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[Intervention Protocol]

Combined pharmacological and psychosocial interventions for alcohol use disorder

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and safety of combined pharmacological and psychosocial interventions for the treatment of alcohol use disorder.

BACKGROUND

Description of the condition

Prevalence of alcohol use disorder

Alcohol use disorder (AUD) is among the most widely prevalent mental disorders (Carvalho 2019; Connor 2016). Worldwide, 12-month and lifetime prevalence of AUDs according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria in the general population is estimated to be equal to 2.2% and 8.6%, respectively (Glantz 2020). A large variability between countries exists (Glantz 2020). A recent study, using the same diagnostic interview throughout 29 different countries worldwide, estimated 12-month AUD prevalence to range from 0.1% in Iraq to 5.9% in Ukraine, and lifetime AUD prevalence from 0.7% in Iraq to 22.7% in Australia (Glantz 2020). This variability is significantly related to drinking cultures, social norms, and income levels (Glantz 2020; Rehm 2015). Regarding income levels, lifetime AUD prevalence ranged from 5.9% in low-to-middle-income countries, to 7.2% in middle-income countries, and 10.3% in high-income countries (Glantz 2020).

AUD prevalence is also higher in men than in women (Glantz 2020). In the US, lifetime AUD prevalence was estimated to be equal to 29.1% of the general population (Grant 2015), with a value of 36.0% and 22.7% among male and female populations, respectively (Grant 2015). In Europe, 12-month prevalence of alcohol dependence corresponded to 3.4% of the general population, and 5.2% and 1.7% of male and female populations, respectively (Rehm 2015). However, the gender gap in AUD is narrowing, particularly in the younger population (Agabio 2021; Slade 2016).

Definition of alcohol use disorder

AUD is a severe mental disorder characterised by a strong desire to consume alcohol, impaired ability to control alcohol consumption, and devastating consequences due to this consumption (American Psychiatric Association 2013). Prior to its 5th version (DSM-5, American Psychiatric Association 2013), DSM classified abuse and dependence as two different mental disorders (e.g. DSM-IV; American Psychiatric Association 1994). A diagnosis of abuse required meeting at least one out of a list of four criteria, while a diagnosis of dependence required three out of seven different criteria. Both these diagnoses required the recurrent presence of these criteria over the same period of at least 12 months (American Psychiatric Association 1994). DSM-5 subsequently added one new criterion (craving), removed another criterion (alcohol-related legal consequences), and combined the criteria for abuse and dependence into a single disorder (AUD; American Psychiatric Association 2013). AUD diagnosis requires meeting at least two symptoms out of the following list of 11 criteria: (1) use of alcohol in amounts larger than intended, (2) persistent desire to control alcohol use, (3) great deal of time spent to obtain, consume, and recover from alcohol effects, (4) craving, (5) failure to fulfil major obligation because of alcohol use, (6) continued use of alcohol despite interpersonal problems, (7) reduction of important activities because of alcohol use, (8) recurrent use in hazardous situations, (9) recurrent use despite knowledge of its negative consequences, (10) tolerance, and (11) withdrawal (American Psychiatric Association 2013). The number of criteria is used to measure AUD severity as mild (2 to 3 symptoms), moderate (4 to 5 symptoms), and severe (6 or more symptoms) (American Psychiatric Association 2013). Finally, AUD is a chronic relapsing disorder, characterised by periods of remission and relapse (American Psychiatric Association 2013). The brain represents the biological substrate from which both alcohol addiction and the capacity for behaviour change arise (Heilig 2021).

Alcohol dependence is the International Classification of Diseases (ICD) equivalent diagnosis of DSM-5 AUD (World Health Organization 2022). According to the latest version of ICD (ICD-11), this disorder is characterised by a strong internal drive to use alcohol, impaired ability to control use, increasing prioritising of alcohol use over other activities, persistence of use despite harm or negative consequences, and physiological features indicative of neuroadaptation to alcohol, such as tolerance and withdrawal syndrome (World Health Organization 2022). Diagnosis requires the presence of at least 2 of these 3 central features over a period of 12 months.

