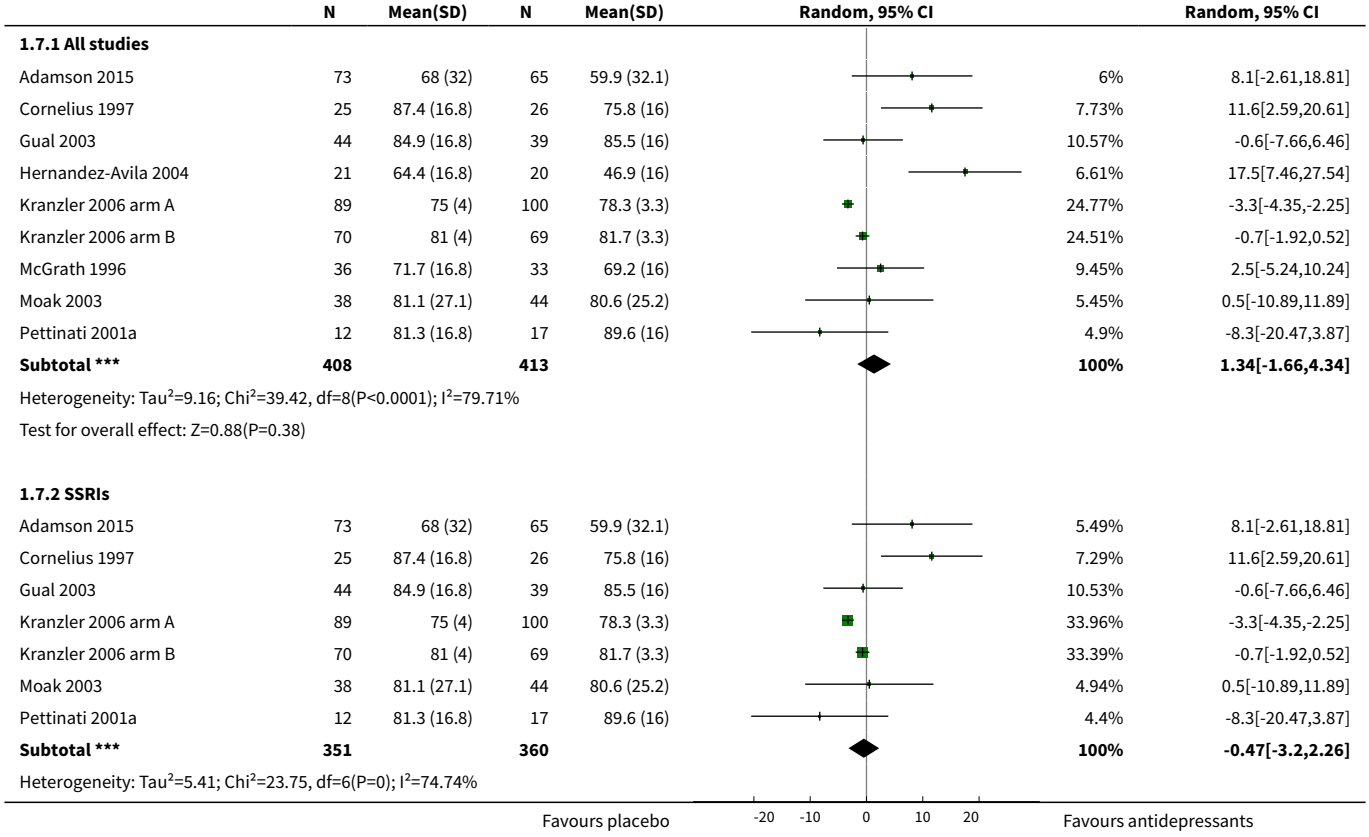


Analysis 1.6. Comparison 1 Antidepressants versus placebo: all studies, Outcome 6 Full remission of depression.

Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 All studies					



Analysis 1.7. Comparison 1 Antidepressants versus placebo: all studies, Outcome 7 Consumption of alcohol: abstinent days (%).



Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.34(P=0.74)							

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Analysis 1.8. Comparison 1 Antidepressants versus placebo: all studies, Outcome 8 Consumption of alcohol: abstinent participants (number).

Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 All studies					
Cornelius 1997	7/25	4/26		9.24%	1.82[0.61,5.46]
Hernandez-Avila 2004	7/21	3/20		7.67%	2.22[0.67,7.42]
McGrath 1996	12/36	6/33		15.13%	1.83[0.78,4.33]
Pettinati 2001a	3/12	5/17		7.42%	0.85[0.25,2.9]
Pettinati 2010 arm A	11/40	9/39		19.18%	1.19[0.56,2.55]
Pettinati 2010 arm B	22/42	10/49		28.68%	2.57[1.38,4.79]
Roy-Byrne 2000	8/32	6/32		12.67%	1.33[0.52,3.41]
Subtotal (95% CI)	**208**	**216**		**100%**	**1.71[1.22,2.39]**
Total events: 70 (Antidepressants), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.23, df=6(P=0.65); I^2=0%					
Test for overall effect: Z=3.15(P=0)					
1.8.2 SSRIs					
Cornelius 1997	7/25	4/26		16.53%	1.82[0.61,5.46]
Pettinati 2001a	3/12	5/17		13.65%	0.85[0.25,2.9]
Pettinati 2010 arm A	11/40	9/39		29.93%	1.19[0.56,2.55]
Pettinati 2010 arm B	22/42	10/49		39.88%	2.57[1.38,4.79]
Subtotal (95% CI)	**119**	**131**		**100%**	**1.66[1.02,2.68]**
Total events: 43 (Antidepressants), 28 (Placebo)					
Heterogeneity: Tau^2=0.05; Chi^2=3.75, df=3(P=0.29); I^2=20.04%					
Test for overall effect: Z=2.06(P=0.04)					
1.8.3 5-HT2 antagonists					
Hernandez-Avila 2004	7/21	3/20		37.71%	2.22[0.67,7.42]
Roy-Byrne 2000	8/32	6/32		62.29%	1.33[0.52,3.41]
Subtotal (95% CI)	**53**	**52**		**100%**	**1.62[0.77,3.39]**
Total events: 15 (Antidepressants), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=1.27(P=0.2)					

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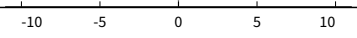
Analysis 1.9. Comparison 1 Antidepressants versus placebo: all studies, Outcome 9 Consumption of alcohol: drinking days (per week).

Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.9.1 All studies							

Favours antidepressants -10 -5 0 5 10 Favours placebo

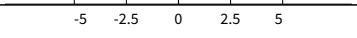
Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cornelius 2016	7	6.4 (5.1)	7	6.4 (6)		4.24%	0[-5.83,5.83]
Hernandez-Avila 2004	21	2.5 (2.2)	20	3.7 (1.8)		95.76%	-1.2[-2.43,0.03]
Subtotal ***	**28**		**27**			**100%**	**-1.15[-2.35,0.05]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%							
Test for overall effect: Z=1.87(P=0.06)							
1.9.2 5-HT2 antagonists							
Cornelius 2016	7	6.4 (5.1)	7	6.4 (6)		4.24%	0[-5.83,5.83]
Hernandez-Avila 2004	21	2.5 (2.2)	20	3.7 (1.8)		95.76%	-1.2[-2.43,0.03]
Subtotal ***	**28**		**27**			**100%**	**-1.15[-2.35,0.05]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%							
Test for overall effect: Z=1.87(P=0.06)							



Favours antidepressants — Favours placebo

Analysis 1.10. Comparison 1 Antidepressants versus placebo: all studies, Outcome 10 Consumption of alcohol: drinks (per drinking days).

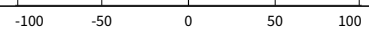
Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.10.1 All studies							
Adamson 2015	73	6.2 (6.1)	65	6.8 (6.4)		10.08%	-0.6[-2.69,1.49]
Cornelius 1997	25	2.4 (2.9)	26	5.4 (5.5)		7.66%	-3[-5.4,-0.6]
Cornelius 2016	7	3.5 (1.6)	7	4.4 (1.5)		16.73%	-0.9[-2.52,0.72]
Hernandez-Avila 2004	21	3.4 (2.4)	20	4.5 (2.4)		20.44%	-1.1[-2.57,0.37]
McGrath 1996	36	3.7 (4.8)	33	4.1 (4.1)		10%	-0.4[-2.5,1.7]
Moak 2003	38	2.3 (3.1)	44	3.5 (3.3)		22.99%	-1.2[-2.59,0.19]
Roy-Byrne 2000	31	2.9 (3.4)	25	4.1 (3.8)		12.09%	-1.2[-3.11,0.71]
Subtotal ***	**231**		**220**			**100%**	**-1.13[-1.79,-0.46]**
Heterogeneity: Tau²=0; Chi²=3.13, df=6(P=0.79); I²=0%							
Test for overall effect: Z=3.32(P=0)							
1.10.2 SSRIs							
Adamson 2015	73	6.2 (6.1)	65	6.8 (6.4)		26.72%	-0.6[-2.69,1.49]
Cornelius 1997	25	2.4 (2.9)	26	5.4 (5.5)		20.95%	-3[-5.4,-0.6]
Moak 2003	38	2.3 (3.1)	44	3.5 (3.3)		52.32%	-1.2[-2.59,0.19]
Subtotal ***	**136**		**135**			**100%**	**-1.42[-2.58,-0.26]**
Heterogeneity: Tau²=0.17; Chi²=2.35, df=2(P=0.31); I²=14.82%							
Test for overall effect: Z=2.4(P=0.02)							
1.10.3 5-HT2 antagonists							
Cornelius 2016	7	3.5 (1.6)	7	4.4 (1.5)		33.96%	-0.9[-2.52,0.72]
Hernandez-Avila 2004	21	3.4 (2.4)	20	4.5 (2.4)		41.5%	-1.1[-2.57,0.37]
Roy-Byrne 2000	31	2.9 (3.4)	25	4.1 (3.8)		24.55%	-1.2[-3.11,0.71]
Subtotal ***	**59**		**52**			**100%**	**-1.06[-2,-0.11]**
Heterogeneity: Tau²=0; Chi²=0.06, df=2(P=0.97); I²=0%							
Test for overall effect: Z=2.19(P=0.03)							



Favours antidepressants — Favours placebo

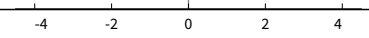
Analysis 1.11. Comparison 1 Antidepressants versus placebo: all studies, Outcome 11 Consumption of alcohol: drinks (per week).

Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.11.1 All studies							
Cornelius 2016	7	25.7 (18.7)	7	24 (16.3)		15.52%	1.7[-16.68,20.08]
Hernandez-Avila 2004	21	6.5 (7.3)	20	12.8 (16.5)		84.48%	-6.3[-14.18,1.58]
Subtotal ***	**28**		**27**			**100%**	**-5.06[-12.3,2.18]**
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=1.37(P=0.17)							
1.11.2 5-HT2 antagonists							
Cornelius 2016	7	25.7 (18.7)	7	24 (16.3)		15.52%	1.7[-16.68,20.08]
Hernandez-Avila 2004	21	6.5 (7.3)	20	12.8 (16.5)		84.48%	-6.3[-14.18,1.58]
Subtotal ***	**28**		**27**			**100%**	**-5.06[-12.3,2.18]**
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=1.37(P=0.17)							

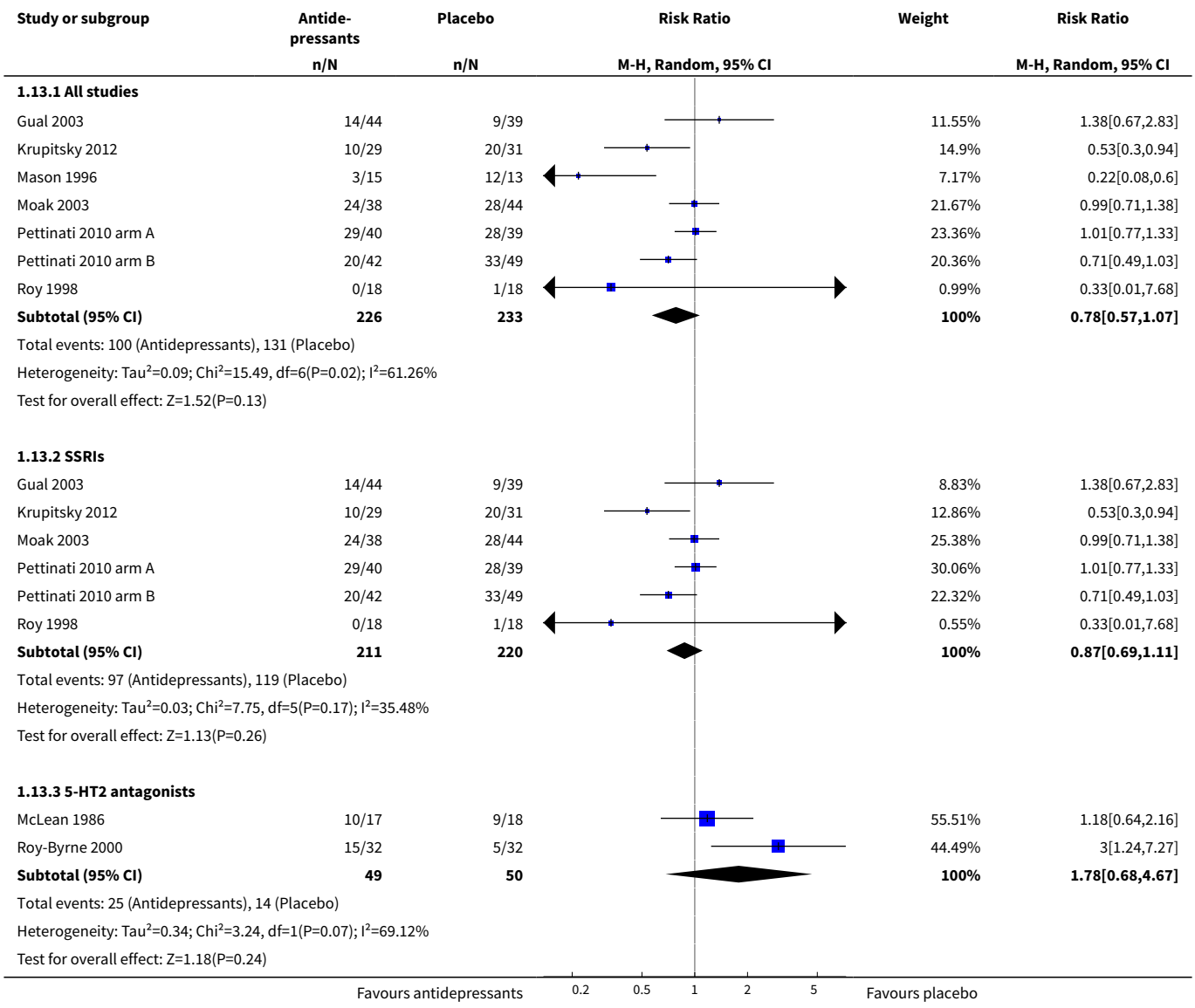


Analysis 1.12. Comparison 1 Antidepressants versus placebo: all studies, Outcome 12 Consumption of alcohol: heavy drinking days (per week).

