Alcohol use disorders module - evidence profile ALC4: Combined pharmacological and psychosocial interventions for adults with alcohol use disorders

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

2023

World Health Organization

Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1. Background

Alcohol Use Disorders (AUD) and alcohol-related impairments belong to the most widespread psychiatric disorders, leading to specific physical, mood, learning and memory problems and consequences for overall well-being and health. The harmful use of alcohol is one of the biggest risks to health worldwide, causing 20% to 30% of oesophageal cancer, liver disease, epilepsy, motor vehicle accidents, homicide, and other intentional injuries.

For many years, the main treatments for AUD have been psychosocial strategies, but using only psychosocial treatments has limited success. A high proportion of people with AUD do not respond to the treatment at all, and those who do respond do not stay alcohol-free in the long-term. In clinical practice, the combination of pharmacotherapy with psychosocial interventions is recommended to enhance the likelihood of success. Presently, only a limited number of medications have been approved by the main international regulatory agencies: acamprosate, disulfiram, and oral naltrexone. Other medications are approved by only one or two regulatory agencies: nalmefene, naltrexone, in its intramuscular long-acting formation, and baclofen.

Despite its large recommendation, support for the combination of pharmacological and psychosocial interventions is limited.

The planned review on the effect of combined psychosocial and pharmacological treatments on abstinence or reduction of alcohol consumption in people with AUD, will provide a systematic integration of the available evidence for health decision makers, therapists and patients, and aims to offer illustrative measures for estimating the therapeutic benefits and risks of combined treatments, while indicating gaps in knowledge and methodological demands for future clinical research.

Note: This methodology and report template is intended to provide a structured approach for evidence review teams in 1) outlining the methods that they will use and; 2) preparing a report detailing the results.

The same document can be used for both purposes with the methodology sections first completed and submitted as v1.0 and then a v2.0 completed with the results included.

The process for evidence retrieval and synthesis is fully outlined in chapter 8 of the WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714. A summary of the process is also available in the process note in Appendix I: mhGAP process note.

This document suggests that one of three main categories of evidence review will apply to each PICO under consideration:

1) Existing systematic reviews are sufficient to prepare the evidence summaries
2) An update of an existing systematic review is required before the evidence summaries can be prepared
3) A new systematic review is required before the evidence summaries can be prepared

The Cochrane Drugs and Alcohol review group did not publish any review on this topic. Therefore, we searched for systematic reviews on the effectiveness of combined treatments of AUD on several databases since databases inception up to 2022.

2. Methodology: PICO question

Population (P): Adults with alcohol dependence (DSM-IV or ICD- 9 10 11) or moderate or severe AUD according to DSM-5.
Intervention (I): Combined pharmacological and psychosocial interventions.
We considered the following pharmacological treatments:

- acamprosate,
- disulfiram,
- naltrexone

and the following psychosocial interventions:

- cognitive behavioural therapy (CBT),
- couples therapy,
- psychodynamic therapy,
- behavioural therapies,
- social network therapy,
- contingency management
- motivational interventions,
- twelve-step facilitation
- mutual help groups

Comparator (C): stand-alone pharmacological or psychosocial interventions, treatment as usual, wait list, no treatment.

Outcomes (O):

List critical outcomes:

- Relapse: return to any drinking, measured by number of people who had returned to any drinking at the end of the study and at follow-up.
- Relapse: return to heavy drinking, measured by number of people who had returned to heavy drinking at the end of the study and at follow-up.
- Frequency of use: measured as percentage abstinent days (ratio of the total sum of days with abstinence, related to the entire duration of the study, multiplied by the factor 100; or percentage of heavy drinking days.
- Amount of use: number of drinks per drinking day or drinking occasion.
- Adverse events: measured by number of people with at least one adverse event, both subjectively or objectively assessed.
- Serious adverse events: measured by number of people with at least one adverse event, both subjectively or objectively assessed.
- Dropouts from treatment: number of participants who did not complete the study.
- Dropout from treatment due to adverse events.

List important outcomes:

- Craving, as measured by validated scales (observer-rated and/or self-administered scales)
- Anxiety, as measured by validated scales (observer-rated and/or self-administered scales)
- Depression, as measured by validated scales (observer-rated and/or self-administered scales)

Subgroups:
We will conduct subgroup analyses for the type of medications:

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

3. Methodology: Phase 1. Search for relevant systematic reviews

3.1. Search strategy

The Cochrane Drugs and Alcohol review group did not publish any SR on this topic. Therefore, we searched for systematic reviews on the effectiveness of combined pharmacological and psychological treatments for the management of alcohol use disorders on MEDLINE, Embase, PsycInfo, Web of Science Core Collection, Epistemonikos and PROSPERO from 2015 to 14 January 2022. The detailed search strategy for each database is provided in Appendix IIa. The inclusion criteria were: systematics reviews of randomized controlled trials that assessed the effect of combined pharmacological and psychosocial treatment listed in our inclusion criteria compared to no treatment, usual care, pharmacological or psychosocial treatments alone to achieve and maintain abstinence or reduce alcohol consumption in adults with alcohol use disorders.

3.2. Data collection and analysis

As the first stage in selecting relevant studies, records retrieved from the bibliographic databases and from other sources were recorded and assessed for eligibility by examining their titles and abstracts only. This assessment was performed in accordance with the inclusion and exclusion criteria developed a priori. The full text of articles found to be potentially relevant on the basis of their titles and abstracts were retrieved and examined in light of the same inclusion criteria in the second stage of study selection. Two reviewers independently screened records retrieved with the search and evaluated full text of potentially relevant reviews.

3.3. Selection and coding of identified records

We used EndNote X7 as reference management software.

3.4. Quality assessment

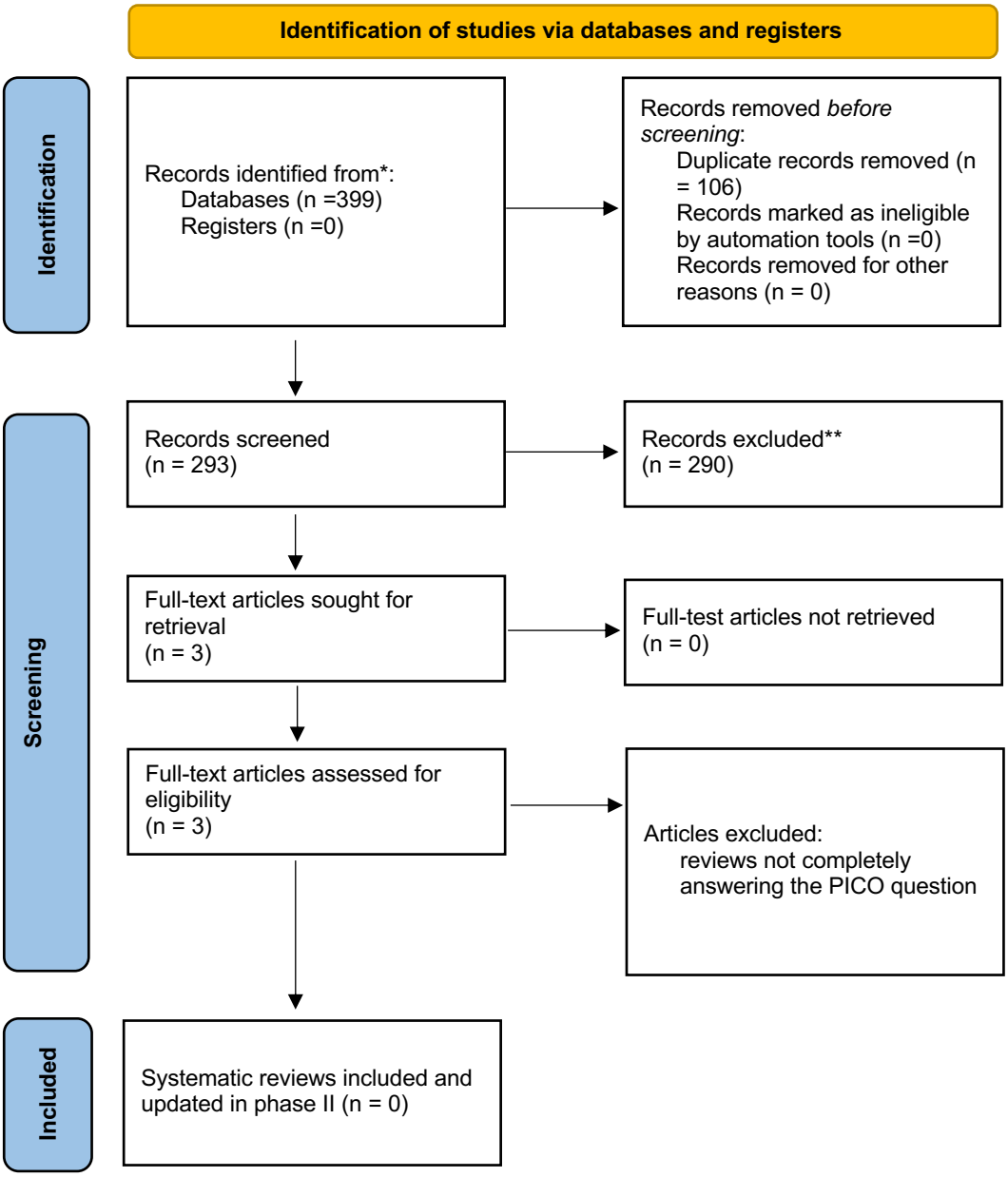
We planned to assess the methodological quality of retrieved reviews that fulfil the inclusion criteria with AMSTAR 2 checklist (https://amstar.ca/Amstar_Checklist.php).

3.5. Analysis of subgroups or subsets

No subgroup analysis was planned in phase 1.

4. Results: Phase 1

Fig. 1. PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

4.1. Systematic reviews and/or studies identified by the search process

After removing duplicates, we screened 293 titles and abstracts. Three reviews were judged as potentially relevant and acquired in full text. Ahmed et al. 2018 assessed the effect of a single medication (naltrexone) combined with psychotherapy. Gao et al 2018 assessed the effect of all types of drugs, including treatments not considered by our inclusion criteria, such as antidepressants and anxiolytic agents, combined with psychotherapy. However, in the results, the authors did not specify which drug was actually evaluated in each of the included studies; furthermore, they measured only one of our outcomes of interest. Ray et al. 2020 assessed the effect of any drugs approved for the treatment of AUD and other substance use disorders combined with only one type of psychosocial treatment (cognitive behavioural therapy).
Therefore, we decided to exclude all these reviews because none of them completely fitted to our PICO. We will use these reviews as a useful source for the references of primary studies.

We decided that the most appropriate approach will be to conduct a new systematic review of randomized controlled trials.

4.2. References of excluded reviews

Ahmed et al. Adding Psychotherapy to the Naltrexone Treatment of Alcohol Use Disorder: Meta-analytic Review. Cureus. 2018 Aug 6;10(8):e3107. doi: 10.7759/cureus.3107. PMID: 30338182; PMCID: PMC6175267.

Gao J, Cao J, Guo T, Xiao Y. Association between alcoholic interventions and abstinence rates for alcohol use disorders: A meta-analysis. Medicine (Baltimore). 2018 Dec;97(50):e13566. doi: 10.1097/MD.0000000000013566. PMID: 30558020; PMCID: PMC6320082.

Ray LA, Meredith LR, Kiluk BD, Walthers J, Carroll KM, Magill M. Combined Pharmacotherapy and Cognitive Behavioral Therapy for Adults With Alcohol or Substance Use Disorders: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Jun 1; 3(6):e208279. doi: 10.1001/jamanetworkopen.2020.8279. PMID: 32558914; PMCID: PMC7305524.

5. Methodology: Phase 2. New systematic review on the effect of combined pharmacological and psychosocial interventions on the management of patients with alcohol use disorders

5.1. Search strategy

We searched the following databases from their inception up to 14 March 2022 to identify published, unpublished and ongoing studies: the Cochrane Central Register of Controlled Trials (CENTRAL) via onlinelibrary.wiley.com; MEDLINE Ovid, Embase; PsycInfo, Web of Science, CINAHL. There was no language restriction. We searched the following trials registries:

ClinicalTrials.gov (www.clinicaltrials.gov); World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). Details of the search strategies are reported in Appendix IIc.

The inclusion criteria were: randomized controlled trials that assess the effect of combined pharmacological and psychosocial interventions compared to no treatment, usual care or stand-alone pharmacological or psychosocial treatment in participants with alcohol use disorders or alcohol dependence. We will consider the following pharmacological treatments:

- acamprosate,
- disulfiram,
- naltrexone

and the following psychosocial interventions:

- cognitive behavioural therapy (CBT),
- couples therapy,
- psychodynamic therapy,
- behavioural therapies,
- social network therapy,
- contingency management
- motivational interventions,
- twelve-step facilitation
- mutual help groups

5.2. Data collection and analysis

As the first stage in selecting relevant studies, records retrieved from the bibliographic databases and other sources were recorded and assessed for eligibility by examining their titles and abstracts only. This assessment was performed in accordance with the inclusion and exclusion criteria developed a priori. The full text of articles found to be potentially relevant on the basis of their titles and abstracts were retrieved and examined in light of the same inclusion criteria in the second stage of study selection. Two reviewers independently screened the records retrieved with the search and evaluated full text of potentially relevant reviews. Two authors independently extracted relevant data from the included studies. We calculated dichotomous outcomes as relative risk (RR) and 95% confidence intervals (CIs). For continuous outcomes, we calculated mean difference (MD) or standardized mean difference (SMD) for the same continuous outcome measured with different metric.
We combined the outcomes from the individual trials through meta-analysis where possible (comparability of intervention and outcomes between trials), using a random-effects model, because we expected a certain degree of heterogeneity across trials. We used data that reflect the intention-to-treat (ITT) analysis including all randomized participants irrespective of different compliance, dropout from treatment or lost at follow up. We used the data reported in the articles without any imputation.
We analysed heterogeneity by means of the IQ statistic, and the ChiQ test. We regarded heterogeneity as substantial if the IQ was greater than 50% or the P value lower than 0.10 for the Cochran's Q test for

heterogeneity. Following the guidance in the Cochrane Handbook for Systematic Reviews of Interventions, we considered the following values to denote no important, moderate, substantial, and considerable heterogeneity, respectively: 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100%.
We used the visual inspection of funnel plots (plots of the effect estimate from each study against the effect standard error) to evaluate possible publication bias if there were at least 10 studies included in the meta-analysis. Note that any asymmetry in the plot indicates the presence of small study effects and not necessarily reporting bias.

5.3. Selection and coding of identified records

We used EndNote X7 and Rayyan as reference management software.

5.4. Quality assessment

Two authors independently assessed the risk of bias of the included studies. We used the criteria recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017). The recommended approach for assessing risk of bias in studies included in Cochrane Reviews is a two-part tool, addressing the following specific domains: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). The first part of the tool involves describing what was reported to have happened in the study.