Risk and consequences of alcohol use disorder

Alcohol use is one of the major risk factors for the global burden of mortality and morbidity worldwide (GBD 2016 Alcohol Collaborators 2018; GBD 2019 Cancer Risk Factors Collaborators 2022; GBD 2020 Alcohol Collaborators 2022). Acutely, it is related to the risks of acute intoxication, injury, violence, emergency room visit, hospitalisation, disability, and premature mortality (Alpert 2022; GBD 2020 Alcohol Collaborators 2022). Further to the risks related to acute alcohol consumption, chronic alcohol consumption also increases the risk of developing a series of major diseases like cancer, liver cirrhosis, heart disease, neurological disorders, fetal alcohol spectrum disorder, with disability, premature mortality, loss of productivity, and huge economic costs (Carvalho 2019; Connor 2016).

Alcohol-related risks are directly related to the amounts of alcohol consumption (GBD 2016 Alcohol Collaborators 2018). Moreover, negative consequences of alcohol consumption are not limited merely to those who consume alcohol, but involve the entire society due to the added harm to users and harm to others (Nutt 2010).

Estimates of the prevalence of these consequences

Globally, alcohol use represents the seventh-leading risk factor for both deaths and disability (GBD 2016 Alcohol Collaborators 2018). Among the general population, alcohol-attributable deaths and disability-adjusted life-years (DALYs) correspond to 5.3% of all deaths and 5.0% of all DALYs (Shield 2020). Mortality and disability rates are approximately three times higher among men compared to women (Shield 2020). Alcohol-attributable deaths and DALYs in males correspond to 6.8% and 6% of total male deaths and DALYs, respectively, and in females, 2.2% and 1.6% of total female deaths and DALYs, respectively (GBD 2016 Alcohol Collaborators 2018).

Mortality and disability rates are also higher in the younger compared to older populations (Shield 2020). In people below the age of 50 years, alcohol use represents the leading risk factor for both deaths and disability (GBD 2016 Alcohol Collaborators 2018). Compared to the general population, the risk of mortality among people with AUD is more than three times higher for men (3.38) and almost five times higher for women (4.57) (Roerecke 2013).

Description of the intervention

Current guidelines for the general population

Current guidelines for the treatment of psychiatric disorders recommend that people with AUD receive a comprehensive and person-centred treatment including both evidence-based psychosocial and pharmacological interventions (Haber 2021; Knox 2019; Reus 2018; World Health Organization 2015).

Psychosocial interventions

The psychosocial interventions most frequently used in people with AUD comprise behavioural therapies, motivational interviewing, mutual help groups, 12-step facilitation, psychodynamic therapy, and social network therapy (Foxcroft 2016; Kelly 2020; Klimas 2018; McCrady 2014; Witkiewitz 2011). Briefly, behavioural therapies comprise a series of treatments including cognitive behavioural therapy, contingency management, and couple therapy (Witkiewitz 2011). Cognitive behavioural therapy is aimed at reducing dysfunctional beliefs, negative thoughts, and unwanted behaviours, through behavioural tasks and coping skills training (Klimas 2018); contingency management uses reinforcing and punishing consequences to alter alcohol consumption (Witkiewitz 2011); and couple therapies (or family therapies) are aimed at improving relationship factors conducive to abstinence (Witkiewitz 2011). Motivational interviewing is aimed at increasing the client's motivation and readiness to change (Foxcroft 2016). Mutual help groups comprise several low-cost or free recovery support services aimed at helping people with AUD prevent relapse and aid recovery, the oldest of which is Alcoholics Anonymous (Kelly 2020). Twelve-step facilitations are clinical interventions that have adapted the methodology and concepts of Alcoholics Anonymous (Kelly 2020). Psychodynamic psychotherapy employs the therapeutic relationship to solve unconscious conflicts and develop insight (Klimas 2018). Social network therapy uses both psychodynamic and behavioural therapy in a support network (Galanter 1993). Other less frequently used psychosocial interventions comprise acceptance and commitment therapy (Lee 2015), mindfulness-based relapse prevention (Goldberg 2021), music therapy (Ghetti 2022), psychoeducation (Magil 2021), and assertive outreach (Wingerson 1999). Acceptance and commitment therapy is a behavioural therapy focused on mindfulness, acceptance, and other strategies to increase psychological flexibility and promoting behaviour change consistent with personal values (Hayes 2006). Mindfulness-based relapse prevention is a group-based psychosocial aftercare, integrating evidence-based practices from mindfulness-based interventions and cognitive behavioural relapse prevention approaches (Grant 2017). Music therapy comprises specific musical interventions to reach individual treatment goals within therapeutic alliance (Ghetti 2022). Psychoeducation comprises several interventions (Magil 2021), such as the Screening, Brief Intervention, and Referral to Treatment (SBIRT) approach, which is aimed at increasing the early identification of substance use, offering a brief intervention, and referring to treatment people with a diagnosis of substance use disorder (Bray 2017). Finally, assertive outreach treatment has been developed to support people with severe mental illnesses (Drake 1993).