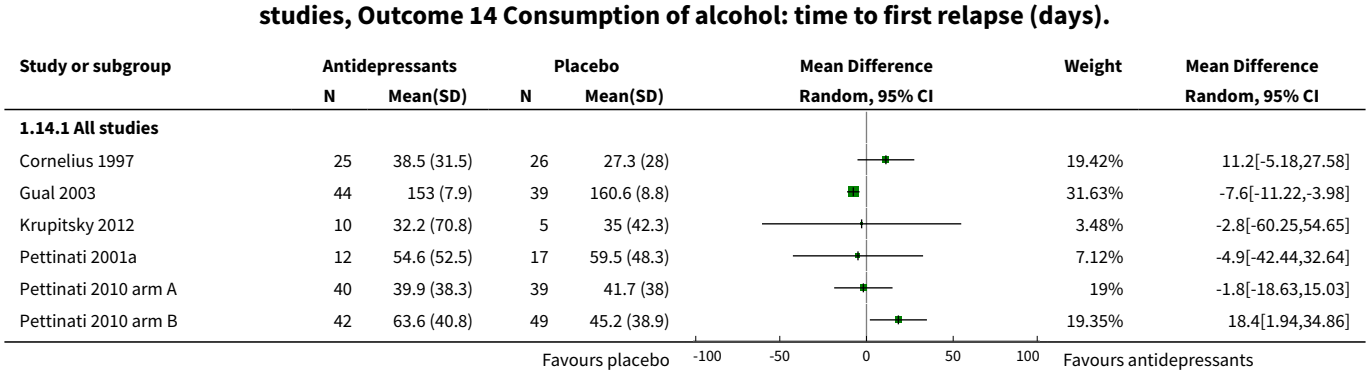
Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.12.1 All studies							
Adamson 2015	73	1.1 (0.6)	65	1.2 (1.4)		25.6%	-0.1[-0.47,0.27]
Cornelius 1997	25	0.9 (0.6)	26	1.7 (1.4)		21.45%	-0.8[-1.39,-0.21]
Cornelius 2016	7	1.9 (1.1)	7	1.4 (1.3)		10.94%	0.5[-0.76,1.76]
Hernandez-Avila 2004	21	0.2 (0.2)	20	1.4 (1.6)		19.17%	-1.2[-1.91,-0.49]
McGrath 1996	36	0.9 (0.6)	33	0.7 (1.4)		22.83%	0.2[-0.32,0.72]
Subtotal ***	**162**		**151**			**100%**	**-0.33[-0.85,0.2]**
Heterogeneity: Tau^2=0.25; Chi^2=15.22, df=4(P=0); I^2=73.72%							
Test for overall effect: Z=1.22(P=0.22)							
1.12.2 SSRIs							
Adamson 2015	73	1.1 (0.6)	65	1.2 (1.4)		55.58%	-0.1[-0.47,0.27]
Cornelius 1997	25	0.9 (0.6)	26	1.7 (1.4)		44.42%	-0.8[-1.39,-0.21]
Subtotal ***	**98**		**91**			**100%**	**-0.41[-1.09,0.27]**
Heterogeneity: Tau^2=0.18; Chi^2=3.92, df=1(P=0.05); I^2=74.52%							
Test for overall effect: Z=1.18(P=0.24)							
1.12.3 5-HT2 antagonists							
Cornelius 2016	7	1.9 (1.1)	7	1.4 (1.3)		45.08%	0.5[-0.76,1.76]
Hernandez-Avila 2004	21	0.2 (0.2)	20	1.4 (1.6)		54.92%	-1.2[-1.91,-0.49]
Subtotal ***	**28**		**27**			**100%**	**-0.43[-2.09,1.22]**
Heterogeneity: Tau^2=1.17; Chi^2=5.31, df=1(P=0.02); I^2=81.17%							
Test for overall effect: Z=0.51(P=0.61)							

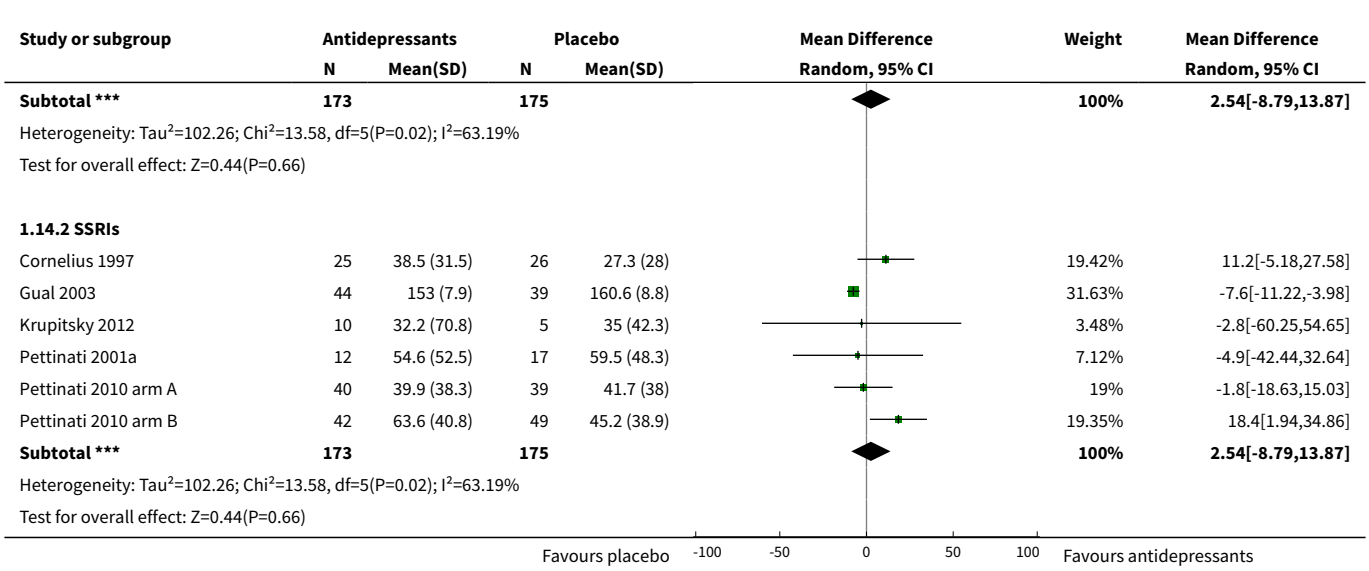


Analysis 1.13. Comparison 1 Antidepressants versus placebo: all studies, Outcome 13 Consumption of alcohol: heavy drinkers (number).

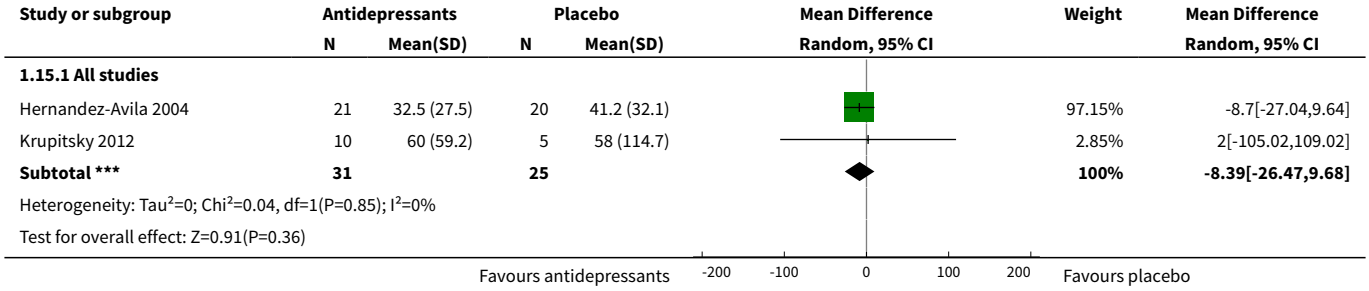


Analysis 1.14. Comparison 1 Antidepressants versus placebo: all studies, Outcome 14 Consumption of alcohol: time to first relapse (days).

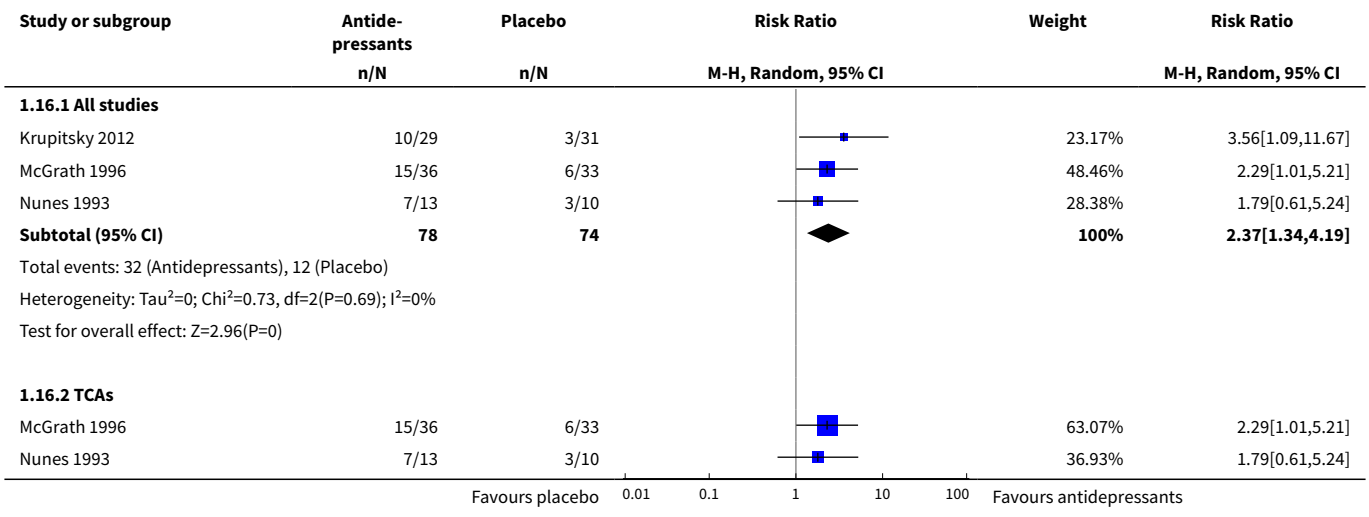




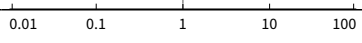
Analysis 1.15. Comparison 1 Antidepressants versus placebo: all studies, Outcome 15 Liver enzyme levels: γ-glutamyltransferase (U/L).



Analysis 1.16. Comparison 1 Antidepressants versus placebo: all studies, Outcome 16 Depression and alcohol: global response.