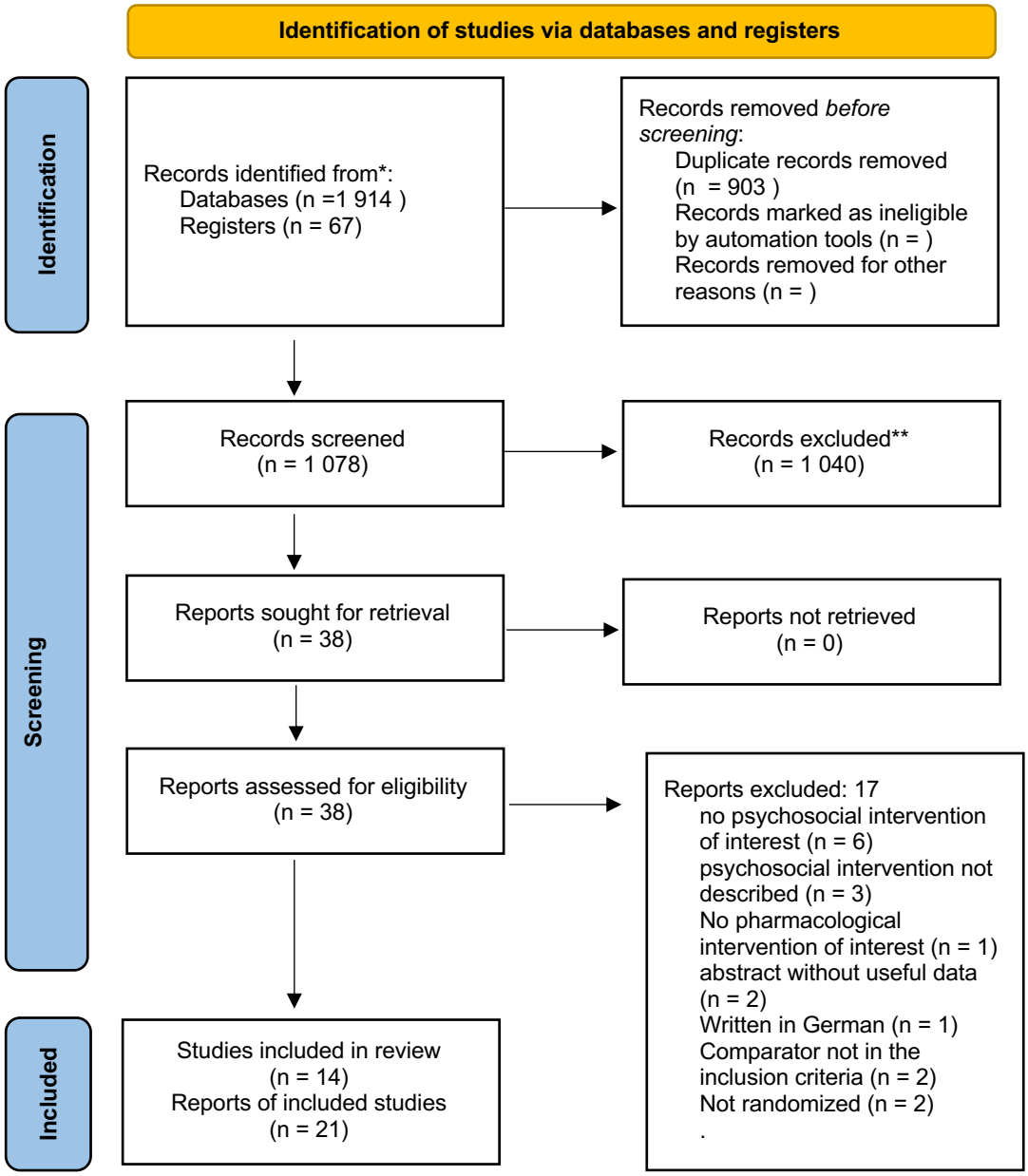
5.5. Analysis of subgroups or subsets

Where possible, we conducted subgroup analyses for the type of medications:

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

6. Results: Phase 2

Fig. 2. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

6.1. List of studies identified by the search process

After removing duplicates, we screened 1078 titles and abstracts. Thirty-eight records were judged as potentially relevant and acquired in full text. Seventeen studies were excluded as not fulfilling the inclusion criteria. Fourteen studies, reported in 21 reports and involving 3030 participants, were finally included.

6.1.1. Included in GRADE tables/footnotes

Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry. 1999 Nov; 156(11):1758-64. doi: 10.1176/ajp.156.11.1758. PMID: 10553740.

Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, Thevos A, Wang W, Woolson R. Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. J Clin Psychopharmacol. 2005 Aug; 25(4):349-57. doi: 10.1097/01.jcp.0000172071.81258.04. PMID: 16012278.

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3; 295(17):2003-17. doi: 10.1001/jama.295.17.2003. PMID: 16670409.

Balldin J, Berglund M, Borg S, Månsson M, Bendtsen P, Franck J, Gustafsson L, Halldin J, Nilsson LH, Stolt G, Willander A. A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. Alcohol Clin Exp Res. 2003 Jul; 27(7):1142-9. doi: 10.1097/01.ALC.0000075548.83053.A9. PMID: 12878920.

De Wildt WA, Schippers GM, Van Den Brink W, Potgieter AS, Deckers F, Bets D. Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? Alcohol and alcoholism (Oxford, Oxfordshire). 2002;37(4):375-82.

Heinälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2001 Jun; 21(3):287-92. doi: 10.1097/00004714-200106000-00006. PMID: 11386491.

Kranzler HR, Modesto-Lowe V, Nuwayser ES. Sustained-release naltrexone for alcoholism treatment: a preliminary study. Alcohol Clin Exp Res. 1998 Aug; 22(5):1074-9. PMID: 9726277

Kranzler HR, Wesson DR, Billot L; DrugAbuse Sciences Naltrexone Depot Study Group. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res. 2004 Jul; 28(7):1051-9. doi: 10.1097/01.alc.0000130804.08397.29. PMID: 15252291.

Morgenstern J, Kuerbis AN, Chen AC, Kahler CW, Bux DA Jr, Kranzler HR. A randomized clinical trial of naltrexone and behavioral therapy for problem drinking men who have sex with men. J Consult Clin Psychol. 2012 Oct; 80(5):863-75. doi: 10.1037/a0028615. Epub 2012 May 21. PMID: 22612306; PMCID: PMC3458143.

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry. 1992 Nov; 49(11):881-7. doi: 10.1001/archpsyc.1992.01820110045007. PMID: 1444726.

O'Malley SS, Sinha R, Grilo CM, Capone C, Farren CK, McKee SA, Rounsaville BJ, Wu R. Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. Alcohol Clin Exp Res. 2007 Apr; 31(4):625-34. doi: 10.1111/j.1530-0277.2007.00347.x. PMID: 17374042.

Oslin DW, Lynch KG, Pettinati HM, Kampman KM, Gariti P, Gelfand L, Ten Have T, Wortman S, Dundon W, Dackis C, Volpicelli JR, O'Brien CP. A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention. Alcohol Clin Exp Res. 2008 Jul; 32(7):1299-308. doi: 10.1111/j.1530-0277.2008.00698.x. PMID: 18540910; PMCID: PMC3812909.

Ulrichsen J, Nielsen MK, Ulrichsen M. Disulfiram in severe alcoholism--an open controlled study. Nord J Psychiatry. 2010 Dec; 64(6):356-62. doi: 10.3109/08039481003686180. Epub 2010 Mar 18. PMID: 20297945.

Wölwer W, Frommann N, Jänner M, Franke PE, Scherbaum N, Lieb B, Falkai P, Wobrock T, Kuhlmann T, Radermacher M, Maier W, Schütz C, Ohmann C, Burtscheidt W, Gaebel W. The effects of combined acamprosate and integrative behaviour therapy in the outpatient treatment of alcohol dependence: a randomized controlled trial. Drug Alcohol Depend. 2011 Nov 1; 118(2-3):417-22. doi: 10.1016/j.drugalcdep.2011.05.001. Epub 2011 May 31. PMID: 21621929

6.1.2. Excluded from GRADE tables/footnotes

Berner MM, Wahl S, Brueck R, Frick K, Smolka R, Haug M, Hoffmann S, Reinhard I, Leménager T, Gann H, Batra A, Mann K; PREDICT study group. The place of additional individual psychotherapy in the treatment of alcoholism: a randomized controlled study in non responders to anticraving medication-results of the PREDICT study. Alcohol Clin Exp Res. 2014 Apr; 38(4):1118-25. doi: 10.1111/acer.12317. Epub 2013 Nov 20. PMID: 24255998.

Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, Labriola D, Marshall J, Moncrieff J, Morgan MY, Peters T, Ritson B. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol. 2000 Nov-Dec; 35(6):587-93. doi: 10.1093/alcalc/35.6.587. PMID: 11093966.

Collins SE, Duncan MH, Saxon AJ, Taylor EM, Mayberry N, Merrill JO, Hoffmann GE, Clifasefi SL, Ries RK. Combining behavioral harm-reduction treatment and extended-release naltrexone for people experiencing homelessness and alcohol use disorder in the USA: a randomised clinical trial. Lancet Psychiatry. 2021 Apr; 8(4):287-300. doi: 10.1016/S2215-0366(20)30489-2. Epub 2021 Mar 10. PMID: 33713622.

Feeney GF, Young RM, Connor JP, Tucker J, McPherson A. Outpatient cognitive behavioural therapy programme for alcohol dependence: impact of naltrexone use on outcome. Aust N Z J Psychiatry. 2001 Aug; 35(4):443-8. doi: 10.1046/j.1440-1614.2001.00935.x. PMID: 11531723.

Feeney GF, Young RM, Connor JP, Tucker J, McPherson A. Cognitive behavioural therapy combined with the relapse-prevention medication acamprosate: are short-term treatment outcomes for alcohol dependence improved? Aust N Z J Psychiatry. 2002 Oct; 36(5):622-8. doi: 10.1046/j.1440-1614.2002.01019.x. PMID: 12225445.

Huang MC, Chen CH, Yu JM, Chen CC. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol dependence in Taiwan. Addict Biol. 2005 Sep; 10(3):289-92. doi: 10.1080/13556210500223504. PMID: 16109592.

Jarosz J, Miernik K, Wachal M, Walczak J. Clinical effectiveness analysis of naltrexone versus acamprosate and placebo in alcohol dependent patients treated with psychotherapy. Value in health [abstracts from the 16th annual international meeting of the international society for

pharmacoeconomics and outcomes research, ISPOR 2011 baltimore, MD united states. 21-25 may 2011] - Volume 0, Issue 0, pp. - published 2011-01-01

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA; Veterans Affairs Naltrexone Cooperative Study 425 Group. Naltrexone in the treatment of alcohol dependence. N Engl J Med. 2001 Dec 13;345(24):1734-9. doi: 10.1056/NEJMoa011127. PMID: 11742047.

Krystal JH, Gueorguieva R, Cramer J, Collins J, Rosenheck R; VA CSP No. 425 Study Team. Naltrexone is associated with reduced drinking by alcohol dependent patients receiving antidepressants for mood and anxiety symptoms: results from VA Cooperative Study No. 425, "Naltrexone in the treatment of alcoholism". Alcohol Clin Exp Res. 2008 Jan; 32(1):85-91. doi: 10.1111/j.1530-0277.2007.00555.x. Epub 2007 Dec 7. PMID: 18070245.

Longabaugh R, Wirtz PW, Gulliver SB, Davidson D. Extended naltrexone and broad spectrum treatment or motivational enhancement therapy. Psychopharmacology (Berl). 2009 Oct; 206(3):367-76. doi: 10.1007/s00213-009-1615-3. Epub 2009 Jul 29. PMID: 19639303.

Monti PM, Rohsenow DJ, Swift RM, Gulliver SB, Colby SM, Mueller TI, Brown RA, Gordon A, Abrams DB, Niaura RS, Asher MK. Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res. 2001 Nov; 25(11):1634-47. PMID: 11707638.

Oslin D, Liberto JG, O'Brien J, Krois S, Norbeck J. Naltrexone as an adjunctive treatment for older patients with alcohol dependence. Am J Geriatr Psychiatry. 1997 Fall;5(4):324-32. doi: 10.1097/00019442-199700540-00007. PMID: 9363289.

Rubio G, Ponce G, Rodriguez-Jiménez R, Jiménez-Arriero MA, Hoenicka J, Palomo T. Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? Alcohol Alcohol. 2005 May-Jun; 40(3):227-33. doi: 10.1093/alcalc/agh151. Epub 2005 Mar 29. PMID: 15797885.

Rubio G, Marín M, Arias F, López-Trabada JR, Iribarren M, Alfonso S, Prieto R, Blanco A, Urosa B, Montes V, Jurado R, Jiménez-Arriero MÁ, de Fonseca FR. Inclusion of Alcoholic Associations Into a Public Treatment Programme for Alcoholism Improves Outcomes During the Treatment and Continuing Care Period: A 6-Year Experience. Alcohol Alcohol. 2018 Jan 1; 53(1):78-88. doi: 10.1093/alcalc/agx078. PMID: 29087443.

Schmitt-Hönl B. Verhaltenstherapie so effektiv wie Naltrexon [Alcohol dependence. Behavior therapy is effective with naltrexone]. Med Monatsschr Pharm. 2006 Oct; 29(10):380-1. German. PMID: 17058899.

Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. Alcohol Alcohol. 2000 Mar-Apr; 35(2):202-9. doi: 10.1093/alcalc/35.2.202. PMID: 10787398.

Waschow B. Psychotherapie und Medikamente verlängern Abstinenz [Psychotherapy and drugs prolong abstinence]. Gesundheitswesen. 2014 Feb; 76(2):69. German. PMID: 24707543.

Table 1. PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
1	Combination of medication plus psychosocial interventions vs psychosocial intervention alone	Relapse: return to any drinking	NA	No published systematic review s identified. New SR and MA performed-
		Frequency of use: measured as percentage abstinent days	NA	No published systematic review s identified. New SR and MA performed-
		Amount of use: number of drinks per drinking day or drinking occasion	NA	No published systematic review s identified. New SR and MA performed-
		Adverse events: number of people with at least one adverse event,	NA	No published systematic review s identified. New SR and MA performed-
		Dropouts from treatment	NA	No published systematic review s identified. New SR and MA performed-
		Dropout from treatment due to adverse events	NA	No published systematic review s identified. New SR and MA performed-
		Cumulative abstinence duration	NA	No published systematic review s identified. New SR and MA performed-
		Craving,	NA	No published systematic review s identified. New SR and MA performed-
		Anxiety,	NA	No published systematic review s identified. New SR and MA performed-
		Depression,	NA	No published systematic review s identified. New SR and MA performed-
2	Combination of medication plus psychosocial interventions vs medication alone	Relapse: return to any drinking.	NA	No published systematic review s identified. New SR and MA performed-
		Frequency of use: measured as percentage abstinent days	NA	No published systematic review s identified. New SR and MA performed-
		Amount of use: number of drinks per drinking day or drinking occasion	NA	No published systematic review s identified. New SR and MA performed-
		Adverse events: number of people with at least one adverse event,	NA	No published systematic review s identified. New SR and MA performed-
		Dropouts from treatment	NA	No published systematic review s identified. New SR and MA performed-
		Dropout from treatment due to adverse	NA	No published systematic review s identified.