Medications

Medications approved by the US Food and Drug Administration (FDA) or the European Medication Agency (EMA), or both, to help people with AUD achieve abstinence or reduce alcohol consumption comprise disulfiram, naltrexone, acamprosate, and nalmefene (Reus 2018; Witkiewitz 2019).

Disulfiram is prescribed to help people who have already achieved abstinence to maintain abstinence (Reus 2018). People who take disulfiram and consume alcohol develop a reaction characterised by facial flush, nausea, vomiting, and, less frequently, bradypnoea and shock (Skinner 2014). Naltrexone reduces the rewarding effects of alcohol and is recommended to help people to both achieve and maintain abstinence and reduce alcohol consumption (Rösner 2010a). Acamprosate is recommended for people who are already abstinent to help them to maintain abstinence (Rösner 2010b); its mechanism of action is not yet well understood (MacKillop 2022). Contrary to disulfiram, people who consume alcohol while being treated with acamprosate do not develop adverse reactions. Nalmefene is the only medication approved to reduce alcohol consumption also in individuals who do not achieve AUD criteria (MacKillop 2022). Other medications have been approved for the treatment of AUD by only one or two national regulatory agencies, such as baclofen in France, Minozzi 2018, and gamma-hydroxybutyrate in Italy and Austria (Leone 2010). Finally, other medications approved for the treatment of other disorders are often used for the treatment of AUD as off-label medications. The most promising among these are topiramate and gabapentin, which are also endorsed by the American Psychiatric Association as potential second-line treatments (Reus 2018).

How the intervention might work

A high proportion of people with AUD do not respond to treatment, and a high risk of recurrence is observed among people who do respond to treatment (Knox 2019). In clinical practice, a combination of pharmacological and psychosocial interventions is highly recommended to enhance the likelihood of success (Knox 2019).

Both psychosocial and pharmacological interventions are indicated in helping people with AUD to achieve and maintain abstinence, and to prevent relapse (McCrady 2014; Reus 2018). In addition, psychosocial interventions are useful in resolving ambivalence with regard to change and dealing with the needs of people with AUD by identifying personalised strategies to maintain abstinence (Reus 2018). Pharmacological interventions are also used to treat alcohol withdrawal syndrome (i.e. benzodiazepines are the gold standard for the treatment of moderate to severe alcohol withdrawal syndrome, Amato 2011) and comorbid physical and/or mental disorders and to facilitate the therapeutic relationship between AUD sufferers and clinicians (Reus 2018).

The aim of this systematic review will be to evaluate the efficacy of medications used for relapse prevention only. Combining pharmacological and psychosocial interventions may enhance the likelihood of efficacy of AUD treatment through different mechanisms of action. It may increase the spectrum of treatment targets compared to use of single interventions, Peacock 2018, and/or simply increase the efficacy through a synergistic effect of the two interventions. Each intervention may facilitate adherence to the other one. Psychological intervention could strengthen the

therapeutic rapport and facilitate the adoption of pharmacological interventions (MacKillop 2022; Witkiewitz 2019). On the other hand, pharmacological interventions can facilitate adherence to psychological interventions by reducing the severity of craving and helping patients abstain from alcohol consumption.