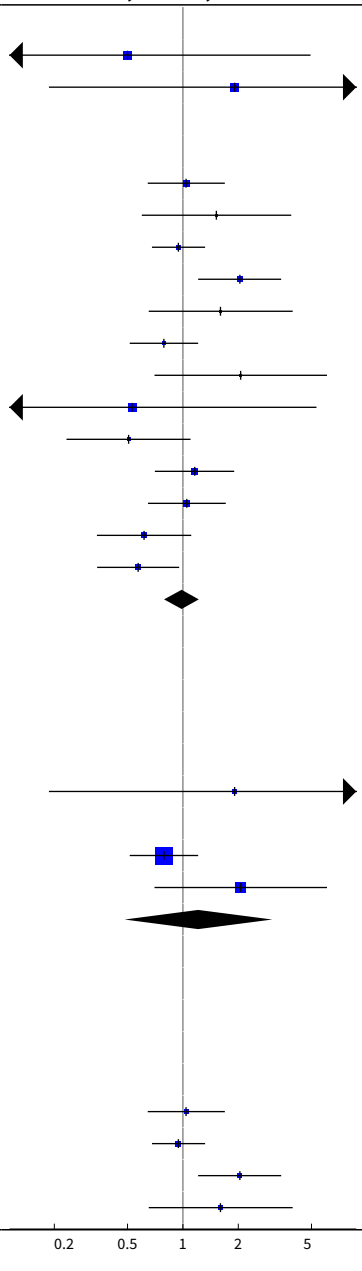
Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**49**	**43**		**100%**	**2.09[1.09,4.02]**
Total events: 22 (Antidepressants), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%					
Test for overall effect: Z=2.22(P=0.03)					



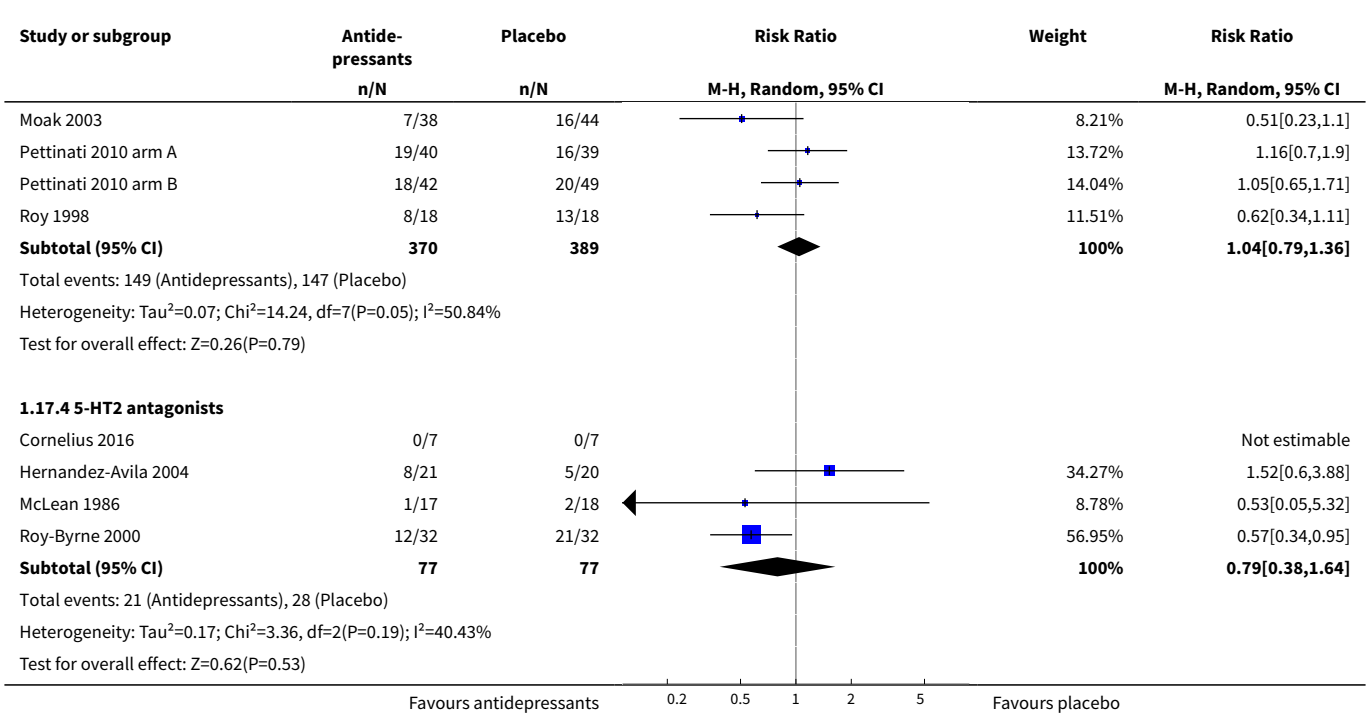
Favours placebo — Favours antidepressants

Analysis 1.17. Comparison 1 Antidepressants versus placebo: all studies, Outcome 17 Acceptability: dropouts.

Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 All studies					
Altamura 1990	1/15	2/15		0.87%	0.5[0.05,4.94]
Butterworth 1971b	2/22	1/21		0.85%	1.91[0.19,19.52]
Cornelius 2016	0/7	0/7			Not estimable
Gallant 1969 arm a	0/47	0/29			Not estimable
Gual 2003	20/44	17/39		9.84%	1.04[0.64,1.69]
Hernandez-Avila 2004	8/21	5/20		4.26%	1.52[0.6,3.88]
Kranzler 2006 arm A	37/89	44/100		13.14%	0.94[0.68,1.32]
Kranzler 2006 arm B	31/70	15/69		9.15%	2.04[1.21,3.42]
Krupitsky 2012	9/29	6/31		4.51%	1.6[0.65,3.95]
Mason 1996	10/15	11/13		10.98%	0.79[0.51,1.21]
McGrath 1996	9/36	4/33		3.39%	2.06[0.7,6.07]
McLean 1986	1/17	2/18		0.86%	0.53[0.05,5.32]
Moak 2003	7/38	16/44		5.62%	0.51[0.23,1.1]
Pettinati 2010 arm A	19/40	16/39		9.54%	1.16[0.7,1.9]
Pettinati 2010 arm B	18/42	20/49		9.78%	1.05[0.65,1.71]
Roy 1998	8/18	13/18		7.95%	0.62[0.34,1.11]
Roy-Byrne 2000	12/32	21/32		9.26%	0.57[0.34,0.95]
Subtotal (95% CI)	**582**	**577**		**100%**	**0.98[0.79,1.22]**
Total events: 192 (Antidepressants), 193 (Placebo)					
Heterogeneity: Tau^2=0.07; Chi^2=23.8, df=14(P=0.05); I^2=41.18%					
Test for overall effect: Z=0.15(P=0.88)					
1.17.2 TCAs					
Butterworth 1971b	2/22	1/21		12.56%	1.91[0.19,19.52]
Gallant 1969 arm a	0/47	0/29			Not estimable
Mason 1996	10/15	11/13		54.09%	0.79[0.51,1.21]
McGrath 1996	9/36	4/33		33.35%	2.06[0.7,6.07]
Subtotal (95% CI)	**120**	**96**		**100%**	**1.21[0.48,3.06]**
Total events: 21 (Antidepressants), 16 (Placebo)					
Heterogeneity: Tau^2=0.36; Chi^2=4.52, df=2(P=0.1); I^2=55.77%					
Test for overall effect: Z=0.41(P=0.68)					
1.17.3 SSRIs					
Gual 2003	20/44	17/39		14.13%	1.04[0.64,1.69]
Kranzler 2006 arm A	37/89	44/100		18.6%	0.94[0.68,1.32]
Kranzler 2006 arm B	31/70	15/69		13.17%	2.04[1.21,3.42]
Krupitsky 2012	9/29	6/31		6.63%	1.6[0.65,3.95]