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
		events		New SR and MA performed-
		Cumulative abstinence duration	NA	No published systematic review s identified. New SR and MA performed-
		Craving,	NA	No studies retrieved that assessed this outcome -
		Anxiety,	NA	No published systematic review s identified. New SR and MA performed-
3	Combination of medication plus psychosocial interventions vs treatment as usual, wait list, n		NA	No studies retrieved that assessed this comparison

6.2. Narrative description of studies that contributed to GRADE analysis

We included 14 RCTs (Anton 1999, Anton 2005, Anton 2006, Balldin 2003, De Wildt 2002, Heinälä 2001, Kranzler 1998, Kranzler 2004, Morgenstern 2012, O'Malley 1992, O'Malley 2007, Oslin 2008, Ulrichsen 2010, Wölwer 2011) involving a total of 3030 participants. The mean study size was 216 participants, ranging from 20 in Kranzler 1998 to 1230 in Anton 2006. Six studies (Balldin 2003, Heinälä 2001, Kranzler 1998, O'Malley 1992, O'Malley 2007, Ulrichsen 2010) recruited less than 100 participants. The mean age of participants was 44.4 (3.4) years, and there were more men (71.3%) than women. One study recruited only women (O'Malley 2007). All studies recruited participants with a diagnosis of alcohol dependence according to the DSM-III TR or DSM-IV. Nine studies took place in the USA (Anton 1999, Anton 2005, Anton 2006, Kranzler 1998, Kranzler 2004, Morgenstern 2012, O'Malley 1992, O'Malley 2007, Oslin 2008), and one in Sweden (Balldin 2003), The Netherlands (De Wildt 2002), Finland (Heinälä 2001), Denmark (Ulrichsen 2010) and Germany (Wölwer 2011).

All trials excluded patients with substance use disorders by substances other than alcohol or nicotine and participants with severe comorbid mental disorders. Most studies required participants to abstain from alcohol for at least three days before the beginning of treatment except two studies that recruited participants who were still drinking (Heinälä 2001; Morgenstern 2012). For one study this information was lacking (Ulrichsen 2010).

Most studies were 12 weeks long (Anton 1999, Anton 2005, Heinälä 2001, Kranzler 2004, Morgenstern 2012, O'Malley 1992, O'Malley 2007) or longer (16 weeks: Anton 2006; 24 weeks: Balldin 2003; Oslin 2008; Ulrichsen 2010; Wölwer 2011; 28 weeks: De Wildt 2002). Only one study had a shorter duration (8 weeks: Kranzler 1998). The mean duration of the interventions was 16.6 weeks (range 8 to 28 weeks).

6.2.1. Types of comparisons

We collected data related a single comparation from eight studies each (Anton 1999, Balldin 2003, Heinälä 2001, Kranzler 1998, Kranzler 2004, O'Malley 1992, O'Malley 2007, Ulrichsen 2010), two comparations from four studies each (Anton 2005a; Anton 2005b; De Wildt 2002a; De Wildt 2002b; Morgenstern 2012a; Morgenstern 2012b; Oslin 2008a; Oslin 2008b; Wölwer 2011a; Wölwer 2011b), and six comparations from one study (Anton 2006a; Anton 2006b; Anton 2006c; Anton 2006d; Anton 2006e; Anton 2006f), for a total of 24 comparisons (Anton 1999; Anton 2005a; Anton 2005b; Anton 2006a; Anton 2006b; Anton 2006c; Anton 2006d; Anton 2006e; Anton 2006f; Balldin 2003; De Wildt 2002a; De Wildt 2002b; Heinälä 2001; Kranzler 1998; Kranzler 2004; Morgenstern 2012a; Morgenstern 2012b; O'Malley 1992; O'Malley 2007; Oslin 2008a; Oslin 2008b; Wölwer 2011a; Wölwer 2011b; Ulrichsen 2010).

Among these 24 comparisons, sixteen compared a combination of a medication plus a psychosocial intervention to the same psychosocial intervention alone: in thirteen comparisons the medication was naltrexone (Anton 1999; Anton 2005a; Anton 2005b; Anton 2006a; Balldin 2003; Heinälä 2001; Kranzler 1998; Kranzler 2004; Morgenstern 2012a; Morgenstern 2012b; O'Malley 1992; O'Malley 2007; Oslin 2008a), and in the other three was acamprosate (Anton 2006b), disulfiram (Ulrichsen 2010), and a combination of naltrexone and acamprosate (Anton 2006c).

The other eight comparisons compared the combination of a medication plus a psychosocial intervention to the same medication alone: in four comparisons the medication was acamprosate (Anton 2006e; De Wildt 2002a; De Wildt 2002b; Wölwer 2011b), in three comparisons naltrexone (Anton 2006d; Morgenstern 2012b; Oslin 2008b), and, in the other one, a combination of naltrexone and acamprosate (Anton 2006f).

Different psychosocial interventions were adopted. In detail, eight comparisons used cognitive behavioral therapy (CBT) (Anton 1999; Anton 2005a; Balldin 2003; De Wildt 2002a; O'Malley 2007; Oslin 2008a; Oslin 2008b; Ulrichsen 2010), six comparisons combined behavioral intervention (CBI) (Anton

2006a; Anton 2006b; Anton 2006c; Anton 2006d; Anton 2006e; Anton 2006f), three comparisons coping skills therapy (Heinälä 2001; Kranzler 1998; O'Malley 1992), two comparisons motivational enhancement treatment (MET) (Kranzler 2004; Anton 2005b), two comparisons Modified Behavioral Self-Control Therapy (MBSCT) (Morgenstern 2012a; Morgenstern 2012b), two comparisons integrative behaviour therapy (IBT) (Wölwer 2011a; Wölwer 2011b), and one comparison minimal intervention (De Wildt 2002b).

None of the included studies compared the combination of psychosocial intervention plus pharmacological intervention versus treatment as usual or no intervention.

6.3. Grading the Evidence

Table 2a. Evidence profile Combination on any pharmacological intervention with psychosocial intervention versus psychosocial intervention alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of any pharmacological intervention with psychosocial intervention versus psychosocial intervention alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Return to any drinking												
4	randomized trials	not serious	not serious	not serious	not serious	none	201/274 (73.4%)	219/265 (82.6%)	**RR 0.91** (0.84 to 0.98)	**74 fewer per 1000** (from 132 fewer to 17 fewer)	⊕⊕⊕⊕ High	
Return to heavy drinking												
10	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[b]	585/875 (66.9%)	544/723 (75.2%)	**RR 0.90** (0.83 to 0.97)	**75 fewer per 1000** (from 128 fewer to 23 fewer)	⊕⊕⊕◯ Moderate	
Abstinent days (percent of days abstinent at the end of treatment)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
11	randomized trials	not serious	not serious	not serious	not serious	none	857	684	-	MD **6.22 higher** (3.82 higher to 8.61 higher)	⨁⨁⨁⨁ High	
Heavy drinking days (percent of heavy drinking days at the end of treatment)												
4	randomized trials	not serious	not serious	not serious	not serious	none	245	239	-	MD **2.32 lower** (6.34 lower to 1.71 higher)	⨁⨁⨁⨁ High	
Adverse events												
3	randomized trials	not serious	not serious	not serious	not serious	none	164/216 (75.9%)	150/204 (73.5%)	**RR 1.05** (0.95 to 1.16)	**37 more per 1000** (from 37 fewer to 118 more)	⨁⨁⨁⨁ High	
Dropout												
13	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[b]	250/1081 (23.1%)	236/917 (25.7%)	**RR 0.93** (0.80 to 1.07)	**18 fewer per 1000** (from 51 fewer to 18 more)	⨁⨁⨁◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Dropout due to adverse events												
9	randomized trials	not serious	not serious	not serious	not serious	none	35/834 (4.2%)	64/622 (10.3%)	**RR 1.81** (0.96 to 3.38)	**83 more per 1000** (from 4 fewer to 245 more)	⊕⊕⊕⊕ High	
Craving												
3	randomized trials	not serious	not serious	not serious	serious[c]	none	117	117	-	SMD **0.47 lower** (0.95 lower to 0.01 higher)	⊕⊕⊕◯ Moderate	
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI)												
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	44	44	-	MD **1.5 higher** (2.38 lower to 5.38 higher)	⊕⊕◯◯ Low	
Depression (measured by Beck Depression Inventory Second Edition-BDI)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	44	44	-	MD **0.8 lower** (3.13 lower to 1.53 higher)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference
a. Not applicable because one study included
b. Asymmetry in the funnel plot suggesting publication bias
c. Downgraded of one level for imprecision because < 400 participants
d. Downgraded of two levels for imprecision because < 100 participants

Subgroup analyses for type of pharmacological treatment combined with psychosocial intervention versus psychosocial intervention alone

Table 2aa. Evidence profile Combination of naltrexone with psychosocial intervention versus psychosocial intervention alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of naltrexone with psychosocial intervention versus psychosocial intervention alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Return to any drinking – Naltrexone												
3	randomized trials	not serious	not serious	not serious	not serious	none	187/255 (73.3%)	203/245 (82.9%)	**RR 0.90** (0.83 to 0.98)	**83 fewer per 1000** (from 141 fewer to 17 fewer)	⊕⊕⊕⊕ High	
Return to heavy drinking – Naltrexone												
8	randomized trials	not serious	not serious	not serious	not serious	none	366/567 (64.6%)	388/515 (75.3%)	**RR 0.87** (0.79 to 0.96)	**98 fewer per 1000** (from 158 fewer to 30 fewer)	⊕⊕⊕⊕ High	
Abstinent days (percent of days abstinent at the end of treatment) – Naltrexone												
8	randomized trials	not serious	not serious	not serious	not serious	none	530	462	-	MD **6.75 higher** (3.95 higher to 9.56 higher)	⊕⊕⊕⊕ High	
Heavy drinking days (percent of heavy drinking days at the end of treatment)- Naltrexone												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
4	randomized trials	not serious	not serious	not serious	not serious	none	245	239	-	MD **2.32 lower** (6.34 lower to 1.71 higher)	⨁⨁⨁⨁ High	
Drinks per drinking days – Naltrexone												
6	randomized trials	not serious	not serious	not serious	not serious	none	212	202	-	SMD **0.31 lower** (0.5 lower to 0.11 lower)	⨁⨁⨁⨁ High	
Adverse events – Naltrexone												
3	randomized trials	not serious	not serious	not serious	not serious	none	164/216 (75.9%)	150/204 (73.5%)	**RR 1.05** (0.95 to 1.16)	**37 more per 1000** (from 37 fewer to 118 more)	⨁⨁⨁⨁ High	
Serious adverse events – Naltrexone												
2	randomized trials	not serious	not serious	not serious	serious[b]	none	1/173 (0.6%)	5/162 (3.1%)	**RR 0.20** (0.02 to 1.68)	**25 fewer per 1000** (from 30 fewer to 21 more)	⨁⨁⨁◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Dropout – Naltrexone												
10	randomized trials	not serious	not serious	not serious	not serious	none	122/649 (18.8%)	123/584 (21.1%)	**RR 0.88** (0.71 to 1.09)	**25 fewer per 1000** (from 61 fewer to 19 more)	⊕⊕⊕⊕ High	
Dropout due to adverse events – Naltrexone												
7	randomized trials	not serious	not serious	not serious	serious[b]	none	23/526 (4.4%)	62/414 (15.0%)	**RR 1.56** (0.78 to 3.10)	**84 more per 1000** (from 33 fewer to 314 more)	⊕⊕⊕◯ Moderate	
Craving – Naltrexone												
3	randomized trials	not serious	not serious	not serious	serious[c]	none	117	117	-	SMD **0.47 lower** (0.95 lower to 0.01 higher)	⊕⊕⊕◯ Moderate	
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI)- Naltrexone												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	44	44	-	MD **1.5 higher** (2.38 lower to 5.38 higher)	⊕⊕◯◯ Low	
Depression (measured by Beck Depression Inventory Second Edition-BDI)- Naltrexone												
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	44	44	-	MD **0.8 lower** (3.13 lower to 1.53 higher)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

a. Not applicable because one study included
b. Downgraded of one level for imprecision because OIS not met
c. Downgraded of one level for imprecision because < 400 participants
d. Downgraded of two levels for imprecision because < 100 participants

Table 2ab. Evidence profile Combination of acamprosate with psychosocial intervention versus psychosocial intervention alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of acamprosate with psychosocial intervention versus psychosocial intervention alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Return to heavy drinking – Acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[b]	none	103/151 (68.2%)	78/104 (75.0%)	**RR 0.91** (0.78 to 1.06)	**67 fewer per 1000** (from 165 fewer to 45 more)	⨁⨁⨁◯ Moderate	
Abstinent days (percent of days abstinent at the end of treatment) – Acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[c]	none	151	101	-	MD **5.2 higher** (1.43 lower to 11.83 higher)	⨁⨁⨁◯ Moderate	
Dropout – Acamprosate												
2	randomized trials	not serious	not serious	not serious	serious[b]	none	91/275 (33.1%)	90/229 (39.3%)	**RR 0.94** (0.76 to 1.18)	**24 fewer per 1000** (from 94 fewer to 71 more)	⨁⨁⨁◯ Moderate	
Dropout due to adverse events – Acamprosate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	3/151 (2.0%)	1/104 (1.0%)	**RR 2.07** (0.22 to 19.59)	**10 more per 1000** (from 8 fewer to 179 more)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

a. Not applicable because one study included

b. Downgraded of one level for imprecision because OIS not met

c. Downgraded of one level for imprecision because < 400 participants

d. Downgraded of two levels for imprecision because < 100 events and CI include important benefits and important harms

Table 2ac. Evidence profile Combination of disulfiram with psychosocial intervention versus psychosocial intervention alone

Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S

Date:

Question: Should combination of disulfiram with psychosocial intervention versus psychosocial intervention alone be used for people with alcohol use disorder

Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Return to any drinking – Disulfiram												
1	randomized trials	not serious	not serious[a]	not serious	very serious[b]	none	14/19 (73.7%)	16/20 (80.0%)	**RR 0.92** (0.65 to 1.30)	**64 fewer per 1000** (from 280 fewer to 240 more)	⨁⨁◯◯ Low	
Abstinent days (percent of days abstinent at the end of treatment)- Disulfiram												
1	randomized trials	not serious	not serious[a]	not serious	very serious[c]	none	19	20	-	MD **0** (27.84 lower to 27.84 higher)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

a. Not applicable because one study included

b. Downgraded of two levels for imprecision because < 100 events

c. Downgraded of two levels for imprecision because < 100 participants

Table 2ad. Evidence profile Combination of naltrexone and acamprosate with psychosocial intervention versus psychosocial intervention alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of naltrexone and acamprosate with psychosocial intervention versus psychosocial intervention alone be used for for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Return to heavy drinking - Naltrexone and acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[b]	none	116/157 (73.9%)	78/104 (75.0%)	**RR 0.99** (0.85 to 1.14)	**8 fewer per 1000** (from 113 fewer to 105 more)	⊕⊕⊕◯ Moderate	
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[c]	none	157	101	-	MD **4.6 higher** (1.99 lower to 11.19 higher)	⊕⊕⊕◯ Moderate	
Dropout - Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[b]	none	37/157 (23.6%)	23/104 (22.1%)	**RR 1.07** (0.67 to 1.68)	**15 more per 1000** (from 73 fewer to 150 more)	⊕⊕⊕◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	psychosocial intervention alone	Relative (95% CI)	Absolute (95% CI)		
Dropout due to adverse events - Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	9/157 (5.7%)	1/104 (1.0%)	**RR 5.96** (0.77 to 46.36)	**48 more per 1000** (from 2 fewer to 436 more)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

a. Not applicable because one study included

b. Downgraded of one level for imprecision because OIS not met

c. Downgraded of one level for imprecision because < 400 participants

d. Downgraded of two levels for imprecision because < 100 events and CI include important benefits and important harms