While combined pharmacological and psychosocial interventions are usually suggested in clinical practice, a limited number of systematic reviews have investigated their efficacy in AUD treatment (Ahmed 2018; Gao 2018; Ray 2020). These studies differed in their aims and inclusion criteria: one study assessed the effect of a single medication (naltrexone) combined with psychotherapy (Ahmed 2018); another study assessed the effect of all medications, including those not approved for AUD treatment, such as antidepressants and anxiolytic agents, combined with psychosocial interventions (Gao 2018); and the final study assessed the effect of any medications approved for AUD and other substance use disorders combined with only one type of psychosocial treatment (cognitive behavioural therapy; Ray 2020). The results of these studies are, at least in part, conflicting. According to two studies, adding the psychological intervention to the pharmacological one did not modify the results obtained by the pharmacological intervention alone (Ahmed 2018; Ray 2020). By contrast, Gao and colleagues found that the combination induced better results compared the single interventions alone (Gao 2018). These apparently conflicting results may be due in part to the different inclusion criteria of the studies evaluated. Another issue that should be investigated relates to the optimal timing how such combined approaches should be integrated, that is if the psychosocial and pharmacological interventions should be used in parallel, simultaneously, and for the same duration, or if one intervention should precede the other one, and if the duration of the two interventions should be different. This important issue has not been investigated yet.

Why it is important to do this review

In clinical practice, a combination of pharmacological and psychosocial interventions is often recommended to enhance treatment success (Knox 2019). However, support for the combination of pharmacological and psychosocial interventions is limited. At present, neither Cochrane Review nor protocol has been focused on the effectiveness and safety of the combination of pharmacological and psychosocial interventions to treat people with AUD. The current systematic review will fill this gap by integrating the available evidence for health decision makers, therapists, and patients.

OBJECTIVES

To assess the efficacy and safety of combined pharmacological and psychosocial interventions for the treatment of alcohol use disorder.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) evaluating the efficacy of a combination of pharmacological and psychosocial interventions in reducing or stopping alcohol consumption in people with AUD. We will include RCTs of at least four weeks treatment duration. We will also include studies employing a cross-over design, and use data from the first active treatment stage only.

Types of participants

Adults (18 years and older), with AUD according to DSM-III (American Psychiatric Association 1980), DSM-III-R (American Psychiatric Association 1987), DSM-IV-TR (American Psychiatric Association 2000), DSM-5 (American Psychiatric Association 2013), ICD-10 (World Health Organization 1992; World Health Organization 2010), and ICD-11 (World Health Organization 2022). There will be no limitations on other participant characteristics such as concomitant substance use disorders or other comorbid psychiatric conditions. We will include individuals actively drinking and those in the postdetoxification phase, if the detoxification was completed no more than 28 days before starting treatment.

We will exclude people younger than 18 years of age and pregnant women because of the substantially different approaches required for the clinical management of these specific populations.

Types of interventions

Experimental group: combination of pharmacological and psychosocial interventions. Specifically, we will only include pharmacological treatments approved by both of the two main international regulatory agencies, namely acamprosate, disulfiram, and naltrexone. Psychosocial interventions will include behavioural therapies (cognitive behavioural therapy, contingency management), motivational interviewing, mutual help groups, 12-step facilitation, psychodynamic therapy, social network therapy, acceptance and commitment therapy, mindfulness-based relapse prevention, music therapy, psychoeducation, and assertive outreach.

Comparison group: 1) treatment as usual (according to the definition provided by the study authors, as treatment as usual can be very heterogeneous across studies and challenging to define within specific types of treatment); 2) pharmacological treatment alone; 3) psychosocial intervention alone.