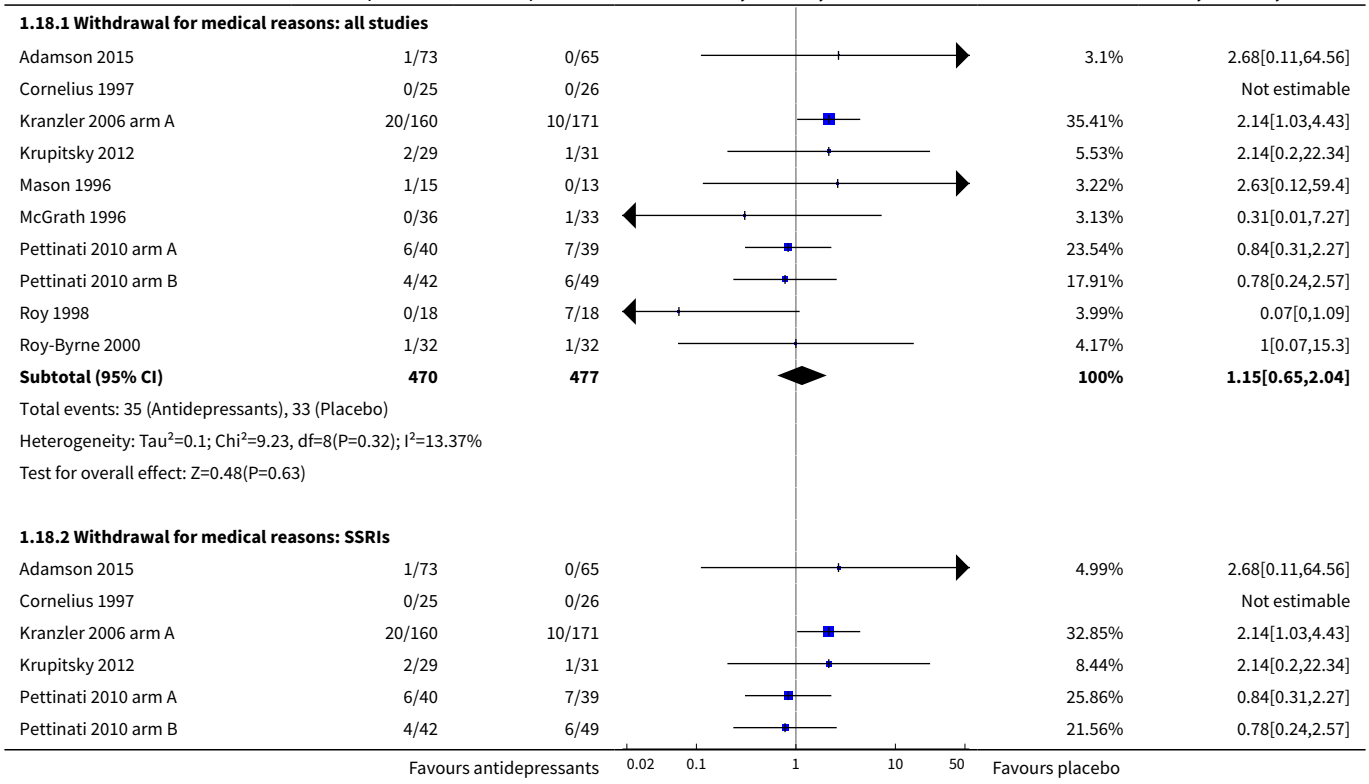


Favours antidepressants — Favours placebo

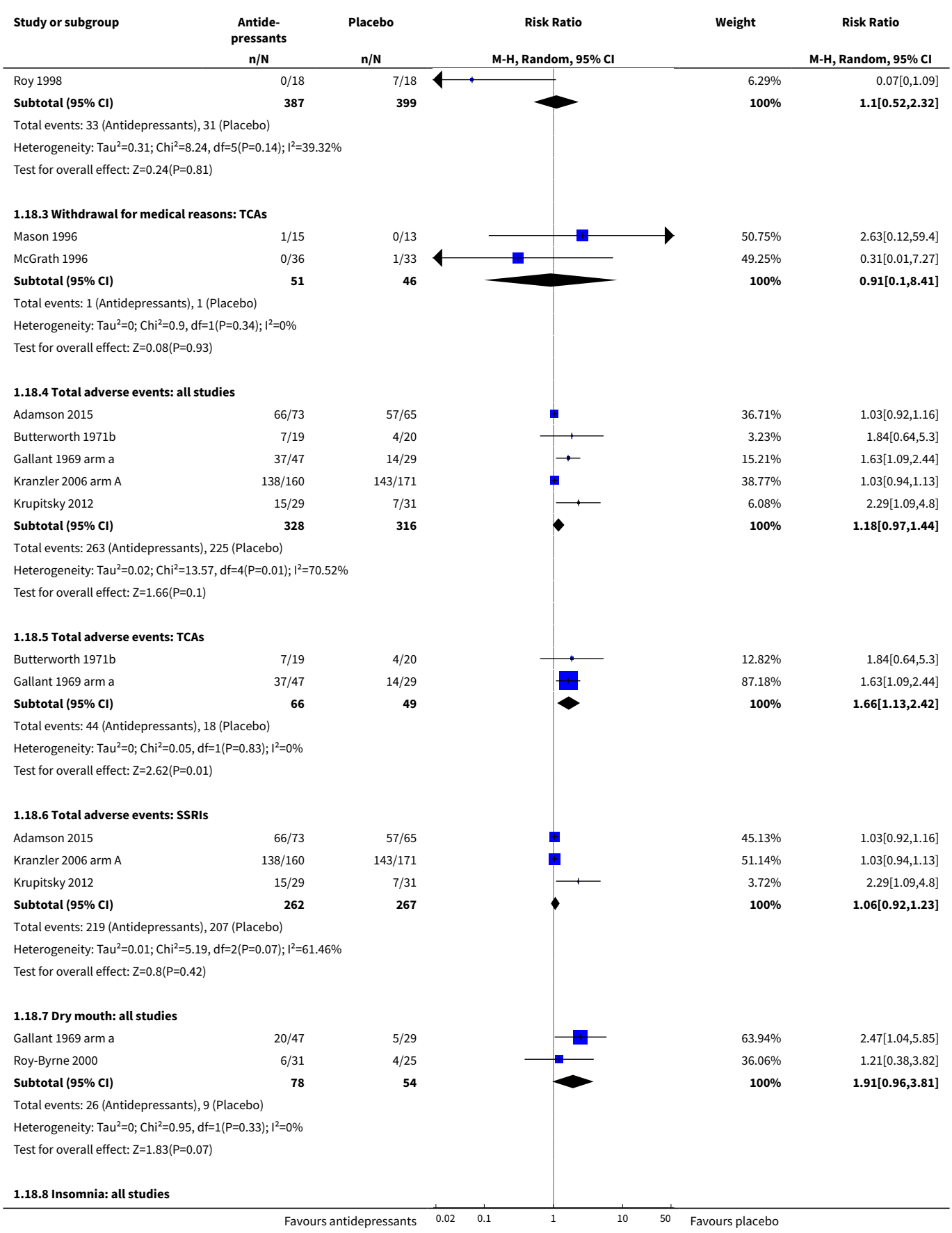


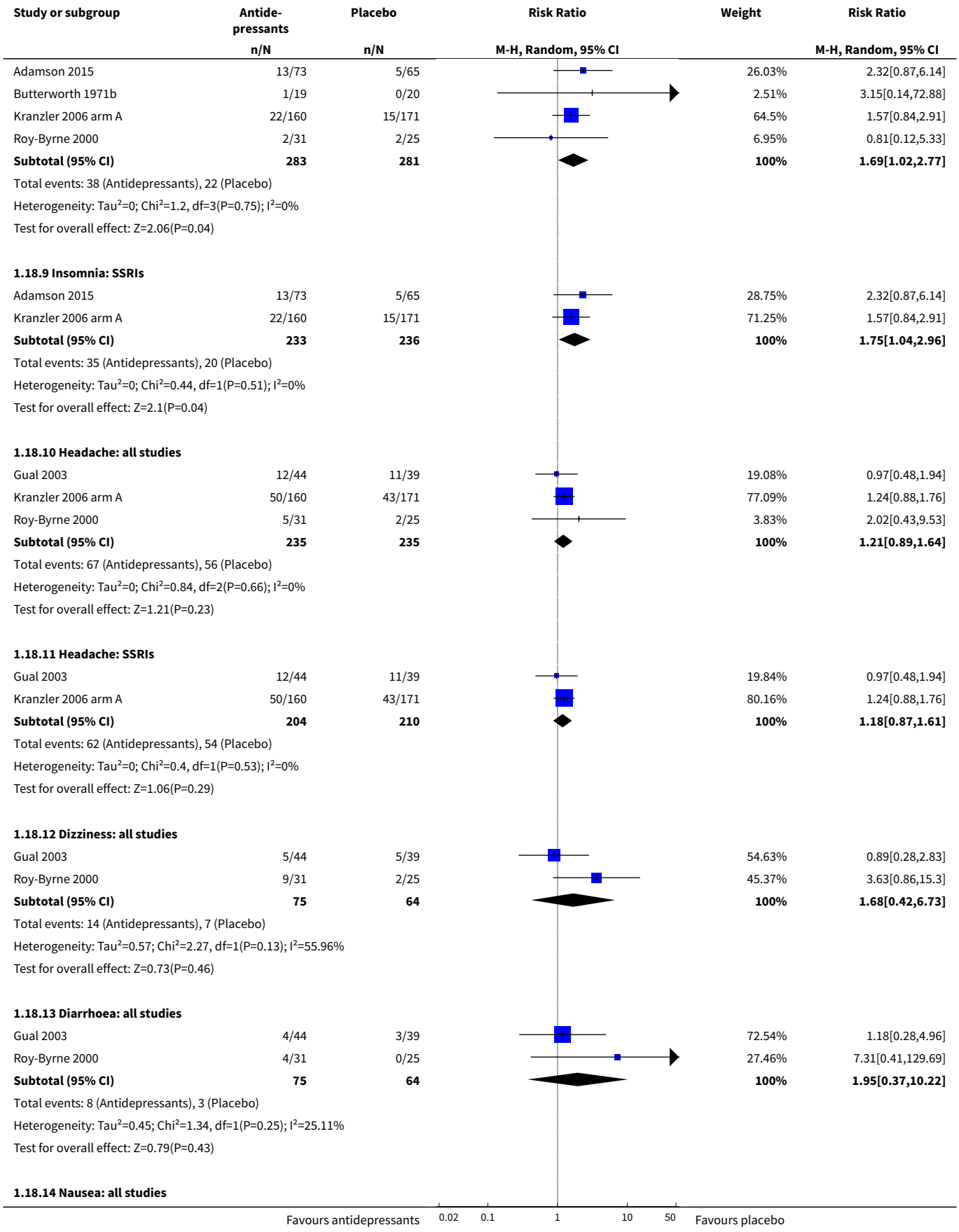
Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Moak 2003	7/38	16/44		8.21%	0.51[0.23,1.1]
Pettinati 2010 arm A	19/40	16/39		13.72%	1.16[0.7,1.9]
Pettinati 2010 arm B	18/42	20/49		14.04%	1.05[0.65,1.71]
Roy 1998	8/18	13/18		11.51%	0.62[0.34,1.11]
Subtotal (95% CI)	**370**	**389**		**100%**	**1.04[0.79,1.36]**
Total events: 149 (Antidepressants), 147 (Placebo)					
Heterogeneity: Tau²=0.07; Chi²=14.24, df=7(P=0.05); I²=50.84%					
Test for overall effect: Z=0.26(P=0.79)					
1.17.4 5-HT2 antagonists					
Cornelius 2016	0/7	0/7			Not estimable
Hernandez-Avila 2004	8/21	5/20		34.27%	1.52[0.6,3.88]
McLean 1986	1/17	2/18		8.78%	0.53[0.05,5.32]
Roy-Byrne 2000	12/32	21/32		56.95%	0.57[0.34,0.95]
Subtotal (95% CI)	**77**	**77**		**100%**	**0.79[0.38,1.64]**
Total events: 21 (Antidepressants), 28 (Placebo)					
Heterogeneity: Tau²=0.17; Chi²=3.36, df=2(P=0.19); I²=40.43%					
Test for overall effect: Z=0.62(P=0.53)					

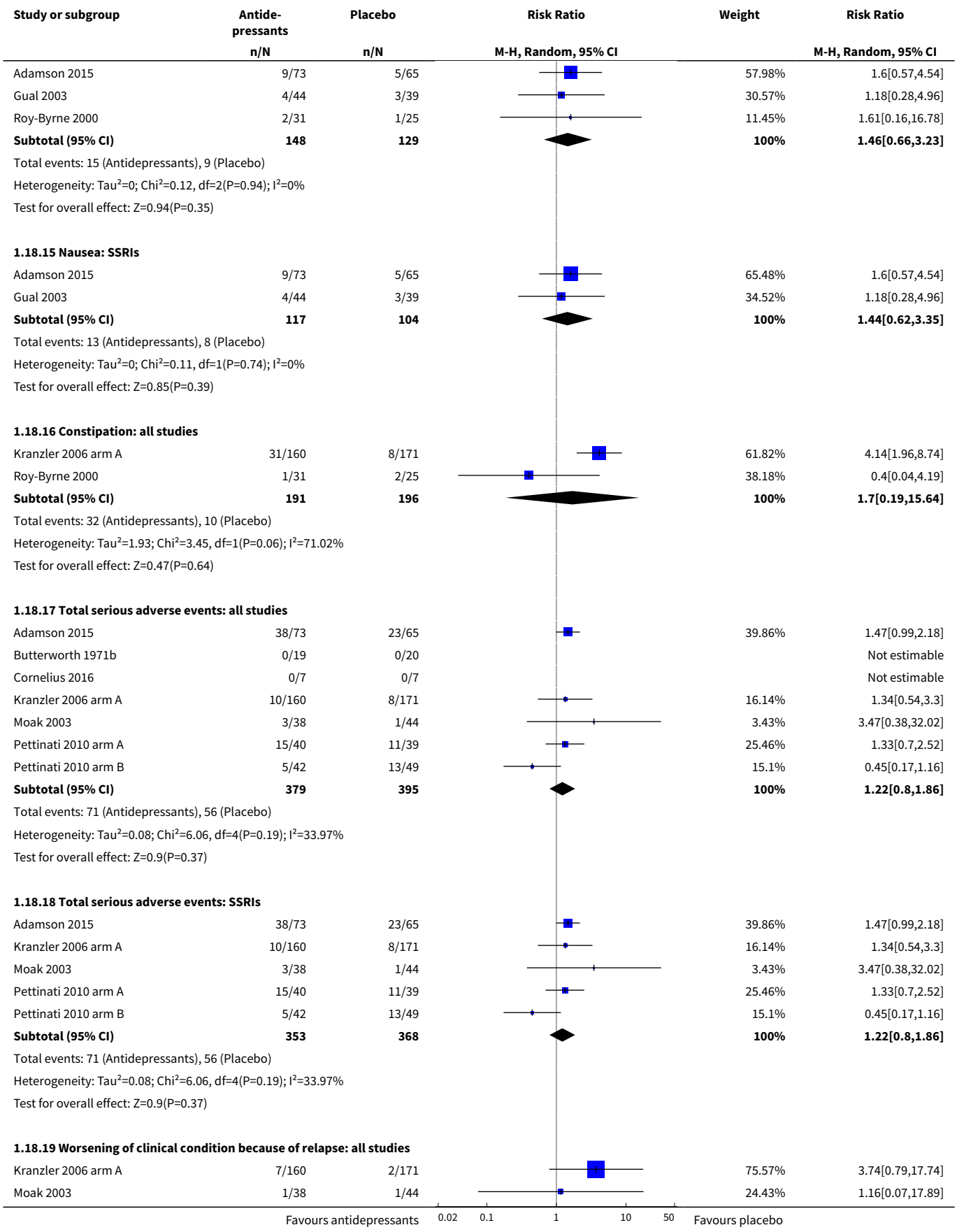
Analysis 1.18. Comparison 1 Antidepressants versus placebo: all studies, Outcome 18 Tolerability of treatment: adverse events.

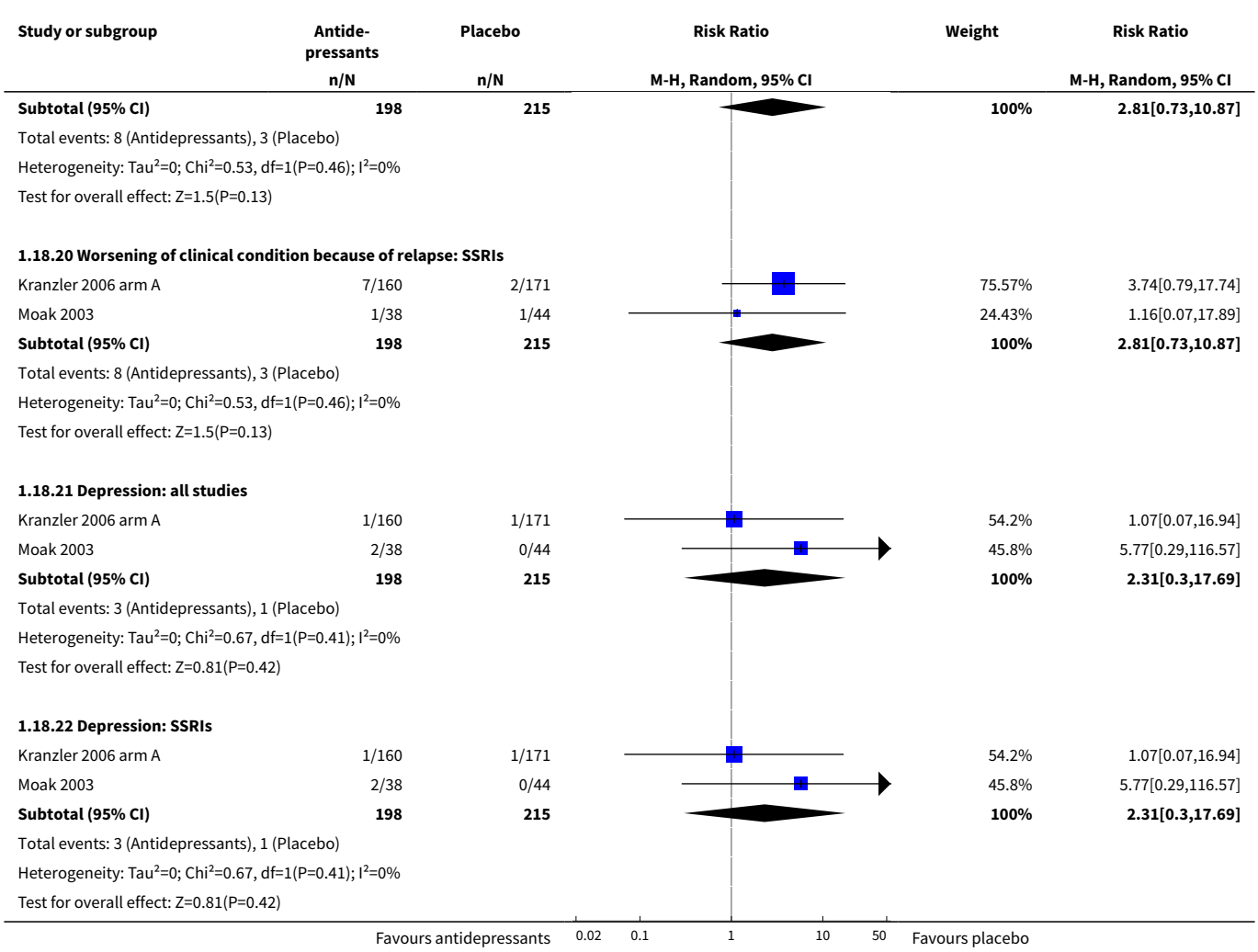


Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Withdrawal for medical reasons: all studies					
Adamson 2015	1/73	0/65		3.1%	2.68[0.11,64.56]
Cornelius 1997	0/25	0/26			Not estimable
Kranzler 2006 arm A	20/160	10/171		35.41%	2.14[1.03,4.43]
Krupitsky 2012	2/29	1/31		5.53%	2.14[0.2,22.34]
Mason 1996	1/15	0/13		3.22%	2.63[0.12,59.4]
McGrath 1996	0/36	1/33		3.13%	0.31[0.01,7.27]
Pettinati 2010 arm A	6/40	7/39		23.54%	0.84[0.31,2.27]
Pettinati 2010 arm B	4/42	6/49		17.91%	0.78[0.24,2.57]
Roy 1998	0/18	7/18		3.99%	0.07[0,1.09]
Roy-Byrne 2000	1/32	1/32		4.17%	1[0.07,15.3]
Subtotal (95% CI)	**470**	**477**		**100%**	**1.15[0.65,2.04]**
Total events: 35 (Antidepressants), 33 (Placebo)					
Heterogeneity: Tau²=0.1; Chi²=9.23, df=8(P=0.32); I²=13.37%					
Test for overall effect: Z=0.48(P=0.63)					
1.18.2 Withdrawal for medical reasons: SSRIs					
Adamson 2015	1/73	0/65		4.99%	2.68[0.11,64.56]
Cornelius 1997	0/25	0/26			Not estimable
Kranzler 2006 arm A	20/160	10/171		32.85%	2.14[1.03,4.43]
Krupitsky 2012	2/29	1/31		8.44%	2.14[0.2,22.34]
Pettinati 2010 arm A	6/40	7/39		25.86%	0.84[0.31,2.27]
Pettinati 2010 arm B	4/42	6/49		21.56%	0.78[0.24,2.57]