Table 2b. Evidence profile Combination on any pharmacological intervention with psychosocial intervention versus pharmacological intervention alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of any pharmacological intervention with psychosocial intervention versus pharmacological intervention alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Return to any drinking												
2	randomized trials	not serious	not serious	not serious	not serious	none	129/164 (78.7%)	63/77 (81.8%)	**RR 0.97** (0.85 to 1.10)	**25 fewer per 1000** (from 123 fewer to 82 more)	⊕⊕⊕⊕ High	
Return to heavy drinking												
4	randomized trials	not serious	not serious	not serious	not serious	none	356/510 (69.8%)	340/500 (68.0%)	**RR 1.03** (0.94 to 1.12)	**20 more per 1000** (from 41 fewer to 82 more)	⊕⊕⊕⊕ High	
Abstinent days (percent of days abstinent at the end of treatment)												
5	randomized trials	not serious	not serious	not serious	not serious	none	627	531	-	MD **1.22 lower** (4.46 lower to 2.02 higher)	⊕⊕⊕⊕ High	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Heavy drinking days (percent of heavy drinking days at the end of treatment)												
1	randomized trials	not serious	not serious[a]	not serious	serious[b]	none	47	46	-	MD **0.76 lower** (1.48 lower to 0.04 lower)	⨁⨁⨁◯ Moderate	
Drinks per drinking days												
3	randomized trials	not serious	not serious	not serious	serious[c]	none	211	123	-	SMD **0.54 lower** (0.77 lower to 0.31 lower)	⨁⨁⨁◯ Moderate	
Adverse events												
2	randomized trials						0/164 (0.0%)	0/77 (0.0%)	not pooled	No event	-	
Serious adverse events												
2	randomized trials						0/164 (0.0%)	0/77 (0.0%)	not pooled	No event	-	
Dropout												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
8	randomized trials	not serious	not serious	not serious	not serious	none	256/842 (30.4%)	240/745 (32.2%)	**RR 0.89** (0.74 to 1.09)	**35 fewer per 1000** (from 84 fewer to 29 more)	⊕⊕⊕⊕ High	
Dropout due to adverse events												
6	randomized trials	not serious	not serious	not serious	serious[d]	none	21/678 (3.1%)	22/582 (3.8%)	**RR 0.83** (0.43 to 1.61)	**6 fewer per 1000** (from 22 fewer to 23 more)	⊕⊕⊕◯ Moderate	
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI)												
1	randomized trials	not serious	not serious[a]	not serious	very serious[e]	none	44	39	-	MD **0.6 lower** (4.48 lower to 3.28 higher)	⊕⊕◯◯ Low	
Depression (measured by Beck Depression Inventory Second Edition-BDI)												
1	randomized trials	not serious	not serious[a]	not serious	very serious[e]	none	44	39	-	MD **0** (2.4 lower to 2.4 higher)	⊕⊕◯◯ Low	

a. Not applicable because one study included
b. Downgraded of one level for imprecision because < 100 participants but CI do not cross the line of no effect

c. Downgraded of one level for imprecision because < 400 participants but CI do not cross the line of no effect
d. Downgraded of one level for imprecision because OIS not met
e. Downgraded of two levels for imprecision because < 100 participants

Subgroup analyses for type of pharmacological treatment combined with psychosocial intervention versus pharmacological intervention alone

Table 2ba. Evidence profile Combination of naltrexone with psychosocial intervention versus naltrexone alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of naltrexone with psychosocial intervention versus naltrexone alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Return to heavy drinking - Naltrexone												
2	randomized trials	not serious	not serious	not serious	not serious	none	137/202 (67.8%)	136/200 (68.0%)	**RR 1.00** (0.87 to 1.14)	**0 fewer per 1000** (from 88 fewer to 95 more)	⊕⊕⊕⊕ High	
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone												
1	randomized trials	not serious	not serious[a]	not serious	serious[b]	none	155	154	-	MD **4.1 lower** (9.91 lower to 1.71 higher)	⊕⊕⊕◯ Moderate	
Heavy drinking days (percent of heavy drinking days at the end of treatment)- Naltrexone												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious[a]	not serious	serious[c]	none	47	46	-	MD **0.76 lower** (1.48 lower to 0.04 lower)	⨁⨁⨁◯ Moderate	
Drinks per drinking days - Naltrexone												
1	randomized trials	not serious	not serious[a]	not serious	serious[c]	none	47	46	-	SMD **0.69 lower** (1.11 lower to 0.27 lower)	⨁⨁⨁◯ Moderate	
Dropout - Naltrexone												
4	randomized trials	not serious	not serious	not serious	serious[d]	none	107/370 (28.9%)	122/368 (33.2%)	**RR 0.90** (0.60 to 1.35)	**33 fewer per 1000** (from 133 fewer to 116 more)	⨁⨁⨁◯ Moderate	
Dropout due to adverse events - Naltrexone												
2	randomized trials	not serious	not serious	not serious	serious[d]	none	7/206 (3.4%)	8/205 (3.9%)	**RR 0.88** (0.32 to 2.40)	**5 fewer per 1000** (from 27 fewer to 55 more)	⨁⨁⨁◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI)- Naltrexone												
1	randomized trials	not serious	not serious[a]	not serious	very serious[e]	none	44	39	-	MD **0.6 lower** (4.48 lower to 3.28 higher)	⨁⨁◯◯ Low	
Depression (measured by Beck Depression Inventory Second Edition-BDI)- Naltrexone												
1	randomized trials	not serious	not serious[a]	not serious	very serious[e]	none	44	39	-	MD **0** (2.4 lower to 2.4 higher)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

a. Not applicable because one study included

b. Downgraded of one level for imprecision because < 400 participants

c. Downgraded of one level for imprecision because < 100 participants but CI do not cross the line of no effect

d. Downgraded of one level for imprecision because OIS not met

e. Downgraded of two levels for imprecision because < 100 participants

Table 2bb. Evidence profile Combination of acamprosate with psychosocial intervention versus acamprosate alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of acamprosate with psychosocial intervention versus acamprosate alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Return to any drinking - Acamprosate												
2	randomized trials	not serious	not serious	not serious	not serious	none	129/164 (78.7%)	63/77 (81.8%)	**RR 0.97** (0.85 to 1.10)	**25 fewer per 1000** (from 123 fewer to 82 more)	⊕⊕⊕⊕ High	
Return to heavy drinking - Acamprosate												
1	randomizzed trials	not serious	not serious[a]	not serious	not serious	none	103/151 (68.2%)	108/152 (71.1%)	**RR 0.96** (0.83 to 1.11)	**28 fewer per 1000** (from 121 fewer to 78 more)	⊕⊕⊕⊕ High	
Abstinent days (percent of days abstinent at the end of treatment)- Acamprosate												
3	randomized trials	not serious	not serious	not serious	not serious	none	315	229	-	MD **2.52 higher** (2.75 lower to 7.79 higher)	⊕⊕⊕⊕ High	
Drinks per drinking days - Acamprosate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	not serious	serious[b]	none	164	77	-	SMD **0.48 lower** (0.75 lower to 0.2 lower)	⨁⨁⨁◯ Moderate	
Adverse events - Acamprosate												
2	randomized trials						0/164 (0.0%)	0/77 (0.0%)	not pooled	see comment	-	
Serious adverse events - Acamprosate												
2	randomized trials						0/164 (0.0%)	0/77 (0.0%)	not pooled	see comment	-	
Dropout - Acamprosate												
3	randomized trials	not serious	not serious	not serious	serious[c]	none	112/315 (35.6%)	82/229 (35.8%)	**RR 0.87** (0.61 to 1.25)	**47 fewer per 1000** (from 140 fewer to 90 more)	⨁⨁⨁◯ Moderate	
Dropout due to adverse events - Acamprosate												
3	randomized trials	not serious	not serious	not serious	serious[c]	none	5/315 (1.6%)	10/229 (4.4%)	**RR 0.40** (0.14 to 1.14)	**26 fewer per 1000** (from 38 fewer to 6 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference
a. Not applicable because one study included
b. Downgraded of one level for imprecision because < 400 participants but CI do not cross the line of no effect
c. Downgraded of one level for imprecision because OIS not met

Table 2bc. Evidence profile Combination of naltrexone and acamprosate with psychosocial intervention versus naltrexone and acamprosate alone
Author(s): Agabio R, Camposeragna A, Saulle R, Minozzi S
Date:
Question: Should combination of naltrexone and acamprosate with psychosocial intervention versus naltrexone and acamprosate alone be used for people with alcohol use disorder
Setting: outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Return to heavy drinking - Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	not serious	none	116/157 (73.9%)	96/148 (64.9%)	**RR 1.14** (0.98 to 1.32)	**91 more per 1000** (from 13 fewer to 208 more)	⊕⊕⊕⊕ High	
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[b]	none	157	148	-	MD **2.9 lower** (8.72 lower to 2.92 higher)	⊕⊕⊕◯ Moderate	
Dropouts - Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	very serious[d]	none	37/157 (23.6%)	36/148 (24.3%)	**RR 0.97** (0.65 to 1.45)	**7 fewer per 1000** (from 85 fewer to 109 more)	⊕⊕◯◯ Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of medication plus psychosocial interventions	medication alone	Relative (95% CI)	Absolute (95% CI)		
Dropouts due to adverse events - Naltrexone plus acamprosate												
1	randomized trials	not serious	not serious[a]	not serious	serious[c]	none	9/157 (5.7%)	4/148 (2.7%)	**RR 2.12** (0.67 to 6.74)	**30 more per 1000** (from 9 fewer to 155 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

a. Not applicable because one study included

b. Downgraded of one level for imprecision because < 400 participants

c. Downgraded of one level for imprecision because OIS not met

d. Downgraded of two levels for imprecision because < 100 events and CI include important benefits and important harms

[1]4 categories of quality of evidence: ÅÅÅÅ (High), ÅÅÅ□(Moderate), ÅÅ□□(Low), Å□□□(Very low). Examples are provided in the table.

[2]Recommendation: 2 grades – conditional or strong (for or against an intervention). Examples are provided in the table.

Note: an alternative categorization of standard or strong is used for the conditions related to stress module.

6.4. Additional evidence not mentioned in GRADE tables

There is no additional evidence not mentioned in GRADE tables

7. From Evidence to Recommendations

7.1. Summary of findings

Table 3a. Summary of findings table combination of any pharmacological treatment with psychosocial treatment versus psychosocial treatment alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to any drinking	826 per 1.000	**752 per 1 000** (694 to 810)	**RR 0.91** (0.84 to 0.98)	539 (4 RCTs)	⊕⊕⊕⊕ High
Return to heavy drinking	752 per 1.000	**677 per 1 000** (625 to 730)	**RR 0.90** (0.83 to 0.97)	1 598 (10 RCTs)	⊕⊕⊕◯ Moderate[b]
Abstinent days (percent of days abstinent at the end of treatment)	The mean abstinent days was 67.3 per 100	MD **6.22 higher** (3.82 higher to 8.61 higher)	-	1 541 (11 RCTs)	⊕⊕⊕⊕ High
Heavy drinking days (percent of heavy drinking days at the end of treatment)	The mean heavy drinking days was 21.7 per 100	MD **2.32 lower** (6.34 lower to 1.71 higher)	-	484 (4 RCTs)	⊕⊕⊕⊕ High
Drinks per drinking days	-	SMD **0.31 lower** (0.5 lower to 0.11 lower)	-	414 (6 RCTs)	⊕⊕⊕⊕ High
Adverse events	735 per 1.000	**772 per 1 000** (699 to 853)	**RR 1.05** (0.95 to 1.16)	420 (3 RCTs)	⊕⊕⊕⊕ High
Dropouts	257 per 1.000	**239 per 1 000** (206 to 275)	**RR 0.93** (0.80 to 1.07)	1 998 (13 RCTs)	⊕⊕⊕◯ Moderate[b]
Dropouts due to adverse events	103 per 1.000	**186 per 1 000** (99 to 348)	**RR 1.81** (0.96 to 3.38)	1 456 (9 RCTs)	⊕⊕⊕⊕ High
Craving	-	SMD **0.47 lower** (0.95 lower to 0.01 higher)	-	234 (3 RCTs)	⊕⊕⊕◯ Moderate[c]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Anxiety (measured by Spielberger State-Trait Anxiety Inventory - STAI**)**	The mean anxiety was **37.3**	MD **1.5 higher** (2.38 lower to 5.38 higher)	-	88 (1 RCT)	⊕⊕◯◯ Low[a,d]
Depression (measured by Beck Depression Inventory Second Edition-BDI)	The mean depression was **13.9**	MD **0.8 lower** (3.13 lower to 1.53 higher)	-	88 (1 RCT)	⊕⊕◯◯ Low[a,d]

a. Not applicable because one study included
b. Asymmetry in the funnel plot suggesting publication bias
c. Downgraded of one level for imprecision because < 400 participants
d. Downgraded of two levels for imprecision because < 100 participants

Subgroup analyses for type of pharmacological treatment combined with psychosocial intervention versus psychosocial intervention alone