Types of outcome measures

Primary outcomes

- Relapse to any drinking (measured as the number of people who had returned to any drinking at the end of the active treatment phase)
- Relapse to heavy drinking (measured as the number of people who had returned to heavy drinking at the end of the active treatment phase, where heavy drinking is defined as an alcohol consumption equal or higher than four standard drinks in a day for women and equal or higher than five standard drinks in a day for men)
- Frequency of use: measured as mean number or percentage of abstinent days (ratio of the total sum of drink-free days, related to the entire duration of the active treatment phase, multiplied by the factor 100)
- Frequency of use: measured as mean number or percentage of heavy drinking days (ratio of the total sum of heavy drinking days, related to the active treatment phase, multiplied by the factor 100)
- Amount of use: mean number of drinks per drinking day or drinking occasion at the end of the active treatment phase

- Adverse events: measured as number of people with at least one adverse event at the end of the active treatment phase
- Serious adverse events: measured as number of people with at least one serious adverse event at the end of the active treatment phase
- Dropouts from treatment: number of participants who did not complete the active treatment phase
- Dropout from treatment due to adverse events at the end of the active treatment phase

We will include drinking outcomes irrespective of the source of information, considering, for example, patient self-reports, breathaliser tests, laboratory tests, and collateral reports of others.

Secondary outcomes

- Craving, as measured by validated scales at the end of the active treatment phase
- Anxiety, as measured by validated scales at the end of the active treatment phase
- Depression, as measured by validated scales at the end of the active treatment phase
- Alcohol-related consequences, as measured by validated scales (e.g. Short Inventory of Problems (SIP), Drinker Inventory of Consequences (DrInC)) at the end of the active treatment phase
- Psychosocial functioning and psychosocial consequences, as measured by validated scales (e.g. the Global Assessment Scale (GAS), the Global Assessment of Functioning Scale (GAF), the Social Functioning Questionnaire (SFQ)) at the end of the active treatment phase

Search methods for identification of studies

Electronic searches

We will identify published, unpublished, and ongoing studies by searching the following databases from their inception.

- Cochrane Drugs and Alcohol Group (CDAG) Specialised Register (most recent)
- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (most recent)
- MEDLINE (Ovid; 1946 onwards)
- Embase (Ovid; January 1974 onwards)
- PsycINFO (Ovid; 1800 onwards)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCOhost; 1982 onwards)
- Web of Science

We will use the search strategy to search MEDLINE shown in Appendix 1, modifying it where necessary for the other databases listed. We will not employ any date or language restrictions.

We will search the following clinical trial registries for unpublished and ongoing studies.

- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov)

Searching other resources

We will search the reference lists of all relevant papers to identify additional studies, as well as conference proceedings that are likely to contain trials relevant to this review. We plan to contact investigators to seek information about unpublished or incomplete trials.

Data collection and analysis

Selection of studies

Two review authors (RA and SM) will independently screen the titles and abstracts of papers retrieved by search. Any disagreements will be resolved by discussion or by deferring to another review author (AC and/or RS). We will acquire potentially relevant papers in full text, and two review authors (RA and SM) will independently assess them for inclusion. Any disagreements will be resolved by discussion or by deferring to another review author (AC and/or RS). We will contact study authors to resolve any uncertainties.

The research team will contact corresponding authors of papers that are not available in full-text format and allow a period of one month for the authors to respond. In the case of lack of response, we will consider studies without full-text access as awaiting classification.

Data extraction and management

Two review authors (RA and AC) will independently extract data from the included studies using standardised data extraction forms, which we will pilot on an initial set of three studies. Any disagreements will be resolved by discussion or by deferring to another review author (SM and/or RS). We will extract the following data.

- Bibliographic details: authors, year, country
- Methods: study design, number of participants
- Participant characteristics: age, gender, severity of AUD, if participants were detoxified (abstinent for at least three days before treatment) or still drinking at the beginning of treatment
- Interventions: type of medication and/or psychosocial intervention, setting, frequency, duration
- Comparator: type of comparison intervention
- Outcomes: primary and secondary outcomes
- Funding of the study and conflicts of interest of study authors

We will examine cases where we find multiple publications from the same study, and ensure that included studies report on unique findings. We will use RevMan Web to organise and store data and to complete the data analysis (RevMan Web 2022).

Assessment of risk of bias in included studies

For the scope of this review, we will assess the effect of the assignment to the intervention (intention-to-treat effect) for primary outcomes, measured as specified in the Types of outcome measures section and assessed at the end of the active treatment phase.