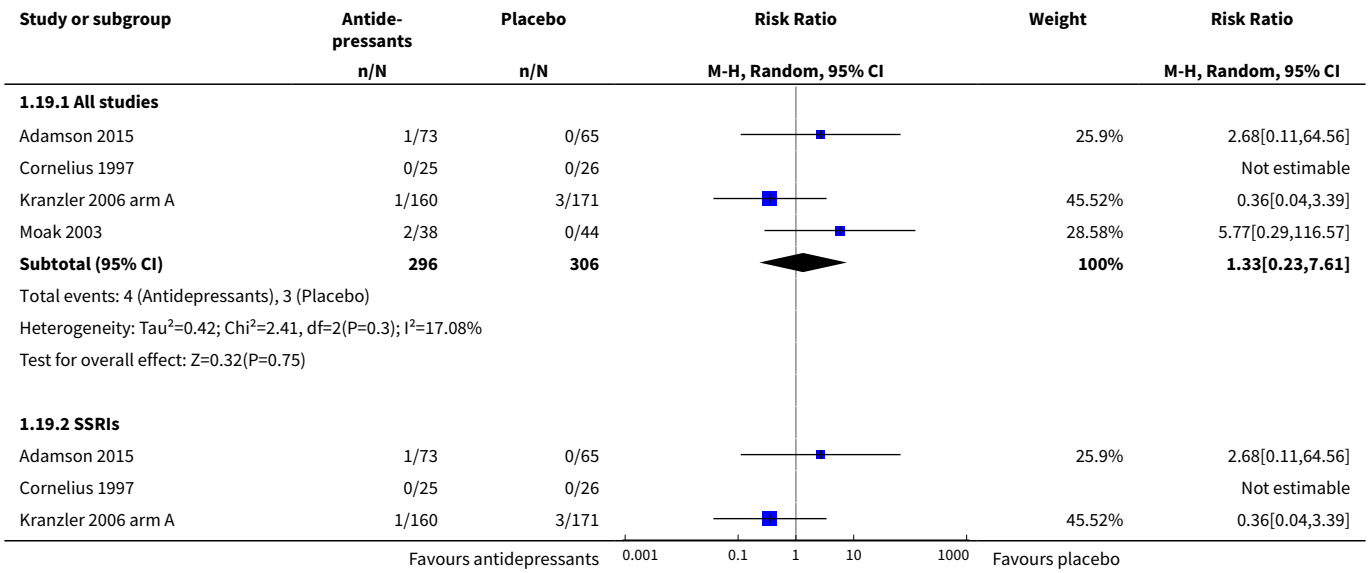


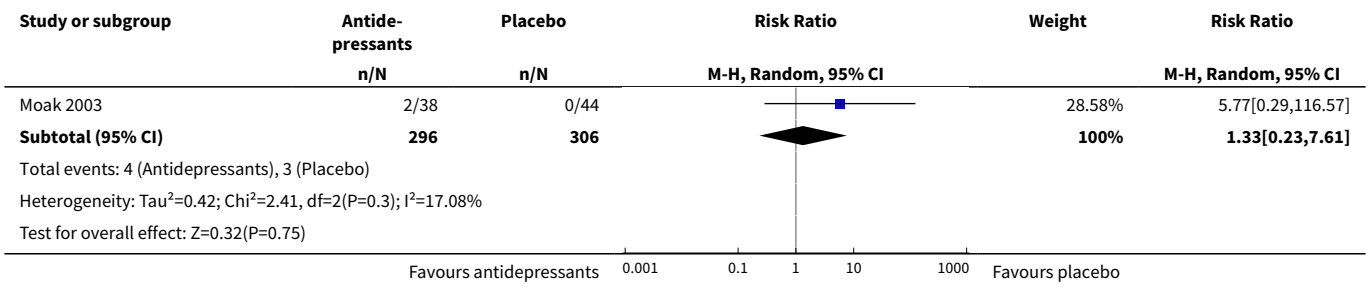




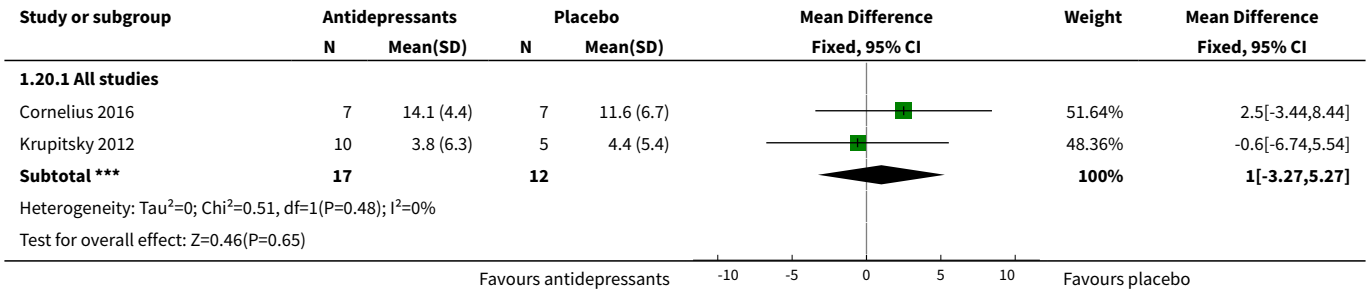


Analysis 1.19. Comparison 1 Antidepressants versus placebo: all studies, Outcome 19 Suicide attempts.

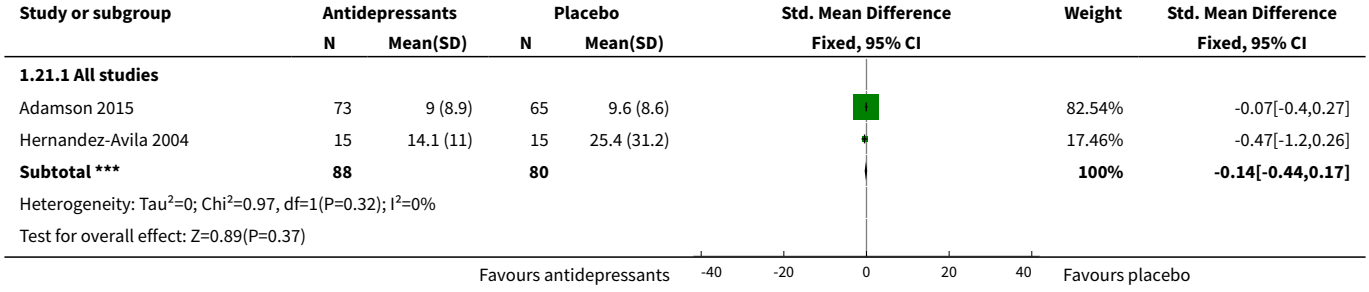




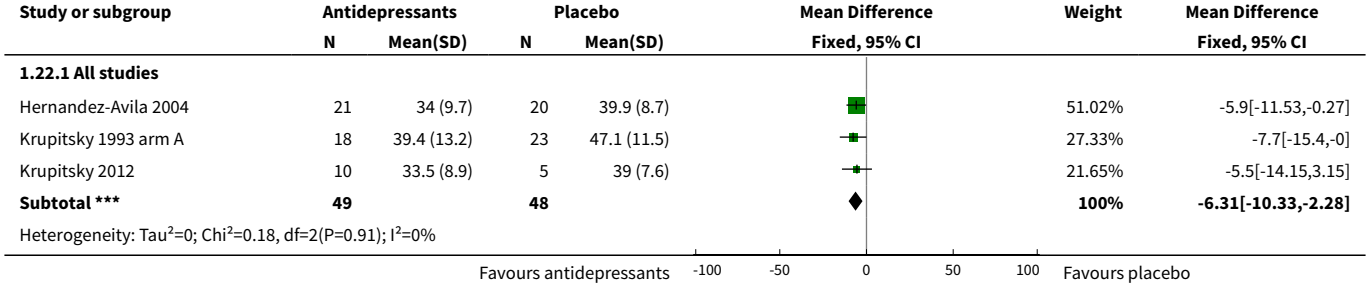
Analysis 1.20. Comparison 1 Antidepressants versus placebo: all studies, Outcome 20 Secondary outcomes: craving.

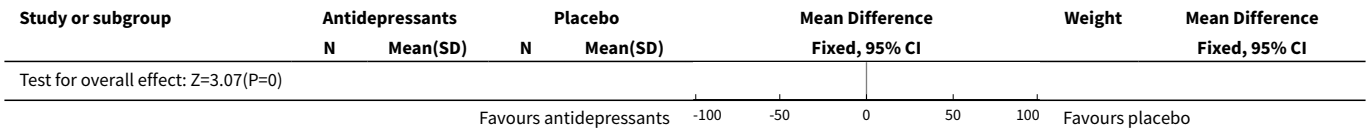


Analysis 1.21. Comparison 1 Antidepressants versus placebo: all studies, Outcome 21 Secondary outcomes: severity of dependence.



Analysis 1.22. Comparison 1 Antidepressants versus placebo: all studies, Outcome 22 Secondary outcomes: severity of anxiety.

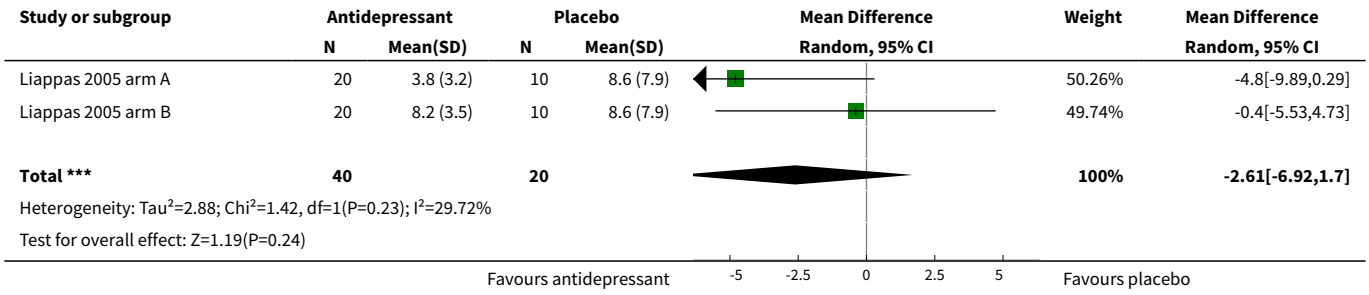




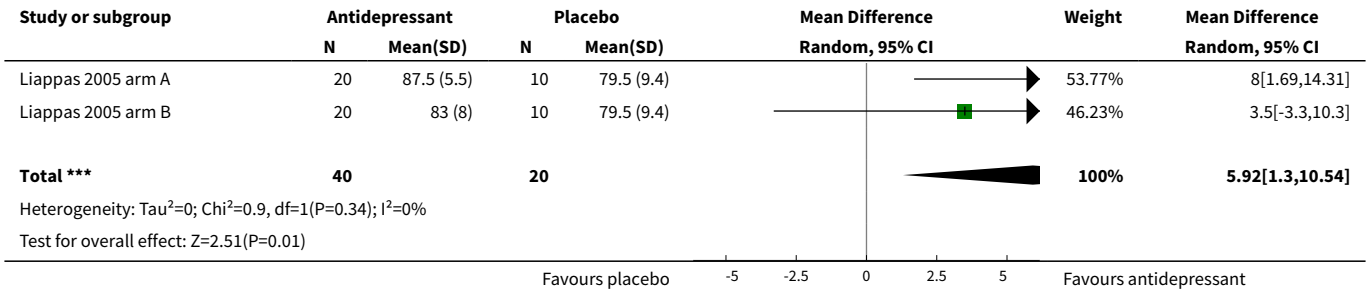
Comparison 2. Antidepressants versus psychotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression severity: final score	2	60	Mean Difference (IV, Random, 95% CI)	-2.61 [-6.92, 1.70]
2 Global assessment: final score	2	60	Mean Difference (IV, Random, 95% CI)	5.92 [1.30, 10.54]
3 Acceptability: dropouts	2	68	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.31, 6.54]

Analysis 2.1. Comparison 2 Antidepressants versus psychotherapy, Outcome 1 Depression severity: final score.

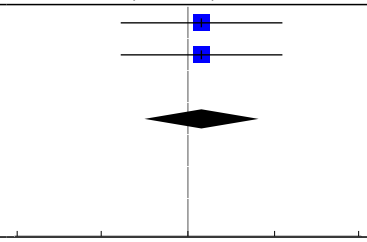


Analysis 2.2. Comparison 2 Antidepressants versus psychotherapy, Outcome 2 Global assessment: final score.



Analysis 2.3. Comparison 2 Antidepressants versus psychotherapy, Outcome 3 Acceptability: dropouts.