Table 3aa: Summary of findings table combination of naltrexone with psychosocial treatment versus psychosocial treatment alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to any drinking - Naltrexone	829 per 1 000	**746 per 1 000** (688 to 812)	**RR 0.90** (0.83 to 0.98)	500 (3 RCTs)	⊕⊕⊕⊕ High
Return to heavy drinking - Naltrexone	753 per 1 000	**655 per 1 000** (595 to 723)	**RR 0.87** (0.79 to 0.96)	1082 (8 RCTs)	⊕⊕⊕⊕ High
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone	The mean abstinent days - Naltrexone was 65.20 per 100	MD **6.75 higher** (3.95 higher to 9.56 higher)	-	992 (8 RCTs)	⊕⊕⊕⊕ High
Heavy drinking days (percent of heavy drinking days at the end of treatment)- Naltrexone	The mean heavy drinking days - Naltrexone was 21.7 per 100	MD **2.32 lower** (6.34 lower to 1.71 higher)	-	484 (4 RCTs)	⊕⊕⊕⊕ High
Drinks per drinking days - Naltrexone	-	SMD **0.31 lower** (0.5 lower to 0.11 lower)	-	414 (6 RCTs)	⊕⊕⊕⊕ High
Adverse events - Naltrexone	735 per 1 000	**772 per 1 000** (699 to 853)	**RR 1.05** (0.95 to 1.16)	420 (3 RCTs)	⊕⊕⊕⊕ High
Serious adverse events - Naltrexone	31 per 1 000	**6 per 1 000** (1 to 52)	**RR 0.20** (0.02 to 1.68)	335 (2 RCTs)	⊕⊕⊕◯ Moderate[b]
Dropouts - Naltrexone	211 per 1 000	**185 per 1 000** (150 to 230)	**RR 0.88** (0.71 to 1.09)	1233 (10 RCTs)	⊕⊕⊕⊕ High
Dropouts due to adverse events - Naltrexone	150 per 1 000	**234 per 1 000** (117 to 464)	**RR 1.56** (0.78 to 3.10)	940 (7 RCTs)	⊕⊕⊕◯ Moderate[b]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Craving - Naltrexone	-	SMD **0.47 lower** (0.95 lower to 0.01 higher)	-	234 (3 RCTs)	⨁⨁⨁◯ Moderate[c]
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI)- Naltrexone	The mean anxiety - Naltrexone was **37.3**	MD **1.5 higher** (2.38 lower to 5.38 higher)	-	88 (1 RCT)	⨁⨁◯◯ Low[a,d]
Depression (measured by Beck Depression Inventory Second Edition-BDI)- Naltrexone	The mean depression - Naltrexone was **13.9**	MD **0.8 lower** (3.13 lower to 1.53 higher)	-	88 (1 RCT)	⨁⨁◯◯ Low[a,d]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because OIS not met
c. Downgraded of one level for imprecision because < 400 participants
d. Downgraded of two levels for imprecision because < 100 participants

Table 3ab. Summary of findings table combination of acamprosate with psychosocial treatment versus psychosocial treatment alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to heavy drinking - Acamprosate	750 per 1 000	**683 per 1 000** (585 to 795)	**RR 0.91** (0.78 to 1.06)	255 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]
Abstinent days (percent of days abstinent at the end of treatment)- Acamprosate	The mean abstinent days - Acamprosate was **73 per 100**	MD **5.2 higher** (1.43 lower to 11.83 higher)	-	252 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]
Dropouts - Acamprosate	393 per 1 000	**369 per 1 000** (299 to 464)	**RR 0.94** (0.76 to 1.18)	504 (2 RCTs)	⊕⊕⊕◯ Moderate[b]
Dropouts due to adverse events - Acamprosate	10 per 1 000	**20 per 1 000** (2 to 188)	**RR 2.07** (0.22 to 19.59)	255 (1 RCT)	⊕⊕◯◯ Low[a,d]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because OIS not met
c. Downgraded of one level for imprecision because < 400 participants
d. Downgraded of two levels for imprecision because < 100 events and CI include important benefits and important harms

Table 3ac. Summary of findings table combination of disulfiram with psychosocial treatment versus psychosocial treatment alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to any drinking - Disulfiram	800 per 1 000	**736 per 1 000** (520 to 1.000)	**RR 0.92** (0.65 to 1.30)	39 (1 RCT)	⨁⨁◯◯ Low[a,b]
Abstinent days (percent of days abstinent at the end of treatment)- Disulfiram	The mean abstinent days - Disulfiram was **59.5%**	MD **0** (27.84 lower to 27.84 higher)	-	39 (1 RCT)	⨁⨁◯◯ Low[a,c]

a. Not applicable because one study included
b. Downgraded of two levels for imprecision because < 100 events
c. Downgraded of two levels for imprecision because < 100 participants

Table 3ad. Summary of findings table combination of naltrexone and acamprosate with psychosocial treatment versus psychosocial treatment alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with psychosocial intervention alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to heavy drinking - Naltrexone and acamprosate	750 per 1 000	**742 per 1 000** (638 to 855)	**RR 0.99** (0.85 to 1.14)	261 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone plus acamprosate	The mean abstinent days - Naltrexone plus acamprosate was **73%**	MD **4.6 higher** (1.99 lower to 11.19 higher)	-	258 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]
Dropouts - Naltrexone plus acamprosate	221 per 1 000	**237 per 1 000** (148 to 372)	**RR 1.07** (0.67 to 1.68)	261 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]
Dropouts due to adverse events - Naltrexone plus acamprosate	10 per 1 000	**57 per 1 000** (7 to 446)	**RR 5.96** (0.77 to 46.36)	261 (1 RCT)	⊕⊕◯◯ Low[a,d]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because OIS not met
c. Downgraded of one level for imprecision because < 400 participants
d. Downgraded of two levels for imprecision because < 100 events and CI include important benefits and important harms

Table 3b. Summary of findings table combination of any pharmacological treatment with psychosocial treatment versus pharmacological treatment alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with medication alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to any drinking	818 per 1 000	**794 per 1 000** (695 to 900)	**RR 0.97** (0.85 to 1.10)	241 (2 RCTs)	⊕⊕⊕⊕ High
Return to heavy drinking	680 per 1 000	**700 per 1 000** (639 to 762)	**RR 1.03** (0.94 to 1.12)	1010 (4 RCTs)	⊕⊕⊕⊕ High
Abstinent days (percent of days abstinent at the end of treatment)	The mean abstinent days was **75.3%**	MD **1.22 lower** (4.46 lower to 2.02 higher)	-	1158 (5 RCTs)	⊕⊕⊕⊕ High
Heavy drinking days (percent of heavy drinking days at the end of treatment)	The mean heavy drinking days was **1.6**	MD **0.76 lower** (1.48 lower to 0.04 lower)	-	93 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]
Drinks per drinking days	-	SMD **0.54 lower** (0.77 lower to 0.31 lower)	-	334 (3 RCTs)	⊕⊕⊕◯ Moderate[c]
Adverse events	0 per 1 000	0 per 1 000	not estimable	241 (2 RCTs)	-
Serious adverse events	0 per 1 000	0 per 1 000	not estimable	241 (2 RCTs)	-
Dropouts	322 per 1 000	**287 per 1 000** (238 to 351)	**RR 0.89** (0.74 to 1.09)	1587 (8 RCTs)	⊕⊕⊕⊕ High
Dropouts due to adverse events	38 per 1 000	**31 per 1 000** (16 to 61)	**RR 0.83** (0.43 to 1.61)	1260 (6 RCTs)	⊕⊕⊕◯ Moderate[d]
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI**)**	The mean anxiety was **39.4**	MD **0.6 lower** (4.48 lower to 3.28 higher)	-	83 (1 RCT)	⊕⊕◯◯ Low[a,e]

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with medication alone	**Risk with Combination of medication plus psychosocial interventions**			
Depression (measured by Beck Depression Inventory Second Edition-BDI)	The mean depression was **13.1**	MD **0** (2.4 lower to 2.4 higher)	-	83 (1 RCT)	⨁⨁◯◯ Low[a,e]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because < 100 participants but CI do not cross the line of no effect
c. Downgraded of one level for imprecision because < 400 participants but CI do not cross the line of no effect
d. Downgraded of one level for imprecision because OIS not met
e. Downgraded of two levels for imprecision because < 100 participants

Subgroup analyses for type of pharmacological treatment combined with psychosocial intervention versus pharmacological treatment alone

Table 3ba. Summary of findings table combination of naltrexone with psychosocial treatment versus naltrexone alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with medication alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to heavy drinking - Naltrexone	680 per 1 000	**680 per 1 000** (592 to 775)	**RR 1.00** (0.87 to 1.14)	402 (2 RCTs)	⊕⊕⊕⊕ High
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone	The mean abstinent days - Naltrexone was **80%**	MD **4.1 lower** (9.91 lower to 1.71 higher)	-	309 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]
Heavy drinking days (percent of heavy drinking days at the end of treatment)- Naltrexone	The mean heavy drinking days - Naltrexone was **1.6**	MD **0.76 lower** (1.48 lower to 0.04 lower)	-	93 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]
Drinks per drinking days - Naltrexone	-	SMD **0.69 lower** (1.11 lower to 0.27 lower)	-	93 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]
Dropouts - Naltrexone	332 per 1 000	**298 per 1 000** (199 to 448)	**RR 0.90** (0.60 to 1.35)	738 (4 RCTs)	⊕⊕⊕◯ Moderate[d]
Anxiety (measured by Spielberger State-Trait Anxiety Inventory -STAI**)**- Naltrexone	The mean anxiety - Naltrexone was **39.4**	MD **0.6 lower** (4.48 lower to 3.28 higher)	-	83 (1 RCT)	⊕⊕◯◯ Low[a,e]
Depression (measured by Beck Depression Inventory Second Edition-BDI)- Naltrexone	The mean depression - Naltrexone was **13.1**	MD **0** (2.4 lower to 2.4 higher)	-	83 (1 RCT)	⊕⊕◯◯ Low[a,e]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because < 400 participants
c. Downgraded of one level for imprecision because < 100 participants but CI do not cross the line of no effect

d. Downgraded of one level for imprecision because OIS not met
e. Downgraded of two levels for imprecision because < 100 participants

Table 3bb. Summary of findings table combination of acamprosate with psychosocial treatment versus acamprosate alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with medication alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to any drinking - Acamprosate	818 per 1 000	**794 per 1 000** (695 to 900)	**RR 0.97** (0.85 to 1.10)	241 (2 RCTs)	⊕⊕⊕⊕ High
Return to heavy drinking - Acamprosate	711 per 1 000	**682 per 1 000** (590 to 789)	**RR 0.96** (0.83 to 1.11)	303 (1 RCT)	⊕⊕⊕⊕ High[a]
Abstinent days (percent of days abstinent at the end of treatment)- Acamprosate	The mean abstinent days - Acamprosate was **68.79%**	MD **2.52 higher** (2.75 lower to 7.79 higher)	-	544 (3 RCTs)	⊕⊕⊕⊕ High
Drinks per drinking days - Acamprosate	-	SMD **0.48 lower** (0.75 lower to 0.2 lower)	-	241 (2 RCTs)	⊕⊕⊕ Moderate[b]
Adverse events - Acamprosate	0 per 1 000	0 per 1 000	not estimable	241 (2 RCTs)	-
Serious adverse events - Acamprosate	0 per 1 000	0 per 1 000	not estimable	241 (2 RCTs)	-
Dropouts - Acamprosate	358 per 1 000	**312 per 1 000** (218 to 448)	**RR 0.87** (0.61 to 1.25)	544 (3 RCTs)	⊕⊕⊕ Moderate[c]
Dropouts due to adverse events - Acamprosate	44 per 1 000	**17 per 1 000** (6 to 50)	**RR 0.40** (0.14 to 1.14)	544 (3 RCTs)	⊕⊕⊕ Moderate[c]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because < 400 participants but CI do not cross the line of no effect
c. Downgraded of one level for imprecision because OIS not met

Table 3bc. Summary of findings table combination of acamprosate and naltrexone with psychosocial treatment versus acamprosate and naltrexone alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with medication alone	**Risk with Combination of medication plus psychosocial interventions**			
Return to heavy drinking - Naltrexone plus acamprosate	649 per 1 000	**739 per 1 000** (636 to 856)	**RR 1.14** (0.98 to 1.32)	305 (1 RCT)	⊕⊕⊕⊕ High[a]
Abstinent days (percent of days abstinent at the end of treatment)- Naltrexone plus acamprosate	The mean abstinent days - Naltrexone plus acamprosate was **80.5%**	MD **2.9 lower** (8.72 lower to 2.92 higher)	-	305 (1 RCT)	⊕⊕⊕ Moderate[a,b]
Dropouts - Naltrexone plus acamprosate	243 per 1 000	**236 per 1 000** (158 to 353)	**RR 0.97** (0.65 to 1.45)	305 (1 RCT)	⊕⊕1 Low[a,d]
Dropouts due to adverse events - Naltrexone plus acamprosate	27 per 1 000	**57 per 1 000** (18 to 182)	**RR 2.12** (0.67 to 6.74)	305 (1 RCT)	⊕⊕⊕ Moderate[a,c]

a. Not applicable because one study included
b. Downgraded of one level for imprecision because < 400 participants
c. Downgraded of one level for imprecision because OIS not met
d. Downgraded of two levels for imprecision because < 100 events and CI include important benefits and important harms

7.2. Evidence to decision

Table 4. Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognized priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	AUD and alcohol-related problems have high prevalence and associated with significant burden due to negative effects on health of individuals and other people.	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	The combination (med + psycho) vs psycho alone (at the end of treatment): 1) ↓ risk to return to any drinking (74 fewer per 1000; HIGH certainty) 2) ↓ risk to return to heavy drinking (75 fewer per 1000; MODERATE certainty) 3) ↑ % of abstinent days (6.22% abstinent days more; HIGH certainty) 4) ↓ the number of drinks per drinking day (SMD 0.31; HIGH certainty)	Subgroup analysis The combination (naltrexone + psycho) vs psycho alone (at the end of treatment): 1) ↓ risk to return to any drinking (83 fewer per 1000; HIGH certainty) 2) ↓ risk to return to heavy drinking (98 fewer per 1000; HIGH certainty) 3) ↑ % of abstinent days (6.75% abstinent days more; HIGH certainty) 4) ↓ the number of drinks per drinking day (SMD 0.31; HIGH certainty)

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		The combination (med + psycho) vs medication alone (at the end of treatment) 1) ↓ % heavy drinking days (0.76 % HDD less; MODERATE certainty) 2) ↓ number of drinks per drinking days (SMD 0.54 less; MODERATE certainty) The combination (med + psycho) does not differ from medication alone (at the end of treatment) in: 1) Return to any drinking (HIGH certainty) 2) Return to heavy drinking (HIGH certainty) 3) % of abstinent days (HIGH certainty)	The combination (acamprosate + psycho) does not differ from psycho alone (at the end of treatment) in: 1) Return to heavy drinking (MODERATE certainty) 2) % of abstinent days (MODERATE certainty) The combination (disulfiram + psycho) does not differ from psycho alone (at the end of treatment) in: 1) Return to heavy drinking (LOW certainty) 2) % of abstinent days (LOW certainty) The combination (naltrexone + psycho) vs naltrexone alone (at the end of treatment) 1) ↓ % heavy drinking days (0.76 % HDD less; MODERATE certainty) 2) ↓ number of drinks per drinking days (SMD 0.69 less; MODERATE certainty) The combination (acamprosate + psycho) does not differ from psycho alone (at the end of treatment) in: 1) Return to heavy drinking (MODERATE certainty) 2) % of abstinent days (MODERATE certainty)

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				The combination (acamprosate + psycho) vs acamprosate alone (at the end of treatment) in: 1) ↓ number of drinks per drinking days (SMD 0.48 less; MODERATE certainty) The combination (acamprosate + psycho) does not differ from acamprosate alone (at the end of treatment) in: 1) Return to any drinking (HIGH certainty) 2) Return to heavy drinking (HIGH certainty) 3) % of abstinent days (HIGH certainty)
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	The combination (med + psycho) does not differ from psycho alone in: 1) Number of people with adverse events (HIGH certainty) 2) Dropout (MODERATE certainty) 3) Dropout due to adverse events (HIGH certainty) The combination (med + psycho) does not differ from medication alone (at the end of treatment) in: 1) Dropout (HIGH certainty) 2) Dropout due to adverse events (MODERATE certainty)	The combination (naltrexone + psycho) does not differ from psycho alone in: 1) Number of people with adverse events (HIGH certainty) 2) Dropout (HIGH certainty) 3) Dropout due to adverse events (MODERATE certainty) The combination (acamprosate + psycho) does not differ from psycho alone (at the end of treatment) in:

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Even though differences for adverse events were not identified, medications for alcohol dependence treatment can have side effects and service providers should monitor them carefully. Side effect profile is generally acceptable with acamprosate, naltrexone and disulfiram. However, patient and carer (i.e. family) education regarding potential adverse events with disulfiram is important. The balance of benefits versus harms in non specialized settings in unclear.	1) Dropouts (MODERATE certainty) The combination (naltrexone + psycho) does not differ from naltrexone alone (at the end of treatment) in: 1) Dropout (HIGH certainty) The combination (acamprosate + psycho) does not differ from acamprosate alone (at the end of treatment) in: 1) Dropout (MODERATE certainty) 2) Dropout due to adverse events (MODERATE certainty)
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates of effects	☐ Very low ☐ Low ☒ **Moderate** ☐ High ☐ No included studies	The combination (med + psycho) vs psycho alone: 4 outcomes (3 HIGH certainty; 1 MODERATE certainty) The combination (med + psycho) vs medication alone: 2 outcomes (MODERATE certainty)	
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called “utility values”.			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value	☐ Important uncertainty or variability	Gronholm et al 2023 qualitative review • *The review very briefly outlined the perceived benefits and attitudes	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	each of the main outcomes?	☐ Possibly important uncertainty or variability ☒ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	of patients towards health outcomes. Some patients reported such incentives/benefits as improvement in health and positive perception of health along with positive changes in family. • However, some of the factors that contributed to the uncertainty were stigma, costs of services, limited availability and confidentiality concerns.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgements regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☒ **Favours the intervention** ☐ Varies ☐ Don't know	.	
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings	Though there are no studies on costs were evaluated, it can be suspected that combined treatment costs more and require additional human resources. However exact value is beyond the scope	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	require or save?	☐ Large savings ☒ **Varies** ☐ Don't know	of the current review. Face-to-face psychological interventions delivered by service providers are human resource-intensive as it requires substantial provider time, training and supervision. Combined psychological and pharmacological interventions may be more resource intensive. Both naltrexone and acamprosate are relatively expensive medications, compared to disulfiram, which is considerably less expensive and may be more readily accessible in low-income settings.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**		
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgements regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour	No reviews examining cost effectiveness identified	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies ☒ **No included studies**		
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favour of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritise and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☒ **Probably increased** ☐ Increased ☐ Varies ☐ Don't know		

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	Most of the studies (except one from India) done in high income countries: USA; Sweden; The Netherlands; Finland, Denmark, and Germany. There is no clear understanding on feasibility in low resource settings. Face-to-face psychological interventions delivered by service providers are human resource-intensive as it requires substantial provider time, training and supervision. Combined psychological and pharmacological interventions may be more resource intensive. Both naltrexone and acamprosate are relatively expensive medications, compared to disulfiram, which is considerably less expensive and may be more readily accessible in low-income settings. However, medications may not be registered and available in all countries. They are not included in the WHO Model List of Essential Medicines (22nd List, 2021). The decision to use of acamprosate, disulfiram or naltrexone should be made taking into consideration harms and benefits considerations, patient preferences and availability.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favour of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socioculturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socioculturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	There was no direct evidence to evaluate alignment with human rights principle and sociocultural acceptability.	

7.3. Summary of judgements

Table 5. Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	- Small	✓ **Moderate**	- Large
Undesirable effects	- Don't know	- Varies		- Large	- Moderate	- Small	✓ **Trivial**
Certainty of the evidence	- No included studies			- Very low	- Low	✓ **Moderate**	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	- No important uncertainty or variability
Balance of effects	- Don't know	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	✓ **Favours intervention**
Resources required	- Don't know	✓ **Varies**	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **No included studies**	- Varies	- Favours no comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Equity, equality and non-discrimination	- Don't know	- Varies	- Reduced	Probably reduced	- Probably no impact	✓ **Probably increased**	- Increased
Feasibility	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes
Human rights and sociocultural acceptability	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes

✓Indicates category selected, -Indicates category not selected

8. References

Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry. 1999 Nov; 156(11):1758-64. doi: 10.1176/ajp.156.11.1758. PMID: 10553740.

Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, Thevos A, Wang W, Woolson R. Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. J Clin Psychopharmacol. 2005 Aug; 25(4):349-57. doi: 10.1097/01.jcp.0000172071.81258.04. PMID: 16012278.

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3; 295(17):2003-17. doi: 10.1001/jama.295.17.2003. PMID: 16670409.

Balldin J, Berglund M, Borg S, Månsson M, Bendtsen P, Franck J, Gustafsson L, Halldin J, Nilsson LH, Stolt G, Willander A. A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. Alcohol Clin Exp Res. 2003 Jul; 27(7):1142-9. doi: 10.1097/01.ALC.0000075548.83053.A9. PMID: 12878920.

De Wildt WA, Schippers GM, Van Den Brink W, Potgieter AS, Deckers F, Bets D. Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? Alcohol and alcoholism (Oxford, Oxfordshire). 2002;37(4):375-82.

Gronholm PC, Makhmud A, Barbui C, et al Qualitative evidence regarding the experience of receiving and providing care for mental health conditions in non-specialist settings in low-income and middle-income countries: a systematic review of reviews. BMJ Ment Health 2023;26:e300755.

Heinälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2001 Jun; 21(3):287-92. doi: 10.1097/00004714-200106000-00006. PMID: 11386491.

Kranzler HR, Modesto-Lowe V, Nuwayser ES. Sustained-release naltrexone for alcoholism treatment: a preliminary study. Alcohol Clin Exp Res. 1998 Aug; 22(5):1074-9. PMID: 9726277

Kranzler HR, Wesson DR, Billot L; DrugAbuse Sciences Naltrexone Depot Study Group. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res. 2004 Jul; 28(7):1051-9. doi: 10.1097/01.alc.0000130804.08397.29. PMID: 15252291.

Morgenstern J, Kuerbis AN, Chen AC, Kahler CW, Bux DA Jr, Kranzler HR. A randomized clinical trial of naltrexone and behavioral therapy for problem drinking men who have sex with men. J Consult Clin Psychol. 2012 Oct; 80(5):863-75. doi: 10.1037/a0028615. Epub 2012 May 21. PMID: 22612306; PMCID: PMC3458143.

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry. 1992 Nov; 49(11):881-7. doi: 10.1001/archpsyc.1992.01820110045007. PMID: 1444726.

O'Malley SS, Sinha R, Grilo CM, Capone C, Farren CK, McKee SA, Rounsaville BJ, Wu R. Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. Alcohol Clin Exp Res. 2007 Apr; 31(4):625-34. doi: 10.1111/j.1530-0277.2007.00347.x. PMID: 17374042.

Oslin DW, Lynch KG, Pettinati HM, Kampman KM, Gariti P, Gelfand L, Ten Have T, Wortman S, Dundon W, Dackis C, Volpicelli JR, O'Brien CP. A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention. Alcohol Clin Exp Res. 2008 Jul; 32(7):1299-308. doi: 10.1111/j.1530-0277.2008.00698.x. PMID: 18540910; PMCID: PMC3812909.

Ulrichsen J, Nielsen MK, Ulrichsen M. Disulfiram in severe alcoholism--an open controlled study. Nord J Psychiatry. 2010 Dec; 64(6):356-62. doi: 10.3109/08039481003686180. Epub 2010 Mar 18. PMID: 20297945.

Wölwer W, Frommann N, Jänner M, Franke PE, Scherbaum N, Lieb B, Falkai P, Wobrock T, Kuhlmann T, Radermacher M, Maier W, Schütz C, Ohmann C, Burtscheidt W, Gaebel W. The effects of combined acamprosate and integrative behaviour therapy in the outpatient treatment of alcohol dependence: a randomized controlled trial. Drug Alcohol Depend. 2011 Nov 1; 118(2-3):417-22. doi: 10.1016/j.drugalcdep.2011.05.001. Epub 2011 May 31. PMID: 21621929

Excluded from GRADE tables/footnotes

Berner MM, Wahl S, Brueck R, Frick K, Smolka R, Haug M, Hoffmann S, Reinhard I, Leménager T, Gann H, Batra A, Mann K; PREDICT study group. The place of additional individual psychotherapy in the treatment of alcoholism: a randomized controlled study in non responders to anticraving medication-results of the PREDICT study. Alcohol Clin Exp Res. 2014 Apr; 38(4):1118-25. doi: 10.1111/acer.12317. Epub 2013 Nov 20. PMID: 24255998.

Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, Labriola D, Marshall J, Moncrieff J, Morgan MY, Peters T, Ritson B. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol. 2000 Nov-Dec; 35(6):587-93. doi: 10.1093/alcalc/35.6.587. PMID: 11093966.

Collins SE, Duncan MH, Saxon AJ, Taylor EM, Mayberry N, Merrill JO, Hoffmann GE, Clifasefi SL, Ries RK. Combining behavioral harm-reduction treatment and extended-release naltrexone for people experiencing homelessness and alcohol use disorder in the USA: a randomised clinical trial. Lancet Psychiatry. 2021 Apr; 8(4):287-300. doi: 10.1016/S2215-0366(20)30489-2. Epub 2021 Mar 10. PMID: 33713622.

Feeney GF, Young RM, Connor JP, Tucker J, McPherson A. Outpatient cognitive behavioural therapy programme for alcohol dependence: impact of naltrexone use on outcome. Aust N Z J Psychiatry. 2001 Aug; 35(4):443-8. doi: 10.1046/j.1440-1614.2001.00935.x. PMID: 11531723.

Feeney GF, Young RM, Connor JP, Tucker J, McPherson A. Cognitive behavioural therapy combined with the relapse-prevention medication acamprosate: are short-term treatment outcomes for alcohol dependence improved? Aust N Z J Psychiatry. 2002 Oct; 36(5):622-8. doi: 10.1046/j.1440-1614.2002.01019.x. PMID: 12225445.

Huang MC, Chen CH, Yu JM, Chen CC. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol dependence in Taiwan. Addict Biol. 2005 Sep; 10(3):289-92. doi: 10.1080/13556210500223504. PMID: 16109592.

Jarosz J, Miernik K, Wachal M, Walczak J. Clinical effectiveness analysis of naltrexone versus acamprosate and placebo in alcohol dependent patients treated with psychotherapy. Value in health [abstracts from the 16th annual international meeting of the international society for

pharmacoeconomics and outcomes research, ISPOR 2011 baltimore, MD united states. 21-25 may 2011] - Volume 0, Issue 0, pp. - published 2011-01-01

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA; Veterans Affairs Naltrexone Cooperative Study 425 Group. Naltrexone in the treatment of alcohol dependence. N Engl J Med. 2001 Dec 13;345(24):1734-9. doi: 10.1056/NEJMoa011127. PMID: 11742047.

Krystal JH, Gueorguieva R, Cramer J, Collins J, Rosenheck R; VA CSP No. 425 Study Team. Naltrexone is associated with reduced drinking by alcohol dependent patients receiving antidepressants for mood and anxiety symptoms: results from VA Cooperative Study No. 425, "Naltrexone in the treatment of alcoholism". Alcohol Clin Exp Res. 2008 Jan; 32(1):85-91. doi: 10.1111/j.1530-0277.2007.00555.x. Epub 2007 Dec 7. PMID: 18070245.

Longabaugh R, Wirtz PW, Gulliver SB, Davidson D. Extended naltrexone and broad spectrum treatment or motivational enhancement therapy. Psychopharmacology (Berl). 2009 Oct; 206(3):367-76. doi: 10.1007/s00213-009-1615-3. Epub 2009 Jul 29. PMID: 19639303.

Monti PM, Rohsenow DJ, Swift RM, Gulliver SB, Colby SM, Mueller TI, Brown RA, Gordon A, Abrams DB, Niaura RS, Asher MK. Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res. 2001 Nov; 25(11):1634-47. PMID: 11707638.

Oslin D, Liberto JG, O'Brien J, Krois S, Norbeck J. Naltrexone as an adjunctive treatment for older patients with alcohol dependence. Am J Geriatr Psychiatry. 1997 Fall;5(4):324-32. doi: 10.1097/00019442-199700540-00007. PMID: 9363289.

Rubio G, Ponce G, Rodriguez-Jiménez R, Jiménez-Arriero MA, Hoenicka J, Palomo T. Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? Alcohol Alcohol. 2005 May-Jun; 40(3):227-33. doi: 10.1093/alcalc/agh151. Epub 2005 Mar 29. PMID: 15797885.

Rubio G, Marín M, Arias F, López-Trabada JR, Iribarren M, Alfonso S, Prieto R, Blanco A, Urosa B, Montes V, Jurado R, Jiménez-Arriero MÁ, de Fonseca FR. Inclusion of Alcoholic Associations Into a Public Treatment Programme for Alcoholism Improves Outcomes During the Treatment and Continuing Care Period: A 6-Year Experience. Alcohol Alcohol. 2018 Jan 1; 53(1):78-88. doi: 10.1093/alcalc/agx078. PMID: 29087443.

Schmitt-Hönl B. Verhaltenstherapie so effektiv wie Naltrexon [Alcohol dependence. Behavior therapy is effective with naltrexone]. Med Monatsschr Pharm. 2006 Oct; 29(10):380-1. German. PMID: 17058899.

Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. Alcohol Alcohol. 2000 Mar-Apr; 35(2):202-9. doi: 10.1093/alcalc/35.2.202. PMID: 10787398.

Waschow B. Psychotherapie und Medikamente verlängern Abstinenz [Psychotherapy and drugs prolong abstinence]. Gesundheitswesen. 2014 Feb; 76(2):69. German. PMID: 24707543.