Two review authors (SM and RS) will independently assess the risk of bias of primary outcomes from the included studies using the revised version of the Cochrane risk of bias tool, RoB 2 (Higgins 2019; Sterne 2019), which considers the following domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To implement RoB 2 assessment, we will use the Excel tool available online (Higgins 2019b).

We will judge each domain as being at low risk of bias, some concerns, or high risk of bias based on the answers to signalling questions and following the RoB 2 algorithm. We will reach an overall risk of bias for each outcome reported in each study according to the following criteria.

- Low risk of bias: low risk of bias for all domains
- Some concerns: some concerns in at least one domain, but not at high risk of bias for any domain
- High risk of bias: high risk of bias in at least one domain, or some concerns for multiple domains such that confidence in the result is substantially lowered

We will make detailed risk of bias assessment data (with consensus responses to the signalling questions) publicly and openly available in a repository.

Measures of treatment effect

For dichotomous outcomes (e.g. relapse), we will summarise trial outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous data (e.g. number of drinks per drinking day), we will summarise trial outcomes as mean difference (MD) and 95% CI. If the studies use different measures of alcohol consumption, we will convert them into one cumulative outcome if possible (e.g. when the equivalent in grams of a drink is provided by the majority of the included trials, we will convert the number of drinks per day into the number of grams per day). If transformation is not possible, or different scales are used to evaluate alcohol consumption, or when data refer to different periods of time, we will use the standardised mean difference (SMD). The SMD is the difference in mean effects in the experimental and control groups divided by the pooled standard deviation of participants' outcomes.

Unit of analysis issues

If we include multi-arm studies in the meta-analyses and one arm is considered more than once in the same comparison (e.g. two different doses of medications compared to the same control group), we will divide the control group into two different groups, each group comprising half of the participants of the original group to avoid double counting. For cross-over studies in meta-analyses, we plan to use data from the first period only (i.e. before cross-over), to address the risk of carry-over effects.

Dealing with missing data

We will contact the authors of the included studies if key study characteristics, including but not limited to outcome data, are missing (e.g. when only a study abstract is available).

Assessment of heterogeneity

We will analyse statistical heterogeneity by means of the I^2 statistic and the Chi^2 test. Following the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*, we will distinguish the following values to denote unimportant, moderate, substantial, and considerable heterogeneity, respectively: 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% (Higgins 2011; Higgins 2019; Higgins 2022). If we find considerable levels of heterogeneity (i.e. ≥ 75%), we will explore possible reasons by visually inspecting the forest plot to identify studies that might be contributing to the heterogeneity.

Assessment of reporting biases

We will use funnel plots (plots of the effect estimate from each study against the sample size or effect standard error) to assess the potential for bias related to study size, which could indicate possible publication bias. We will inspect funnel plot symmetry if there are at least 10 studies included in the meta-analysis.

Data synthesis

We will combine the outcomes from the individual trials through meta-analysis where possible (comparability of intervention and outcomes between trials) using a random-effects model, given that we expect a certain degree of heterogeneity between trials. If the clinical or statistical heterogeneity between trials is too high (i.e. 75% to 100%), we will investigate possible causes of the heterogeneity, and consider not pooling data if heterogeneity cannot be explained by subgroup analysis. If we include studies with incompletely reported outcomes or effect measures, we will consider other methods for summarising and displaying results, such as vote counting based on the direction of effect or structured tabulation of the results across studies according to the comparisons considered (Higgins 2022).

The primary analysis will include all eligible studies, irrespective of their overall risk of bias.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses based on specific medication, as follows.

- Acamprosate plus any type of psychosocial interventions
- Disulfiram plus any type of psychosocial interventions
- Naltrexone plus any type of psychosocial interventions

We will also conduct subgroup analyses based on the psychosocial interventions most frequently used (cognitive behavioural therapy, contingency management, motivational interviewing) plus any type of pharmacological interventions.

Sensitivity analysis

We will perform sensitivity analyses to assess the impact of excluding studies with high risk of bias.