Study or subgroup	Antidepressant n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Liappas 2005 arm A	3/23	1/11		50%	1.43[0.17,12.27]
Liappas 2005 arm B	3/23	1/11		50%	1.43[0.17,12.27]
Total (95% CI)	**46**	**22**		**100%**	**1.43[0.31,6.54]**
Total events: 6 (Antidepressant), 2 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.47(P=0.64)					



APPENDICES

Appendix 1. Abbreviations

- ADS: Alcohol Dependence Scale
- ALT: alanine aminotransferase
- ASI: Addiction Severity Index
- AST: aspartate aminotransferase
- AUD: Alcohol Use Disorder
- AUDIT: Alcohol Use Disorders Identification Test
- BAI: Beck Anxiety Inventory
- BDI: Beck Depression Inventory
- BPRS: Brief Psychiatric Rating Scale
- BSCS: Brief Substance Craving Scale
- CBT: cognitive behavioural therapy
- CCT: controlled clinical trial
- CDAG: Cochrane Drugs and Alcohol Group
- CDT: carbohydrate deficient transferrin
- CGI: Clinical Global Impression scale
- CI: confidence intervals
- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol scale, Revised
- ADS: Alcohol Dependence Scale
- ALT: alanine aminotransferase
- ASI: Addiction Severity Index
- AST: aspartate aminotransferase
- AUD: Alcohol Use Disorder
- AUDIT: Alcohol Use Disorders Identification Test
- BAI: Beck Anxiety Inventory
- BDI: Beck Depression Inventory
- BPRS: Brief Psychiatric Rating Scale
- BSCS: Brief Substance Craving Scale
- CBT: cognitive behavioural therapy
- CCT: controlled clinical trial
- CDAG: Cochrane Drugs and Alcohol Group
- CDT: carbohydrate deficient transferrin
- CGI: Clinical Global Impression scale
- CI: confidence intervals
- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol scale, Revised

- DBI: Drinking Behaviour Interview
- DOTES: Dosage Record and Treatment Emergent Symptoms Scale
- DrInC: Drinker Inventory of Consequences scale
- DSM: Diagnostic and Statistic Manual of Mental Disorders
- ECT: electroconvulsive therapy
- GAD: generalized anxiety disorder
- GAF: General Assessment of Functioning scale
- GAS: Global Assessment Scale
- GGT: γ-glutamyltransferase
- HRSA: Hamilton Anxiety Rating Scale
- HRSD: Hamilton Depression Rating Scale
- HSCL: Hopkins Symptom Checklist
- ICD: International Classification of Diseases
- LDQ: Leeds Dependence Questionnaire
- LDRS: Lehmann Depression Rating Scale
- MADRS: Montgomery and Åsberg Depression Rating Scale
- MAOI: monoamine oxidase inhibitor
- MAST: Michigan Alcoholism Screening Test
- MD: mean difference
- MET: motivational enhancement therapy
- MINI: Mini International Neuropsychiatric Interview
- MMPI: Minnesota Multiphasic Personality Inventory
- MMSE: Mini-Mental State Examination
- OCDS: Obsessive-Compulsive Drinking Scale
- PACS: Penn Alcohol Craving scale
- PANSS: Positive and Negative Syndrome Scale
- PRISM: Psychiatric Rating Instrument for Mental Disorders and Substance Abuse
- PSQI: Pittsburgh Sleep Quality Index
- RCT: randomized controlled trial
- RR: risk ratio
- STAI: State Trait Anxiety Inventory
- SAFTEE: Systematic Assessment for Treatment of Emergent Events
- SCID: Structured Clinical Interview for DSM
- SCL-90: Symptom Check List-90
- SD: standard deviation
- SDS: Severity of Dependence Scale
- SF-36: 36-item Short Form (health-related quality of life questionnaire)
- SMD: standardized mean difference
- SNRI: serotonin-noradrenaline reuptake inhibitor
- SOFAS: Social and Occupational Functioning Assessment Scale
- SSRI: selective serotonin reuptake inhibitor
- SUD: substance-use disorder
- TCA: tricyclic antidepressant
- TLFB: timeline follow-back
- UKU: Udvalg for Kliniske Undersogelser Side Effect Rating Scale
- VAS: Visual Analogue Scale
- WHO: World Health Organization
- ZUNG: Zung Self-Assessment Depression Scale

Appendix 2. Cochrane Drug and Alcohol Group Specialised Register search strategy

CDAG Specialised register (via CRSLive)

4 July 2017 (197 hits)

1. (antidepressant*) AND (INREGISTER)

2. (citalopram OR escitalopram OR paroxetine OR fluoxetine OR fluvoxamine OR sertraline OR trazodone OR nefazodone OR venlafaxine OR desvenlafaxine OR duloxetine OR reboxetine OR bupropion OR amoxapine OR amitriptyline OR maprotiline OR nortriptyline OR desipramine OR trimipramine OR imipramine OR protriptyline OR doxepin OR clomipramine OR mirtazapine OR mianserin OR moclobemide OR phenelzine OR tranylcypromine OR agomelatine OR Acetylcarnitine OR Alaproclate OR Amersergide OR Amiflamine OR Amineptine OR Amisulpride OR Befloxatone OR Benactyzine OR Brofaromine OR Butriptyline OR Caroxazone OR Chlorpoxiten OR Cilosamine OR Cimoxatone OR Clorgyline OR Clorimipramine OR Clovoxamine OR Deanol OR Demexiptiline OR Deprenyl OR Dibenzipin OR Diclofensine OR Dothiepin OR Etoperidone OR Femoxetine OR Fluotracen OR Fluparoxan OR Idazoxan OR Iprindole OR Iproniazid OR isocarboxazid OR Litoxetine OR Lofepramine OR Medifoxamine OR Melitracen OR Metapramine OR Milnacipran OR Minaprine OR Nialamide OR Nomifensine OR Noxiptiline OR Opipramol OR Oxaflozane OR Oxaprotiline OR Pargyline OR Piribedil OR Pirlindole OR Pivagabine OR Prosulpride OR Protriptyline OR Quinupramine OR Rolipram OR SSRI OR Setiptiline OR Sulpiride OR Teniloxine OR Tetrindole OR Thiazesim OR Thozalinone OR Tianeptine OR Toloxatone OR Tomoxetine OR Viloxazine OR Viqualine OR Zimeldine) AND (INREGISTER)

3. #1 OR #2

4. (alcohol:TI) AND (INREGISTER)

5. (alcohol:AB) AND (INREGISTER)

6. (alcohol*:XDI) AND (INREGISTER)

7. #4 OR #5 OR #6

8. #3 AND #7

Appendix 3. CENTRAL search strategy

CENTRAL (via onlinelibrary.wiley.com)

2017, Issue 7 (695 hits)

1. MeSH descriptor: (Alcohol-Related Disorders) explode all trees

2. ((alcohol) near (dependen* or disorder* or drink* or misuse or abuse* or consumption)):ti,ab,kw

3. alcohol*:ti,ab,kw

4. MeSH descriptor: (Drinking Behavior) explode all trees

5. #1 or #2 or #3 or #4

6. MeSH descriptor: (Antidepressive Agents) explode all trees

7. anti next depres*:ti,ab,kw

8. Antidepress* or "Monoamine Oxidase Inhibitors" or "Selective Serotonin Reuptake Inhibitors" or "Tricyclic Drugs" or acetylcarnitine or agomelatine or alaproclate or amesergide or amiflamine or amineptine or amitriptyline or amoxapine or befloxatone or benactyzine or brofaromine or bupropion or butriptyline or caroxazone or chlorproxithene or cilobamine or cimoxatone or citalopram or clomipramine or clorgyline or chlorimipramine or clovoxamine or deanol or demexiptiline or deprenyl or desipramine or dibenzepin or diclofensine or dothiepin or doxepin or duloxetine or escitalopram or etoperidone or femoxetine or fluotracen or fluoxetine or fluparoxan or fluvoxamine or idazoxan or imipramine or Iprindol* or iproniazid or isocarboxazid or Litoxetin* or Lofepramin* or Maprotilin* or Medifoxamin* or melitracene or Metapramin* or mianserin or milnacipran or Minaprin* or Mirtazapin* or Moclobemid* or Nefazodon* or Nialamid* or Nomifensin* or Nortriptylin* or Noxiptilin* or opipramol or Oxaflozan* or Oxaprotilin* or Pargylin* or Paroxetin* or Phenelzin* or piribedil or Pirlindol* or Pivagabin* or Prosulprid* or Protriptylin* or Quinupramin* or Reboxetin* or rolipram or selegiline or Sertralin* or Setiptilin* or teniloxazine or Tetrindol* or thiazesim or Thozalinon* or Tianeptin* or Toloxaton* or Tomoxetin* or Tranylcypromin* or Trazodon* or Trimipramin* or Venlafaxin* or Viloxazin* or Viqualin* or Zimeldin*:ti,ab,kw

9. #6 or #7 or #8

10. #5 and #9

Appendix 4. MEDLINE search strategy

MEDLINE (via PubMed)

4 July 2017 (4174 hits)

1. Alcohol-Related Disorders(MeSH)

2. ((alcohol) AND (dependen* OR disorder* OR drink* OR misuse OR abuse* OR consumption))

3. alcohol* (tiab)

4. Drinking behaviour(MeSH)

5. #1 OR #2 OR #3 OR #4

6. Antidepressive Agents(MeSH)

7. anti-depres*(tiab)

8. Antidepress* OR "Monoamine Oxidase Inhibitors" OR "Selective Serotonin Reuptake Inhibitors" OR "Tricyclic Drugs" OR acetylcarnitine OR agomelatine OR alaproclate OR amesergide OR amiflamine OR amineptine OR amitriptyline OR amoxapine OR befloxatone OR benactyzine OR brofaromine OR bupropion OR butriptyline OR caroxazone OR chlorproxithene OR cilobamine OR cimoxatone OR citalopram OR clomipramine OR clorgyline OR chlorimipramine OR clovoxamine OR deanol OR demexiptiline OR deprenyl OR desipramine OR dibenzepin OR diclofensine OR dothiepin OR doxepin OR duloxetine OR escitalopram OR etoperidone OR femoxetine OR fluotracen OR fluoxetine OR fluparoxan OR fluvoxamine OR idazoxan OR imipramine OR Iprindol* OR iproniazid OR isocarboxazid OR Litoxetin* OR Lofepramin* OR Maprotilin* OR Medifoxamin* OR melitracene OR Metapramin* OR mianserin OR milnacipran OR Minaprin* OR Mirtazapin* OR Moclobemid* OR Nefazodon* OR Nialamid* OR Nomifensin* OR Nortriptylin* OR Noxiptilin* OR opipramol OR Oxaflozan* OR Oxaprotilin* OR Pargylin* OR Paroxetin* OR Phenelzin* OR piribedil OR Pirlindol* OR Pivagabin* OR Prosulprid* OR Protriptylin* OR Quinupramin* OR Reboxetin* OR rolipram OR selegiline OR Sertralin* OR Setiptilin* OR teniloxazine OR Tetrindol* OR thiazesim OR Thozalinon* OR Tianeptin* OR Toloxaton* OR Tomoxetin* OR Tranylcypromin* OR Trazodon* OR Trimipramin* OR Venlafaxin* OR Viloxazin* OR Viqualin* OR Zimeldin*

9. #6 OR #7 OR #8

10. randomized controlled trial(pt)

11. controlled clinical trial(pt)

12. randomized(tiab)

13. placebo(tiab)

14. drug therapy(sh)

15. randomly(tiab)

16. trial(tiab)

17. groups(tiab)

18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

19. animals(mh) NOT humans(mh)

20. #18 NOT #19

21. #5 AND #9 AND #20

Appendix 5. Embase search strategy

Embase (via embase.com)

4 July 2017 (3466 hits)

exp alcoholism'/exp OR alcohol NEAR/6 (dependen* OR disorder* OR drink* OR misuse OR abuse* OR consumption) OR alcohol*:ab,ti OR 'drinking behavior'/exp AND ('clinical trial'/exp OR 'controlled clinical trial'/exp OR 'crossover procedure'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled 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)) AND ('antidepressant agent'/exp OR antidepress*:ab,ti OR antidepress* OR 'monoamine oxidase inhibitors'/exp OR 'selective serotonin reuptake inhibitors' OR 'tricyclic drugs' OR 'acetylcarnitine'/exp OR 'agomelatine'/exp OR 'alaproclate'/exp OR amersergide OR 'amiflamine'/exp OR 'amineptine'/exp OR 'amitriptyline'/exp OR 'amoxapine'/exp OR 'befloxatone'/exp OR 'benactyzine'/exp OR 'brofaromine'/exp OR 'bupropion'/exp OR 'butriptyline'/exp OR caroxazone OR chlorpoxiten OR cilosamine OR 'cimoxatone'/exp OR

'citalopram'/exp OR 'clomipramine'/exp OR 'clorgyline'/exp OR clorimipramine OR 'clovoxamine'/exp OR 'deanol'/exp OR 'demexiptiline'/exp OR 'deprenyl'/exp OR 'desipramine'/exp OR dibenzipin OR 'diclofensine'/exp OR 'dothiepin'/exp OR 'doxepin'/exp OR 'duloxetine'/exp OR 'escitalopram'/exp OR 'etoperidone'/exp OR 'femoxetine'/exp OR fluotracen OR 'fluoxetine'/exp OR 'fluparoxan'/exp OR 'fluvoxamine'/exp OR 'idazoxan'/exp OR 'imipramine'/exp OR iprindol* OR 'iproniazid'/exp OR 'isocarboxazid'/exp OR litoxetin* OR lofepramin* OR maprotilin* OR medifoxamin* OR 'melitracen'/exp OR metapramin* OR 'mianserin'/exp OR 'milnacipran'/exp OR minaprin* OR mirtazapin* OR moclobemid* OR nefazodon* OR nialamid* OR nomifensin* OR nortriptylin* OR noxiptilin* OR 'opipramol'/exp OR oxaflozan* OR oxaprotilin* OR pargylin* OR paroxetin* OR phenelzin* OR 'piribedil'/exp OR pirlindol* OR pivagabin* OR prosulprid* OR protriptylin* OR quinupramin* OR reboxetin* OR 'rolipram'/exp OR seleginine OR sertralin* OR setiptilin* OR teniloxine OR tetrindol* OR thiazesim OR thozalinon* OR tianeptin* OR toloxaton* OR tomoxetin* OR tranylcypromin* OR trazodon* OR viqualin* OR zimeldin*)

Appendix 6. Criteria for risk of bias assessment

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because 1 of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because 1 of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias)	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.

(Continued)

4. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
5. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
6. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or dropout	Low risk	No missing outcome data. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods. All randomized participants are reported/analyzed in the group they were allocated to by randomization irrespective of non-compliance and cointerventions (intention to treat).
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.

(Continued)

		'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization.
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomized not stated, no reasons for missing data provided; number of dropouts not reported for each group).
7. Selective reporting (reporting bias)	Low risk	Study protocol is available and all of study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way. Study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	High risk	Not all of study's prespecified primary outcomes have been reported. One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified. One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. Study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear risk	Insufficient information to permit judgement of low or high risk.