Appendix I: mhGAP process note

mhGAP Guideline Update: Notes on process for identifying level of evidence review required v2_0 (13/12/2021)

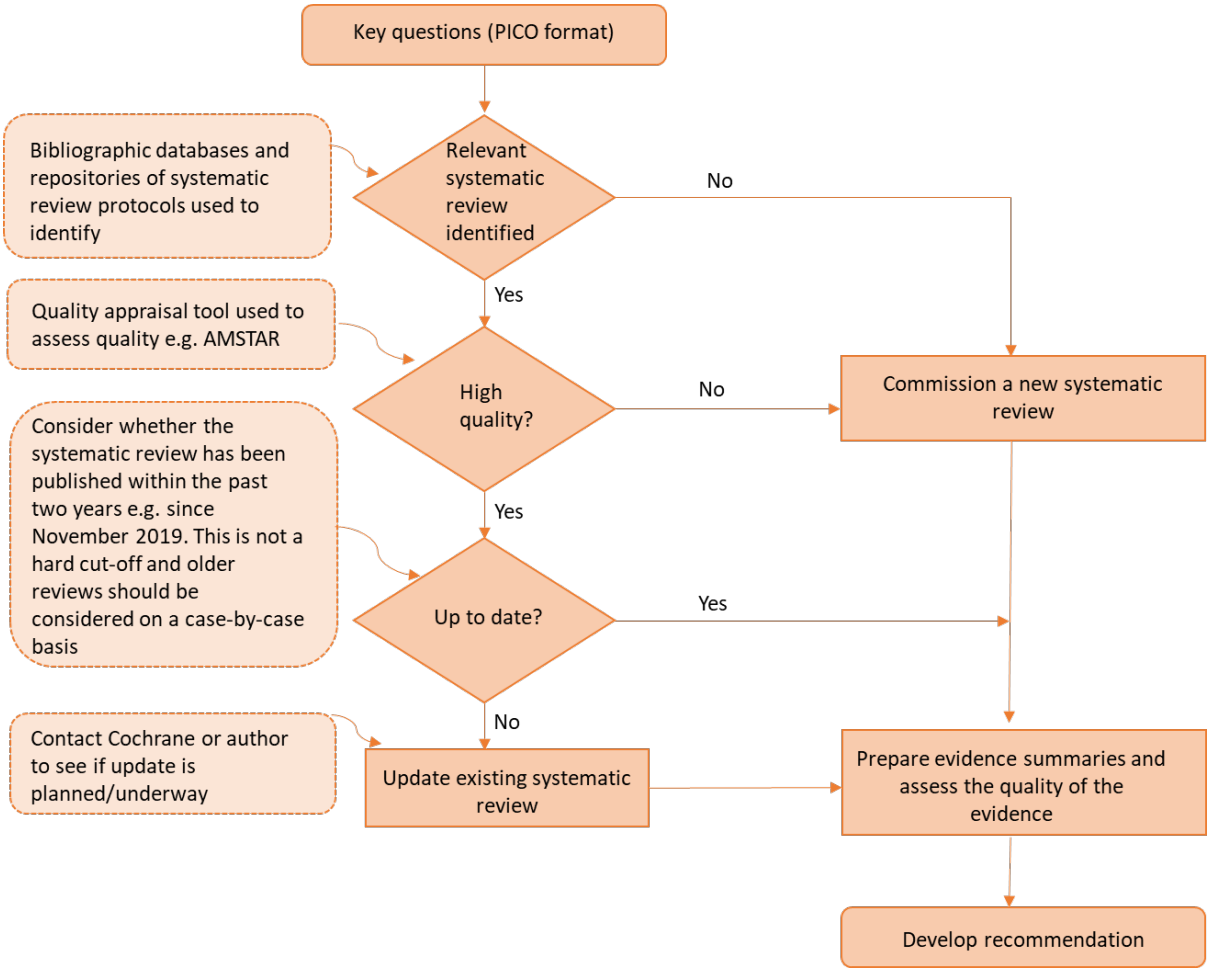
This document is intended to provide guidance to focal points on the level of evidence review required as part of the evidence retrieval process for the mhGAP guideline update process. As a general rule, the update process should be informed by existing high quality systematic reviews.
The process for evidence retrieval and synthesis is fully outlined in chapter 8 of the WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714.

Three main categories of evidence review are proposed in this document:

1) Existing relevant, up to date, high quality systematic review(s) provide the evidence required. **An existing systematic review is sufficient to prepare the evidence summaries**. It may be possible to include more than one systematic review for the same PICO, as different reviews may match different outcomes of a PICO. However, if more than one systematic review is available for the same PICO outcome, one review should be selected, based on quality, relevance, search comprehensiveness and date of last update. The selection process should be transparently reported, with justification of choices.
2) Existing high quality systematic reviews are either out of date or do not fully address the PICO, though it is considered that the review can be updated to meet these requirements. **An update of an existing systematic review is required before the evidence summaries can be prepared**. The update process may require addition of new studies published after the review, or inclusion of outcomes not covered by the existing reviews.
3) Existing systematic reviews are either not of sufficiently high quality or cannot be updated to fully address the PICO. **A new systematic review is required before the evidence summaries can be prepared**

Figure 1 below details the process to identify which level of evidence review is required to support the evidence retrieval process for a PICO.

Fig. 3.: Is a new systematic review needed



All key questions are currently in PICO format as presented in the Appendix of the planning proposal PICOs. Subsequent steps include the following:

1. **Identify and evaluate existing systematic reviews**: Identify one or more systematic review(s) to address each PICO question. Existing systematic reviews will inform the guideline development process, whether or not a new systematic review or an update of an existing review is required, and the evidence review team will detail existing systematic reviews in each case. The method for identifying existing systematic reviews should be fully detailed in the evidence summary and include the following sources:
    a. Search of bibliographic databases, such as PubMed/MEDLINE, Embase, PsycInfo, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHIL, Scopus, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Latin American and Caribbean Health Sciences Literature, and Western Pacific Region Index Medicus.
    b. Search of repositories of systematic reviews protocols, including PROSPERO, Open Science Framework (OSF), and Cochrane.
2. **Assess if systematic review is up to date:** It is preferred that identified systematic reviews have been published within the past two years e.g. since November 2019. This is not a hard cut-off and older reviews should be considered on a case-by-case basis, particularly those covering the time period since the last update of the mhGAP guideline in 2015. It is acknowledged that COVID has led to a pausing of many mental health research activities over the past two years, and this may also impact the availability of systematic reviews within the preferred two year period. For any reviews that fall outside the two year period, the guideline methodologist will advise on suitability.

3. **Appraise quality of systematic review:** Use the AMSTAR-2 quality appraisal tool to assess the quality of the identified systematic review(s) https://amstar.ca/docs/AMSTAR-2.pdf . This includes consideration of the extent to which the PICO is fully addressed by the systematic review(s) identified.

By following the process outlined in figure 1, and steps 1-3 above, the FP and evidence review team will have sufficient evidence to assess which of the three main categories of evidence review apply to each PICO under consideration:

1) Existing systematic reviews are sufficient to prepare the evidence summaries
2) An update of an existing systematic review is required before the evidence summaries can be prepared
3) A new systematic review is required before the evidence summaries can be prepared

Appendix IIa: Search terms used to identify systematic reviews

Database: Ovid MEDLINE(R) ALL < 2015 to 14 January 2022 >

1. Alcohol Deterrents/ (1479)
2. Acamprosate/ or (Acamprosate or Campral).tw. (924)
3. exp Anticonvulsants/ or anticonvulsant*.tw. (156685)
4. exp Antidepressive Agents/ or antidepress*.mp. (182950)
5. Baclofen.mp. (8339)
6. Disulfiram/ or (Disulfiram or Antabuse).tw. (4619)
7. (Naltrexone or Revia or Vivitrol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10724)
8. exp Naltrexone/ (8357)
9. (pharmacotherapy or phamacological or mediacation* or drug therapy).tw. (68516)
10. drug therapy/ or drug therapy, combination/ (203232)
11. or/1-10(595378)
12. exp Alcohol-Related Disorders/ (117644)
13. Alcohol Drinking/ (71786)
14. (alcohol adj3 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention$)).tw. (140938)
15. (drink$ adj3 (excess or heavy or heavily or harm or harmful or hazard$ or binge or harmful or problem$)).tw. (22012)
16. "alcohol use".tw. (40120)
17. alcoholic*.tw. (69672)
18. drunk*.tw. (4651)
19. or/10-18 (275062)
20. exp Psychotherapy/ (208974)
21. (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent* or biofeedback or community or stimulation or education* or counsel*).tw. (2025789)
22. (social adj2 skill*).tw. (7702)
23. (coping adj2 skill).tw. (128)
24. exp Counseling/ (46902)
25. (behavi* adj2 therap*).tw. (27959)
26. exp Reinforcement, Psychology/ (58439)
27. ((brief or minimal or early or motivat$) adj3 (intervention$ or therap$ or interview$ or advice)).tw. (84403)
28. (cognitive adj3 therapy).tw. (23738)
29. (family adj2 therapy).tw. (4034)
30. stress management training.tw. (296)
31. supportive expressive therapy.tw. (41)
32. exp Social Support/ (76713)
33. exp Case Management/ (10408)
34. self control training.tw. (63)
35. (behavio* adj2 (change or modification)).tw. (31832)
36. (behavio* adj2 (change or modification)).tw. (31832)
37. CBT.tw. (12412)
38. psychodynamic*.tw. (6687)
39. talking therap*.tw. (180)
40. (self help group* or (alcoholic* adj2 anonymou*) or mutual help or mutual aid or twelve step* or 12 step* or 12-step*).tw. (4472)
41. or/20-40 (2362267)

42. meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ (284355)
43. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. (254204)
44. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. (13228)
45. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. (33063)
46. (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. (33584)
47. (handsearch* or hand search*).ti,ab,kf,kw. (10276)
48. (handsearch* or hand search*).ti,ab,kf,kw. (10276)
49. (meta regression* or metaregression*).ti,ab,kf,kw. (11779)
50. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (387274)
51. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. (280617)
52. (cochrane or (health adj2 technology assessment) or evidence report).jw. (20609)
53. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. (15512)
54. (outcomes research or relative effectiveness).ti,ab,kf,kw. (10386)
55. ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw. (2525)
56. or/42-55 (554607)
57. 11 and 19 and 41 ad 56(136)
58. limit 61 to yr = "2015 -Current" (53)

Database: Embase < 2015 to 14 January 2022 >

1 "drugs used in the treatment of addiction"/ (885)
2 Acamprosate/ or (Acamprosate or Campral).tw. (2695)
3 anticonvulsive agent/ or anticonvulsant*.tw. (95126)
4 exp antidepressant agent/ or antidepress*.mp. (535855)
5 Baclofen.mp. (20135)
6 Disulfiram/ or (Disulfiram or Antabuse).tw. (8992)
7 (Naltrexone or Revia or Vivitrol).mp. (17463)
8 exp Naltrexone/ (15801)
9 (pharmacotherapy or phamacological or mediacation* or drug therapy).tw. (100019)
10 drug therapy/ or combination drug therapy/ (852543)
11 exp alcoholism/ (123877)
12 alcohol abuse/ (32259)
13 drinking behavior/ (52008)
14 (alcohol adj3 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention)).tw. (198317)
15 (drink$ adj3 (excess or heavy or heavily or hazard$ or binge or harmful or problem$)).tw. (29837)
16 ("alcohol use" or alcoholic$).tw. (156880)
17 counseling/ (73211)
18 exp *psychotherapy/ (128037)
19 psychologic test/ (31072)
20 motivation/ (112561)
21 (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent* or biofeedback or community or stimulation or education* or counsel*).tw. (2564894)
22 (social adj2 skill*).tw. (10403)
23 (coping adj2 skill).tw. (211)
24 (behavi* adj2 therap*).tw. (39314)
25 CBT.ti. (2059)
26 "reinforcement (psychology)"/ (1530)
27 ((brief or minimal or early or motivat$) adj3 (intervention$ or therap$ or interview$ or advice)).tw. (124004)

28 (cognitive adj3 therapy).tw. (33193)
29 (family adj2 therapy).tw. (6021)
30 stress management training.tw. (376)
31 supportive expressive therapy.tw. (67)
32 exp Social Support/ (101873)
33 case management/ (12598)
34 self control training.tw. (95)
35 (behavio* adj2 (change or modification)).tw. (39489)
36 psychodynamic*.tw. (9525)
37 talking therap*.tw. (231)
38 (self help group* or (alcoholic* adj2 anonymou*) or mutual help or mutual aid or twelve step* or 12 step* or 12-step*).tw. (6183)
39 "systematic review"/ or meta analysis/ (438261)
40 "meta analysis (topic)"/ (47958)
41 "systematic review (topic)"/ (28049)
42 biomedical technology assessment/ (15414)
43 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. (309136)
44 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. (15368)
45 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. (46564)
46 (data synthes* or data extraction* or data abstraction*).ti,ab. (40901)
47 (handsearch* or hand search*).ti,ab. (12473)
48 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. (40764)
49 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab. (16119)
50 (meta regression* or metaregression*).ti,ab. (14391)
51 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (606972)
52 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab. (349193)
53 (cochrane or (health adj2 technology assessment) or evidence report).jw. (29072)
54 (comparative adj3 (efficacy or effectiveness)).ti,ab. (21641)
55 (outcomes research or relative effectiveness).ti,ab. (12275)
56 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. (4630)
57 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 (816827)
58 or/1-10 (1508837)
59 or/11-16 (362722)
60 or/17-38 (2929591)
61 58 and 59 and 60 (7992)
62 57 and 61 (470)
63 limit 62 to yr = "2015 -Current" (213)

Database: APA PsycInfo < 2015 to January Week 2 2022 >
1 acamprosate/ or (Acamprosate or Campral).tw. (519)
2 exp Anticonvulsive Drugs/ or anticonvulsant*.tw. (15014)
3 exp Antidepressant Drugs/ or antidepress*.mp. (64192)
4 Baclofen.mp. (1746)
5 Disulfiram/ or (Disulfiram or Antabuse).tw. (840)
6 Naltrexone/ or (Naltrexone or Revia or Vivitrol).mp. (4506)

7 Drug Therapy/ or (pharmacotherapy or phamacological or mediacation* or drug therapy).tw. (149634)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (190128)
9 exp alcohol intoxication/ (3341)
10 exp alcohol abuse/ (50203)
11 alcohol rehabilitation/ (8594)
12 alcohol drinking patterns/ (25083)
13 (alcohol adj3 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention)).ti,ab. (81823)
14 (drink$ adj3 (excess or heavy or heavily or hazard$ or binge or harmful or problem$)).ti,ab. (17798)
15 ("alcohol use" or alcoholic$).ti,ab. (52453)
16 9 or 10 or 11 or 12 or 13 or 14 or 15 (115463)
17 counseling/ or rehabilitation counseling/ (25868)
18 psychotherapy/ (55769)
19 brief psychotherapy/ (5882)
20 motivational interviewing/ (2776)
21 cognitive behavior therapy/ or behavior therapy/ (36373)
22 (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent* or biofeedback or community or stimulation or education* or counsel*).tw. (1267660)
23 (social adj2 skill*).tw. (20588)
24 (coping adj2 skill).tw. (282)
25 (behavi* adj2 therap*).tw. (43927)
26 CBT.ti. (1744)
27 ((brief or minimal or early or motivat$) adj3 (intervention$ or therap$ or interview$ or advice)).tw. (44812)
28 (cognitive adj3 therapy).tw. (36400)
29 (family adj2 therapy).tw. (19691)
30 stress management training.tw. (425)
31 supportive expressive therapy.tw. (73)
32 (behavio* adj2 (change or modification)).tw. (29928)
33 psychodynamic*.tw. (23868)
34 talking therap*.tw. (272)
35 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (1382869)
36 16 and 35 (34024)
37 "systematic review"/ or meta analysis/ (5699)
38 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. (44782)
39 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. (10200)
40 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. (5594)
41 (data synthes* or data extraction* or data abstraction*).ti,ab. (3158)
42 (handsearch* or hand search*).ti,ab. (1425)
43 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. (5487)
44 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab. (948)
45 (meta regression* or metaregression*).ti,ab. (2149)
46 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (71383)
47 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab. (29976)
48 (comparative adj3 (efficacy or effectiveness)).ti,ab. (2203)