Summary of findings and assessment of the certainty of the evidence

Two review authors (RS and SM) will assess the certainty of the evidence using the GRADE approach (Atkins 2004; Guyatt 2008; Guyatt 2011; Schünemann 2006). We will present a summary of findings table for each of the three comparisons: combined treatment versus treatment as usual, combined treatment versus pharmacological treatment alone; and combined treatment versus psychosocial treatment alone. We will assess the certainty of

evidence of primary outcomes as evaluated at the end of treatment. The *overall* RoB 2 judgement will be used to feed into the GRADE assessment.

The GRADE approach 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 included studies and those under consideration in our systematic review)
- Serious (−1) or very serious (−2) imprecision of the pooled estimate
- Publication bias strongly suspected (−1)

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APPENDICES

Appendix 1. Ovid MEDLINE search strategy

1. exp Alcohol-Related Disorders/
2. (alcohol$ adj5 (abstinen$ or abstain$ or abus$ or addict$ or cessation or crav$ or dependen$ or detox$ or disease$ or disorder$ or excess* or heavy or intoxicat$ or intervention* or misus$ or overdos$ or problem$ or rehab$ or reduc* or relaps$ or treat* or therap* or withdraw$)).mp.
3. alcoholic*.tw.
4. 1 or 2 or 3
5. exp Alcohol Deterrents/
6. Acamprosate/
7. (Acamprosate or Campral).tw.
8. Disulfiram/
9. Naltrexone/
10. (Naltrexone or Revia or Vivitrol).tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. psychotherapy/
13. psychosocial intervention/
14. (psychotherap* or psychosocial or psychodynamic* or psychoeducation* or voucher or reinforcement or motivation* or contingent*).tw.
15. ((coping or social) adj2 skill*).tw.
16. (behavi* adj2 therap*).tw.
17. exp Reinforcement, Psychology/
18. exp Cognitive Behavioral Therapy/
19. ((cognitive adj3 therapy) or CBT).tw.

20.((family or couple*) adj2 therapy).tw.
21.stress management training.tw.
22.exp Social Support/
23.contingency management.tw.
24.self control training.tw.
25.(behavio* adj2 (change or modification)).tw.
26.talking therap*.tw.
27.exp Self-Help Groups/
28.self help group*.tw.
29.(alcoholic* adj2 anonymou*).tw.
30.mutual help.tw.
31.mutual aid.tw.
32.twelve step*.tw.
33.exp Mindfulness/
34.Meditation/
35.(ACT or acceptance or meditation or mindful* or vipassana or zen or yoga or yogic or relaxation).tw.
36.Music Therapy/
37.(choir* or choral* or lyric* or melod* or music* or sing* or singing or song*).tw.
38.assertive outreach.tw.
39.or/12-38
40.4 and 11 and 39
41.randomized controlled trial.pt.
42.controlled clinical trial.pt.
43.random*.ti,ab,kf.
44.placebo.ab.
45.clinical trials as topic.sh.
46.random allocation.sh.
47.trial.ti.
48.or/41-48
49.exp animals/ not humans.sh.
50.48 not 49
51.40 and 50

CONTRIBUTIONS OF AUTHORS

All review authors (RA, AC, DK, LL, RS, and SM) contributed to writing of the Background section. SM, RS, and RA wrote the Methods section. RA and AC will conduct screening and extract study data. SM and RS will conduct risk of bias assessment and data analysis. RA, AC, RS, and SM will write the Results section. All review authors (RA, AC, DK, LL, RS, and SM) will contribute to writing the Discussion.

DECLARATIONS OF INTEREST

Roberta Agabio is an Editor of Cochrane Drugs and Alcohol Group. She was not involved in the editorial process of the current protocol.

Antonella Camposeragna: no conflict of interest known.

Rosella Saulle: no conflict of interest known.

Dzmitry Krupchanka: no conflict of interest known.

Lorenzo Leggio, outside of his work as a US Federal employee at the National Institutes of Health, receives an honorarium from the UK Medical Council on Alcohol (editor-in-chief for *Alcohol and Alcoholism*) and royalties from Routledge (editor, textbook).

Silvia Minozzi is the Joint-Coordinating Editor of Cochrane Drugs and Alcohol Group. She was not involved in the editorial process of the current protocol.

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