Appendix 7. Treatment regimens in included studies

Antidepressants versus placebo

22 studies compared the efficacy of an antidepressant versus placebo (Adamson 2015; Altamura 1990; Butterworth 1971b; Cornelius 1997; Cornelius 2016; Gallant 1969 arm a; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 1993 arm A; Krupitsky 2012; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Nunes 1993; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000; 1438 participants).

- Amitriptyline (75 mg/day) or placebo for 3 weeks (Krupitsky 1993 arm A; 41 participants)
- Citalopram (up to 60 mg/day) plus naltrexone (up to 100 mg/day) or placebo plus naltrexone (up to 100 mg/day) for 12 weeks (Adamson 2015; 138 participants)
- Desipramine (200 mg/day) or placebo for 6 months (Mason 1996; 28 participants)
- Doxepin (75 mg/day or 150 mg/day) or placebo for 3 weeks (Gallant 1969 arm a; 76 participants)
- Escitalopram (10 mg/day) or placebo for 13 weeks (Krupitsky 2012; 60 participants)
- Fluoxetine (20 mg/day) or placebo for 12 weeks (Cornelius 1997; 51 participants)
- Imipramine (25 mg/day) or placebo for 3 weeks (Butterworth 1971b; 40 participants)
- Imipramine (up to 300 mg/day) or placebo for 12 weeks (McGrath 1996; 69 participants)
- Imipramine (dose not available) or placebo for 24 weeks (Nunes 1993; 23 participants)
- Mianserin (60 mg/day) or placebo for 4 weeks (McLean 1986; 35 participants)
- Mirtazapine (30 mg/day) or placebo for 12 weeks (Cornelius 2016; 14 participants)
- Nefazodone (up to 600 mg/day) or placebo for 10 weeks (Hernandez-Avila 2004; 41 participants)
- Nefazodone (up to 500 mg/day) or placebo for 12 weeks (Roy-Byrne 20000; 64 participants)
- Sertraline (up to 150 mg/day) or placebo for 24 weeks (Gual 2003; 83 participants)
- Sertraline (200 mg/day) or placebo for 10 weeks (Kranzler 2006 arm A; score HRSD ≥ 17; 189 participants)
- Sertraline (200 mg/day) or placebo for 10 weeks (Kranzler 2006 arm B; score HRSD ≤ 16; 139 participants)

- Sertraline (200 mg/day) or placebo for 12 weeks (Moak 2003; 82 participants)
- Sertraline (up to 200 mg/day) or placebo for 14 weeks (Pettinati 2001a; 29 participants)
- Sertraline (200 mg/day) or placebo for 14 weeks (Pettinati 2010 arm A; 79 participants)
- Sertraline (200 mg/day) plus naltrexone (100 mg/day) or placebo plus naltrexone for 14 weeks (Pettinati 2010 arm B; 91 participants)
- Sertraline (100 mg/day) or placebo for 6 weeks (Roy 1998; 36 participants)
- Vilofaxine (400 mg/day) or placebo for 12 weeks (Altamura 1990; 30 participants)

Antidepressants versus psychotherapy

Two studies compared the efficacy of an antidepressant versus psychotherapy (Liappas 2005 arm A; Liappas 2005 arm B; 60 participants).

- Mirtazapine (up to 60 mg/day) or psychotherapy for 3 weeks (Liappas 2005 arm A; 30 participants)
- Venlafaxine (up to 300 mg/day) or psychotherapy for 3 weeks (Liappas 2005 arm B; 30 participants)

Antidepressants versus other medications

Four studies compared the efficacy of antidepressants to that of other medications (Butterworth 1971a; Gallant 1969 arm b; Krupitsky 1993 arm B; Muhonen 2008; 228 participants).

- Amitriptyline (75 mg/day) or diazepam (15 mg/day) for 3 weeks (Krupitsky 1993 arm B; 29 participants)
- Doxepin (25 mg/day) or diazepam (5 mg/day) for 3 weeks (Butterworth 1971a; 39 participants)
- Doxepin (75 mg/day or 150 mg/day) or diazepam (15 mg/day) for 3 weeks (Gallant 1969 arm b; 71 participants)
- Escitalopram (20 mg/day) or memantine (20 mg/day) for 26 weeks (Muhonen 2008; 80 participants)

One antidepressant versus another antidepressant

Five studies compared the efficacy of an antidepressant versus another (Altintoprak 2008; Cocchi 1997; Habrat 2006; Liappas 2005 arm C; Lôo 1988; 621 participants).

- Mirtazapine (up to 60 mg/day) or amitriptyline (up to 150 mg/day) for 8 weeks (Altintoprak 2008; 44 participants)
- Mirtazapine (up to 60 mg/day) or venlafaxine (up to 300 mg/day) for 3 weeks (Liappas 2005 arm C; 40 participants)
- Paroxetine (20 mg/day) or amitriptyline (25 mg/day) for 3-4 weeks (Cocchi 1997; 122 participants)
- Tianeptine (37.5 mg/day) or amitriptyline (75 mg/day) for 4-8 weeks (Lôo 1988; 129 participants)
- Tianeptine (37.5 mg/day) versus fluvoxamine (100 mg/day) for 6 weeks (Habrat 2006; 286 participants)

Appendix 8. Rating instruments utilized

Depression

Diagnostic criteria and interviews

- DSM-III (APA 1980) utilized in Lôo 1988.
- DSM III-R (APA 1987) utilized in Altamura 1990; Cornelius 1997; Mason 1996; McGrath 1996; Moak 2003; Nunes 1993; Pettinati 2001a; Roy 1998; Roy-Byrne 2000.
- DSM-IV (APA 1994) utilized in Adamson 2015; Altintoprak 2008; Cocchi 1997; Cornelius 1997; Cornelius 2016; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Pettinati 2010 arm A; Pettinati 2010 arm B.
- DSM-IV-TR (APA 2000) utilized in Muhonen 2008.
- ICD-10 (WHO 1993) utilized in Gual 2003; Habrat 2006; Krupitsky 2012.
- MINI (Sheehan 1998) utilized in Cornelius 2016; Mason 1996.
- SCID (Spitzer 1992) utilized in Adamson 2015; Altintoprak 2008; Cornelius 1997; Hernandez-Avila 2004; Moak 2003; Pettinati 2001a; Roy-Byrne 2000.
- SCID-P (First 1995) utilized in Muhonen 2008; Pettinati 2010 arm A; Pettinati 2010 arm B.

Severity

Observer-rated scales

- BPRS utilized in Butterworth 1971a; Krupitsky 2012.
- CGI (Guy 1975) utilized in Butterworth 1971b; Gallant 1969 arm a; Gallant 1969 arm b; Habrat 2006; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; McGrath 1996; Roy 1998; Roy-Byrne 2000.
- HRSD (Hamilton 1960; Hamilton 1967; 17 items utilized in Altintoprak 2008; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B.
- HRSD (Hamilton 1960; 21 items utilized in Altamura 1990; Krupitsky 2012; McGrath 1996; Moak 2003; Nunes 1993; Roy 1998;

- HRSD (Hamilton 1960; 24 items utilized in Cornelius 1997; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Mason 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B.
- HRSD (Hamilton 1960; number of items unknown in Habrat 2006; Lôo 1988; Roy-Byrne 2000.
- LDRS (Rockliff 1971) utilized in Butterworth 1971b.
- MADRS (Montgomery 1979) utilized in Adamson 2015; Gual 2003; Krupitsky 2012; Lôo 1988; Muhonen 2008.
- PRISM (Hasin 1996) utilized in Moak 2003.

Self-administered scales

- BDI (Beck 1961) utilized in Cornelius 1997; Cornelius 2016; Kranzler 2006 arm A; Kranzler 2006 arm B; Moak 2003; Pettinati 2001a; Roy 1998.
- BDI-II (Beck 1996) utilized in Muhonen 2008.
- HRSD as described by Carr 1981 utilized in McLean 1986.
- MMPI utilized in Krupitsky 1993 arm A; Krupitsky 1993 arm B.
- SCL-90 (Derogatis 1974) utilized in Adamson 2015; Lôo 1988.
- Zung (Zung 1965) utilized in Butterworth 1971a; Cocchi 1997; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012.

Remission

Observer-rated scales and cut-off values

- HRSD (Hamilton 1960); final score < 8 utilized in Roy-Byrne 2000.
- HRSD (Hamilton 1960); final score ≤ 9 utilized in 3 final weeks of treatment in Pettinati 2010 arm A; Pettinati 2010 arm B.
- MADRS (Montgomery 1979); final score < 10 utilized in Adamson 2015.
- MADRS (Montgomery 1979); final score < 7 utilized in Gual 2003.

Self-administered scales and cut-off values

- HRSD (Hamilton 1960); final score < 17 utilized in McLean 1986.
- Zung (Zung 1965); participants no longer depressed utilized in Cocchi 1997.

These studies were not included in the analysis as they used self-administered scales.

Response

Observer-rated scales and cut-off values

- BPRS, marked improvement or moderate improvement in final score utilized in Butterworth 1971a.
- CGI (Guy 1975); final score equal to 'Excellent' (very much improved) + 'Good' (improved) utilized in Butterworth 1971b; Gallant 1969 arm a; Gallant 1969 arm b; Roy 1998; Roy-Byrne 2000.
- HRSD (Hamilton 1960; reduction in final score > 50% utilized in Habrat 2006; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Roy 1998.
- MADRS (Montgomery 1979); reduction in final score > 50% utilized in Gual 2003; Lôo 1988.

Self-administered scales and cut-off values

- DBI, Reduction in final score > 50% utilized in Roy 1998.
- Zung, participants improved but depressed utilized in Cocchi 1997.

These data were not included in the analysis as a self-reported scale was used.

Significant depression

Observer-rated scales and cut-off values

- HRSD (Hamilton 1960); final score ≥ 50% utilized in Moak 2003.

Alcohol dependence and consumption of alcohol

Diagnostic criteria

- DSM-III (APA 1980) utilized in Lôo 1988.
- DSM-III-R (APA 1987) utilized in Altamura 1990; Cornelius 1997; Mason 1996; McGrath 1996; Moak 2003; Nunes 1993; Pettinati 2001a; Roy 1998; Roy-Byrne 2000.

- DSM-IV (APA 1994) utilized in Adamson 2015; Altintoprak 2008; Cocchi 1997; Cornelius 2016; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B.
- DSM-IV-TR (APA 2000) utilized in Muhonen 2008.
- ICD-10 (WHO 1993) utilized in Gual 2003; Habrat 2006; Krupitsky 2012.
- MINI (Sheehan 1998) utilized in Cornelius 2016.
- SCID (Spitzer 1992) utilized in Adamson 2015; Altintoprak 2008; Cornelius 1997; Hernandez-Avila 2004; Moak 2003; Pettinati 2001a; Roy 1998; Roy-Byrne 2000.
- SCID-P (First 1995) utilized in Muhonen 2008; Pettinati 2010 arm A; Pettinati 2010 arm B.

Observer-rated scales

- ASI (McLellan 1992) utilized in Cornelius 1997; Krupitsky 2012; Pettinati 2010 arm A; Pettinati 2010 arm B.
- CGI (Guy 1975) utilized in Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Roy 1998.
- TLFB (Sobell 1992) utilized in Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Mason 1996; McGrath 1996; Moak 2003; Nunes 1993; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000.

Self-administered scales

- ADS (Skinner 1982; Skinner 1984) utilized in Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003.
- AUDIT (Saunders 1993) utilized in Muhonen 2008; Roy-Byrne 2000.
- DBI (Shelton 1969) utilized in Altamura 1990.
- DrInC (Miller 1995) utilized in Hernandez-Avila 2004.
- LDQ (Raistrick 1994) utilized in Adamson 2015.
- MAST (Selzer 1971) utilized in Altintoprak 2008; Nunes 1993.

Alcohol outcomes

- Abstinent days per week utilized by Muhonen 2008.
- Abstinent patients: percentage of participants abstinent for the treatment period utilized by Muhonen 2008; Pettinati 2010 arm A; Pettinati 2010 arm B.
- CDT values utilized in Moak 2003.
- Cumulative abstinence duration defined as the number of days of abstinence recorded during the study utilized in Gual 2003.
- Heavy drinking days 1 = ≥ 4 drinks per day (women) and ≥ 5 drinks per day (men) utilized by Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Pettinati 2010 arm A; Pettinati 2010 arm B.
- Heavy drinking days 2 = ≥ 5 drinks per day utilized by Cornelius 1997; Cornelius 2016.
- Heavy drinking days 3 = > 6 drinks per day utilized by Mason 1996.
- Heavy drinking days 4 = ≥ 6 oz per day utilized by McGrath 1996.
- Heavy drinking days 5 = ≥ 80 g/day (men) and 60 g/day (women) utilized by Adamson 2015.
- Heavy drinking days 6 = According to AUDIT-3 utilized by Muhonen 2008
- Relapse 1 = 50 g alcohol per day for at least 3 days per week or 100 g alcohol in a single dose utilized by Gual 2003.
- Relapse 2 = ≥ 5 drinks per day utilized by Pettinati 2001a.
- Relapse 3 = > 2 heavy-drinking days (> 6 drinks per day) per week for 2 consecutive weeks or if collateral report of heavy drinking coincided with participant refusal to continue in the trial utilized by Mason 1996.
- Relapse 4 = 3 or 4 consecutives heavy drinking days utilized by Krupitsky 2012.
- Relapse 5 = A heavy drinking day utilized by Pettinati 2010 arm A; Pettinati 2010 arm B.
- Relapse 6 = Failure to meet the response criteria for 2 consecutive weeks utilized by Nunes 1993.
- Treatment failure = Occurrence of at least 3 relapses utilized by Gual 2003; Mason 1996.

Liver enzyme levels

- γ-Glutamyltransferase (GGT) levels utilized in Hernandez-Avila 2004; Krupitsky 2012.