49 (outcomes research or relative effectiveness).ti,ab. (3735)
50 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. (213)
51 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (112091)
52 8 and 36 (2052)
53 51 and 52 (102)
54 limit 53 to yr = "2015 -Current" (31)

78 results from Web of Science Core Collection for:

1. TS=(((systematic* NEAR/3 (review* OR overview*)) OR "meta-analysis"))
2. TS=(("contingency management" OR "financial incentives" OR voucher OR reinforcement OR counsel* OR psychoeducat* OR (psychological NEAR/2 (therap* OR treatment*)) OR psychotherap* OR psychosocial* OR psychoanalytic OR ((social OR peer OR group) NEAR/2 support) OR (self NEXT help) OR (cognitive NEAR/2 (therap* OR behav*)) OR mindfulness OR relax* OR ((family OR couple) NEAR/2 therap*) OR (twelve NEAR/2 step) OR "12-step"))
3. TS=((pharmacotherapy or phamacological or mediacation* or drug therapy or Acamprosate or Campral or anticonvulsant* or antidepress* or Baclofen or Disulfiram or Antabuse or Naltrexone or Revia or Vivitrol))
4. TS=((((alcohol$ or drink$) NEAR/5 (abstinen$ or abstain$ or abus$ or addict$ or crav$ or dependen$ or detox$ or disease$ or disorder$ or excessiv$ or heavy or intoxicat$ or misus$ or overdos$ or problem$ or rehab$ or relaps$ or treatment$ or withdraw$))))
5. #4 AND #3 AND #2 AND #1 and 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 (Publication Years)

24 results from Epistemonikos for
Publication year: Last 5 years
Publication type: Systematic Review

(title:((title:((alcohol$ AND (abstinen$ OR abstain$ OR abus$ OR addict$ OR crav$ OR dependen$ OR detox$ OR disease$ OR disorder$ OR excessiv$ OR heavy OR intoxicat$ OR misus$ OR overdos$ OR problem$ OR rehab$ OR relaps$ OR treatment$ OR withdraw$))) OR abstract:((alcohol$ AND (abstinen$ OR abstain$ OR abus$ OR addict$ OR crav$ OR dependen$ OR detox$ OR disease$ OR disorder$ OR excessiv$ OR heavy OR intoxicat$ OR misus$ OR overdos$ OR problem$ OR rehab$ OR relaps$ OR treatment$ OR withdraw$))))) OR abstract:((title:((alcohol$ AND (abstinen$ OR abstain$ OR abus$ OR addict$ OR crav$ OR dependen$ OR detox$ OR disease$ OR disorder$ OR excessiv$ OR heavy OR intoxicat$ OR misus$ OR overdos$ OR problem$ OR rehab$ OR relaps$ OR treatment$ OR withdraw$))) OR abstract:((alcohol$ AND (abstinen$ OR abstain$ OR abus$ OR addict$ OR crav$ OR dependen$ OR detox$ OR disease$ OR disorder$ OR excessiv$ OR heavy OR intoxicat$ OR misus$ OR overdos$ OR problem$ OR rehab$ OR relaps$ OR treatment$ OR withdraw$)))))) AND (title:(pharmacotherapy OR phamacological OR mediacation* OR "drug therapy" OR Acamprosate OR Campral OR anticonvulsant* OR antidepress* OR Baclofen OR Disulfiram OR Antabuse OR Naltrexone OR Revia OR Vivitrol) OR abstract:(pharmacotherapy OR phamacological OR mediacation* OR "drug therapy" OR Acamprosate OR Campral OR anticonvulsant* OR antidepress* OR Baclofen OR Disulfiram OR Antabuse OR Naltrexone OR Revia OR Vivitrol)) AND (title:("contingency management" OR "financial incentives" OR voucher OR reinforcement OR counsel* OR psychoeducat* OR psychological OR psychotherap* OR psychosocial* OR psychoanalytic OR "social support "OR "peer support "OR "support group" OR "self help" OR (cognitive AND (therap* OR behav*)) OR mindfulness OR relax* OR ((family OR couple) AND therap*) OR "twelve step" OR "12-step" OR "12 step") OR abstract:("contingency management" OR "financial incentives" OR voucher OR reinforcement OR counsel* OR psychoeducat* OR psychological OR psychotherap* OR psychosocial* OR psychoanalytic OR "social support "OR "peer support "OR "support group" OR "self help" OR (cognitive AND (therap* OR behav*)) OR mindfulness OR relax* OR ((family OR couple) AND therap*) OR "twelve step" OR "12-step" OR "12 step"))

Appendix II b

Cochrane Central Register of Controlled Trials
Issue 3, March 2022 (382 results)

#1 MeSH descriptor: [Alcohol-Related Disorders] explode all trees
#2 MeSH descriptor: [Alcohol-Induced Disorders, Nervous System] explode all trees
#3 (alcohol NEAR/3 (abstin* 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)):ti,ab
#4 alcoholic*:ti,ab
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Alcohol Deterrents] explode all trees
#7 MeSH descriptor: [Acamprosate] explode all trees
#8 (Acamprosate or Campral):ti,ab,kw
#9 MeSH descriptor: [Disulfiram] explode all trees
#10 (Disulfiram or Antabuse):ti,ab,kw
#11 MeSH descriptor: [Naltrexone] explode all trees
#12 (Naltrexone or Revia or Vivitrol):ti,ab,kw
#13 nalmefene:ti,ab,kw
#14 {OR #6-#13}
#15 MeSH descriptor: [Psychotherapy] explode all trees
#16 (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent*):ti,ab
#17 ((coping or social) near/2 skill*):ti,ab
#18 (behavi* near/2 therap*):ti,ab
#19 MeSH descriptor: [Reinforcement, Psychology] explode all trees 2361
#20 (cognitive near/3 therapy):ti,ab
#21 ((family or couple*) near/2 therapy):ti,ab
#22 "stress management training" or "supportive expressive therapy" or "self control training"
#23 MeSH descriptor: [Social Support] explode all trees
#24 (contingency next management):ti,ab
#25 "self control training"
#26 (behavio* near/2 (change or modification)):ti,ab
#27 psychodynamic*:ti,ab,kw
#28 (talking next therap*):ti,ab,kw
#29 MeSH descriptor: [Self-Help Groups] explode all trees
#30 (self next help next group*):ti,ab
#31 alcoholic* near/2 anonymou*
#32 mutual next help
#33 mutual next aid
#34 twelve next step*
#35 {OR #15-#34}
#37 #5 AND #14 AND #35 in Trials

Database: Ovid MEDLINE(R)
Searched: from 1946 to 14 March 2022 (296 results)

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*.ti,ab.
4 1 or 2 or 3
5 exp Alcohol Deterrents/

6 Acamprosate/
7 (Acamprosate or Campral).ti,ab.
8 Disulfiram/
9 Naltrexone/
10 (Naltrexone or Revia or Vivitrol).ti,ab.
11 nalmefene.ti,ab.
12 5 or 6 or 7 or 8 or 9 or 10 or 11
13 (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent*).ti,ab.
14 ((coping or social) adj2 skill*).ti,ab.
15 (behavi* adj2 therap*).ti,ab.
16 exp Reinforcement, Psychology/
17 ((cognitive adj3 therapy) or CBT).ti,ab.
18 ((family or couple*) adj2 therapy).ti,ab.
19 stress management training.ti,ab.
20 exp Social Support/
21 contingency management.tw.
22 self control training.tw.
23 (behavio* adj2 (change or modification)).tw.
24 psychodynamic*.tw.
25 talking therap*.tw.
26 exp Self-Help Groups/
27 self help group*.tw.
28 (alcoholic* adj2 anonymou*).tw.
29 mutual help.tw.
30 mutual aid.tw.
31 twelve step*.tw.
32 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 4 and 12 and 32
34 randomized controlled trial.pt.
35 controlled clinical trial.pt.
36 random*.ti,ab,kf.
37 placebo.ab.
38 clinical trials as topic.sh.
39 random allocation.sh.
40 trial.ti.
41 34 or 35 or 36 or 37 or 38 or 39 or 40
42 exp animals/ not humans.sh.
43 41 not 42
44 33 and 43

Database: Ovid Embase
Searched: from 1974 to 14 March 2022 (583 results)
1 exp alcoholism/
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*.ti,ab.
4 1 or 2 or 3
5 acamprosate/
6 (Acamprosate or Campral).ti,ab.
7 Disulfiram/
8 Naltrexone/

9 (Naltrexone or Revia or Vivitrol).ti,ab.
10 nalmefene.ti,ab.
11 5 or 6 or 7 or 8 or 9 or 10
12 (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent*).ti,ab.
13 ((coping or social) adj2 skill*).ti,ab.
14 (behavi* adj2 therap*).ti,ab.
15 exp "reinforcement (psychology)"/
16 ((cognitive adj3 therapy) or CBT).ti,ab.
17 ((family or couple*) adj2 therapy).ti,ab.
18 stress management training.ti,ab.
19 exp social support/
20 contingency management.tw.
21 CM.ti.
22 self control training.tw.
23 (behavio* adj2 (change or modification)).tw.
24 psychodynamic*.tw.
25 talking therap*.tw.
26 self help group*.tw.
27 (alcoholic* adj2 anonymou*).tw.
28 mutual help.tw.
29 mutual aid.tw.
30 twelve step*.tw.
31 (social network adj2 (intervention* or therap*)).tw.
32 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 4 and 11 and 32
34 Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/
35 (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab.
36 34 or 35
37 33 and 36
38 limit 37 to human

Database: Ovid PsycInfo
Searched: from 1806 to March Week 2 2022 (197 results)
1 exp "Alcohol Use Disorder"/
2 exp Alcohol Treatment/
3 exp Alcoholism/
4 (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$)).tw.
5 alcoholic*.ti,ab.
6 1 or 2 or 3 or 4 or 5
7 acamprosate/
8 (Acamprosate or Campral).ti,ab.
9 Naltrexone.mp. or exp Naltrexone/
10 (Revia or Vivitrol).ti,ab.
11 Disulfiram.mp. or exp Disulfiram/
12 nalmefene.ti,ab.
13 7 or 8 or 9 or 10 or 11 or 12
14 (psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent*).ti,ab.

15 ((coping or social) adj2 skill*).ti,ab.
16 (behavi* adj2 therap*).ti,ab.
17 reinforcement psychology.mp.
18 ((cognitive adj3 therapy) or CBT).ti,ab.
19 ((family or couple*) adj2 therapy).ti,ab.
20 stress management training.ti,ab.
21 exp Social Support/
22 contingency management.mp. or exp Contingency Management/
23 CM.ti.
24 self control training.tw.
25 (behavio* adj2 (change or modification)).tw.
26 psychodynamic*.tw.
27 talking therap*.tw.
28 talking therap*.tw.
29 self help group*.tw.
30 (alcoholic* adj2 anonymou*).tw.
31 mutual help.tw.
32 mutual aid.tw.
33 twelve step*.tw.
34 (social network adj2 (intervention* or therap*)).tw.
35 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36 6 and 13 and 35
37 exp Clinical Trials/
38 (random* or (clinical adj3 trial*) or (reserch adj3 design*) or (evaluat adj3 stud*) or (prospective* adj3 stud*)).tw.
39 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).tw.
40 37 or 38 or 39
41 36 and 40

Database: CINAHL(EBSCOhost)
Searched: from 1982 to 14 March 2022 (248 results)

S42 S40 AND S41
S41 (MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (control W5 group) OR MH (crossover design) OR MH (comparative studies) OR AB (cluster W3 RCT)) NOT ((MH animals+ OR MH animal studies OR TI animal model*) NOT MH human)
S40 S7 AND S15 AND S40
S39 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S38 TI(alcoholic* W2 anonymou*) or AB(alcoholic* W2 anonymou*)
S37 (MH "Alcoholics Anonymous")
S36 TI mutual W2 aid OR AB mutual W2 aid
S35 TI mutual W2 help OR AB mutual W2 help
S34 TI(twelve W2 step) or TI(12 W2 step) or AB(twelve W2 step) or AB(12 W2 step
S33 TI twelve W2 step OR AB twelve W2 step
S32 TI self help w2 group* OR AB self help w2 group*
S31 (MH "Alcohol Rehabilitation Programs+")
S30 TX "self help group" OR "self help groups"
S29 TX talking N2 therap*
S28 TX psychodynamic*

S27 TX (behavio* N2 (change OR modification))
S26 TX (behavio* N2 (change OR modification))
S25 "self control training"
S24 TX (Contingency N2 Management) OR TI CM
S23 (MH "Contingency Management") OR "Contingency Management"
S22 ("social network" AND (intervention* OR therap*)) OR AB ("social network" AND (intervention* OR therap*))
S21 (MH "Stress Management") OR TX "stress management training"
S20 TX ((family OR couple*) N2 therapy)
S19 TX cognitive N3 therapy OR TI CBT OR AB CBT
S18 (MH "Reinforcement (Psychology)+")
S17 TX behavi* N2 therap*
S16 TX ((coping OR social) N2 skill*)
S15 TI (psychotherap* OR psychosocial OR voucher OR reinforcement OR motivation* OR contingent*) OR AB (psychotherap* OR psychosocial OR voucher OR reinforcement OR motivation* OR contingent*)
S14 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S13 TX nalmefene
S12 TX Disulfiram
S11 (MH "Disulfiram")
S10 TX Revia OR Vivitrol
S9 (MH "Naltrexone") OR TX Naltrexone
S8 TX Acamprosate OR Campral
S7 (MH "Acamprosate Calcium")
S6 S1 OR S2 OR S3 OR S4 OR S5
S5 TI alcoholic* OR AB alcoholic*
S4 AB alcohol* AND AB (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*))
S3 TI alcohol* AND TI (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*))
S2 (MH "Alcoholism")
S1 (MH "Alcohol-Related Disorders+")

Database: Web of Science
Searched: from 1990 to 14 March 2022 (208 results)

1. TI=((alcohol NEAR/3 (abstin* 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)))
2. TS=(Acamprosate or Campral) OR TS=(Disulfiram or Antabuse) OR TS=(Naltrexone or Revia or Vivitrol) OR TS=(nalmefene)
3. TS=(psychotherap* or psychosocial or voucher or reinforcement or motivation* or contingent*)
4. TS=((coping or social) NEAR/2 skill*)
5. TS=(behavi* NEAR/2 therap*)
6. TS=(cognitive NEAR/3 therapy)
7. TS=((family or couple*) NEAR/2 therapy)
8. TS=("stress management training" or "supportive expressive therapy" or "self control training")
9. TS=("contingency management")
10. TS=("self control training")
11. TS=(behavio* near/2 (change or modification))

12. TS=(psychodynamic*)
13. TS=(talking next therap*)
14. TS=("Self-Help Groups") OR TS=(Self-Help Group)
15. TS=("mutual help" or "mutual AID" or "twelve-step" or "twelve step" or "12-step" or "twelve-steps" or "twelve steps" or "12-steps" or "alcoholic anonymous")
16. #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17. #16 AND #2 AND #1
18. TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* NEAR/2 (allocat* OR assign*)) OR (blind* NEAR/2 (single OR double OR treble OR triple)))
19. #18 AND #17