Craving

- A 24-item questionnaire prepared by authors (Altintoprak 2008) utilized in Altintoprak 2008.
- OCDS (Anton 1996) utilized in Cornelius 2016; Habrat 2006; Krupitsky 2012; Muhonen 2008.
- PACS (Flannery 1999) utilized in Krupitsky 2012.

- VAS utilized in Krupitsky 2012.

Global response (depression and alcohol use)

- CGI, much improved or very much improved on both depression and on alcohol utilized in McGrath 1996.
- Participants rating of much improved in depression and either abstinence or a marked reduction in drinking with minimal functional impairment utilized in Nunes 1993.

Psychiatric symptoms/psychological distress

Anxiety

Observer-rated scales

- HRSA (Hamilton 1959; Hamilton 1969) utilized in Habrat 2006; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Lôo 1988; Muhonen 2008; Roy-Byrne 2000.

Self-administered scales

- BAI (Beck 1988) utilized in Muhonen 2008.
- MMPI utilized in Krupitsky 1993 arm A; Krupitsky 1993 arm B.
- STAI (Spielberger 1970; Spielberger 1983) utilized in Altintoprak 2008; Hernandez-Avila 2004; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012.

Cognitive functioning

- MMSE (Fillenbaum 1997) utilized in Mason 1996; Muhonen 2008.

Quality of life

- SF-36 (Ware 1992) utilized in Gual 2003.
- SOFAS (Goldman 1992) utilized in Muhonen 2008.
- VAS (Scott 1976) utilized in Muhonen 2008.

Quality of sleep

- PSQI (Buysse 1989) utilized in Hernandez-Avila 2004.

Global assessment

- BPRS (Overall 1962) utilized in Butterworth 1971a; Krupitsky 2012.
- CGI (Busner 2009) utilized in Nunes 1993.
- GAF (APA 1994) utilized in Krupitsky 2012.
- GAS (Endicott 1976) utilized in Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C.

Tolerability and suicide and suicide attempts

- DOTES (Guy 1976) utilized in Altamura 1990.
- SAFTEE (Levine 1986) utilized in Altintoprak 2008; Cornelius 2016; Hernandez-Avila 2004.
- UKU (Lingjaerde 1987) utilized in Altintoprak 2008; Habrat 2006.

Appendix 9. Outcomes

Primary outcomes

Depression

- Final score in interviewer-rated scales (see Appendix 8) reported by Adamson 2015; Altamura 1990; Altintoprak 2008; Butterworth 1971a; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Lôo 1988; Mason 1996; McGrath 1996; Moak 2003; Muhonen 2008; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000. Three studies reported data obtained using two interviewer-rated scales (MADRS and HRSD) and only data obtained using HRSD were included (Gual 2003; Krupitsky 2012; Lôo 1988). Data from one study were excluded because they were expressed as medians and interquartile ranges (Mason 1996).
- Final score in self-administered scales (see Appendix 8) reported by Adamson 2015; Butterworth 1971a; Cocchi 1997; Cornelius 2016; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012; Lôo 1988; McLean 1986; Moak 2003; Pettinati 2001a; Roy 1998. Two studies reported data obtained using the MMPI and ZUNG and only data obtained with ZUNG were included (Krupitsky 1993 arm A; Krupitsky 1993 arm B).

- Differences between baseline and final score in interviewer-rated scales (see Appendix 8) reported by Butterworth 1971b; Cornelius 1997; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; Pettinati 2001a. Data from one study were excluded because they were expressed as medians and interquartile ranges (Mason 1996).
- Differences between baseline and final score in self-administered scales (see Appendix 8) reported by Cornelius 1997; Cornelius 2016; McLean 1986; Pettinati 2001a.
- Response criteria (see Appendix 8) were reported by Butterworth 1971b; Butterworth 1971a; Gallant 1969 arm a; Gallant 1969 arm b; Gual 2003; Habrat 2006; Kranzler 2006 arm A; Kranzler 2006 arm B; Mason 1996; McGrath 1996; Moak 2003; Roy-Byrne 2000.
- Remission criteria (see Appendix 8) were reported by Adamson 2015; Gual 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000.

Consumption of alcohol

- Abstinent participants (number) during the trial evaluated by Cornelius 1997; Hernandez-Avila 2004; McGrath 1996; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy-Byrne 2000.
- Abstinent days (%) evaluated by Adamson 2015; Cornelius 1997; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; McGrath 1996; Moak 2003; Pettinati 2001a.
- Abstinent days (cumulative number) evaluated by Gual 2003.
- Carbohydrate deficient transferrin (CDT) utilized in Moak 2003.
- DrInC score (% of mean reduction) evaluated by Hernandez-Avila 2004.
- Drinking days (cumulative number) during the trial evaluated by Cornelius 1997; Krupitsky 2012.
- Drinking days (number per week) evaluated by Cornelius 2016; Hernandez-Avila 2004.
- Drinking days (%) evaluated by Hernandez-Avila 2004; Krupitsky 2012; McGrath 1996; Pettinati 2001a.
- Drinks during the trial (cumulative number) evaluated by Cornelius 1997.
- Drinks per drinking day evaluated by Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996; Moak 2003; Roy-Byrne 2000.
- Drinks (number per week) evaluated by Cornelius 2016; Hernandez-Avila 2004.
- Global response in depression and in alcohol consumption reported by Krupitsky 2012; McGrath 1996; Nunes 1993.
- Heavy drinkers (number) evaluated by Gual 2003; Krupitsky 2012; Mason 1996; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998.
- Heavy drinking days (number per week) evaluated by Adamson 2015; Cornelius 1997; Cornelius 2016; Hernandez-Avila 2004; McGrath 1996.
- Heavy drinking days (%) evaluated by Adamson 2015; McGrath 1996.
- Time to first heavy drinking (number of weeks) evaluated by Cornelius 1997.
- Time to first relapse (in number of days) evaluated by Cornelius 1997; Gual 2003; Krupitsky 2012; Pettinati 2001a; Pettinati 2010 arm A; Pettinati 2010 arm B.
- Treatment failure (%) evaluated by Mason 1996.

Liver enzyme levels

- Final levels of GGT reported by Hernandez-Avila 2004; Krupitsky 2012.

Acceptability

- Number of dropouts reported by Altamura 1990; Butterworth 1971b; Butterworth 1971a; Cornelius 2016; Gallant 1969 arm a; Gallant 1969 arm b; Gual 2003; Hernandez-Avila 2004; Kranzler 2006 arm A; Kranzler 2006 arm B; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Mason 1996; McGrath 1996; McLean 1986; Moak 2003; Pettinati 2010 arm A; Roy 1998; Roy-Byrne 2000.

Tolerability

- Abdominal cramps reported by Adamson 2015.
- Anxiety evaluated by Roy-Byrne 2000.
- Back pain evaluated by Gual 2003.
- Blood in the stool evaluated by Kranzler 2006 arm A.
- Blurred vision evaluated by Butterworth 1971a; Roy-Byrne 2000.
- Bodyweight (final values) reported by Altintoprak 2008.
- Constipation evaluated by Altintoprak 2008; Butterworth 1971a; Kranzler 2006 arm A; Roy-Byrne 2000.
- Coughing evaluated by Gual 2003.
- Depression evaluated by Kranzler 2006 arm A; Moak 2003.
- Diarrhoea evaluated by Gual 2003; Roy-Byrne 2000.

- Difficulty sleeping evaluated by Adamson 2015.
- Dizziness evaluated by Altintoprak 2008; Gual 2003; Roy-Byrne 2000.
- Drowsiness evaluated by Butterworth 1971a.
- Dry mouth evaluated by Altintoprak 2008; Butterworth 1971a; Gallant 1969 arm a; Gallant 1969 arm b; Roy-Byrne 2000.
- Dyspepsia evaluated by Gual 2003.
- Fatigue/weakness evaluated by Roy-Byrne 2000.
- Headache evaluated by Gual 2003; Kranzler 2006 arm A; Roy-Byrne 2000.
- Heart palpitations evaluated by Roy-Byrne 2000.
- Increase in bodyweight reported by Altintoprak 2008; Cornelius 2016.
- Influenza-like symptoms evaluated by Gual 2003.
- Insomnia evaluated by Adamson 2015; Butterworth 1971b; Kranzler 2006 arm A; Roy-Byrne 2000.
- Low energy evaluated by Adamson 2015.
- Nausea evaluated by Adamson 2015; Gual 2003; Roy-Byrne 2000.
- Other adverse effects evaluated by Roy-Byrne 2000.
- Paraesthesia evaluated by Gual 2003.
- Poor memory evaluated by Roy-Byrne 2000.
- Procedure (medical/surgical/health service) evaluated by Gual 2003.
- Sedation evaluated by Altintoprak 2008; Roy-Byrne 2000.
- Sexual dysfunction evaluated by Roy-Byrne 2000.
- Skin rash evaluated by Roy-Byrne 2000.
- Syncope evaluated by Kranzler 2006 arm A.
- Total adverse effects evaluated by Adamson 2015; Butterworth 1971b; Butterworth 1971a; Gallant 1969 arm a; Gallant 1969 arm b; Habrat 2006; Kranzler 2006 arm A; Krupitsky 2012.
- Total serious adverse events evaluated by Adamson 2015; Butterworth 1971b; Cornelius 2016; Kranzler 2006 arm A; Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B.
- Visual trails evaluated by Roy-Byrne 2000.
- Weight gain reported by Cornelius 2016.
- Withdrawal for medical reasons evaluated by Adamson 2015; Cornelius 1997; Kranzler 2006 arm A; Krupitsky 2012; Mason 1996; McGrath 1996; Pettinati 2010 arm A; Pettinati 2010 arm B; Roy 1998; Roy-Byrne 2000.
- Worsening of clinical condition because of relapse evaluated by Kranzler 2006 arm A; Moak 2003.

Suicide and suicide attempts

- Suicidal ideation or attempts evaluated by Adamson 2015; Cornelius 1997; Habrat 2006; Kranzler 2006 arm A; Moak 2003.

Secondary outcomes

Use of other substances

- Participants with substance use disorders were included by Adamson 2015; McGrath 1996.
- Participants with abuse of other substances were included by Cornelius 1997; Roy-Byrne 2000.

Craving for alcohol

- Final score in a self-administered scale (see Appendix 8) reported by Altintoprak 2008; Cornelius 2016; Habrat 2006; Krupitsky 2012.

Severity of alcohol dependence

- Final score in a self-administered scale a (see Appendix 8) reported by Adamson 2015; Hernandez-Avila 2004; Muhonen 2008; Roy-Byrne 2000.

Psychiatric symptoms/psychological distress

Anxiety severity

- Final score in an interviewer-rated scale reported by Habrat 2006; Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C; Lôo 1988; Muhonen 2008.
- Final score in a self-administered scale reported by Altintoprak 2008; Hernandez-Avila 2004; Krupitsky 1993 arm A; Krupitsky 1993 arm B; Krupitsky 2012; Muhonen 2008.

Sleep quality

- Difference between baseline and final score reported by Hernandez-Avila 2004.

Global assessment

- Difference between basal and final score reported by Cornelius 1997.
- Final score in a rating scale reported by Krupitsky 2012; Liappas 2005 arm A; Liappas 2005 arm B; Liappas 2005 arm C.

Quality of life

- Final score in a rating scale evaluated by Muhonen 2008.

Appendix 10. Psychosocial therapy

- CBT (Kadden 1992) utilized by Moak 2003; Pettinati 2010 arm A; Pettinati 2010 arm B.
- MET (Miller 1992) utilized by Cornelius 2016.

CONTRIBUTIONS OF AUTHORS

PP and ET wrote the protocol.

RA and ET inspected the search hits by reading titles and abstracts, obtained the full text, assessed studies for inclusion, and assess study quality.

All three authors resolved disagreements.

RA and ET wrote the results.

PP wrote the discussion.

All three authors read and agree the final version.

DECLARATIONS OF INTEREST

RA: no interests to declare relating to this work.

ET: no interests to declare relating to this work.

PP: no interests to declare relating to this work.

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The present meta-analysis presents the following differences from the protocol.

- **Primary and secondary outcomes**

In the present review, the number of participants that reported use of alcohol was not used as a primary outcome as we planned in the Protocol (see Primary outcomes). This difference is due to the fact that the studies included did not report the number of participants who used alcohol to descrive alcohol consumption but other outcomes such as rate of drinking days, cumulative number of drinking days, number of drinks per drinking day, weekly number of heavy drinking days, rate of heavy drinkers, number of heavy drinkers, and son on (see Appendix 9). Whenever possible, we combined togethar these outcomes and used them to evaluate the effects of antidepressants in alcohol consumption.

Similarly, in the present meta-analysis the number of participants that used other substances was not used as a secondary outcome as we planned in the Protocol (see Secondary outcomes). This difference is due to the fact that most of the studies excluded participants with substance use disorders or participants that used other substances of abuse.

- **Sources of electronic searches**

Given that the original protocol was published in 2010, some sections needed updating to fulfill the current methodological guidelines for Cochrane Reviews. In detail, we changed the databases that we planned to search in the protocol, because of lack of access to some of these databases and because of some changes to standard search routines. We were unable to include searches from CINAHL as we lost access to it prior to searching whereas we added EMBASE (embase.com) search. Since the protocol for this review was published, Current Controlled Trials has been replaced by the ISTRCN Registry (isrctn.com), and we have searched ICTRP Registry instead.

- **'Summary of findings' table**

We prepared a 'Summary of findings' table, including assessing the quality of evidence using GRADE (GRADEpro 2014).

INDEX TERMS

Medical Subject Headings (MeSH)

Alcohol Abstinence [statistics & numerical data]; Alcohol Drinking [epidemiology]; Alcoholism [complications] [*drug therapy]; Antidepressive Agents [*therapeutic use]; Depressive Disorder, Major [complications] [*drug therapy]; Diagnosis, Dual (Psychiatry); Placebos [therapeutic use]; Psychotherapy; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male