Alcohol use disorders module – evidence profile ALC1: baclofen for adults with alcohol dependence post-detoxification

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

According to the International Classification of Diseases 11th revision (ICD-11) alcohol use disorder (AUD) comprises two major health conditions: “harmful pattern of alcohol use” and “alcohol dependence” and associated health conditions (e.g. intoxication, withdrawal syndrome and a range of alcohol-induced mental disorders). The harmful pattern of alcohol use is defined as a pattern of continuous, recurrent or sporadic use of a drug that has caused clinically significant damage to a person’s physical or mental health or has resulted in behaviour leading to harm to the health of others. Alcohol dependence is defined as a disorder of regulation of alcohol use arising from repeated or continuous use. The characteristic feature of dependence is a strong internal drive to use alcohol, which manifests itself by: (i) impaired ability to control alcohol use; (ii) increasing priority given to alcohol use over other activities; (iii) persistence of use despite the occurrence of harm or negative consequences. Physiological features of dependence may also be present, including: (i) increased tolerance to the effects of alcohol or a need to use increasing amounts to achieve the same effect; (ii) withdrawal symptoms following cessation of or reduction in the use of alcohol, or (iii) repeated use of the alcohol or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. AUD as a disease category has been introduced in the latest version of the *Diagnostic and statistical manual of mental disorders (DSM), fifth edition* (DSM-5). While the DSM-IV version and ICD-10 subdivided substance-use disorders into dependence and a secondary category, called “abuse” in DSM-IV and “harmful use” in ICD-10, DSM-5 integrates both categories into a single substance-use disorder concept that ranges along a continuum from mild to severe.

AUD belongs 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 leading risks factors for ill-health and is associated with significant burden.

For many years, the main treatments for AUD have been psychosocial strategies, but using only psychosocial treatments has limited success. Medicines such as baclofen could play an important role in treating people with AUD. However, due to questionable evidence, controversial approach and side-effects, there is concern regarding the recommendation of baclofen, especially in non-specialized settings.

This review of use of baclofen to achieve abstinence or to reduce alcohol consumption in people with AUD will provide a systematic integration of the available evidence for health decision-makers, clinicians and patients, and aims to offer illustrative measures for estimating the therapeutic benefits and risks of baclofen while indicating gaps in knowledge and methodological demands for future clinical research.

2. Methodology: PICO question

Question: ALC1. In adults with alcohol dependence post-detoxification, is baclofen effective for relapse prevention and management of alcohol dependence?

Population (P): adults (18 years and older), currently with AUD according to DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV-TR (APA 2000), DSM-5 (APA 2013), and ICD-10 (WHO 1992; WHO 2010) currently drinking or in the post-detoxification phase, i.e. if the detoxification has been completed at least three days before starting treatment.

Intervention (I): baclofen in any dose and route of administration.
Comparator (C): placebo or any other pharmacological relapse prevention treatment, including acamprosate, naltrexone or nalmefene.

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;
- 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, either subjectively or objectively assessed;
- dropouts from treatment: number of participants who did not complete the study protocol;
- dropout from treatment due to adverse events.

List important outcomes:

- craving, as measured by validated scales
- anxiety, as measured by validated scales
- depression, as measured by validated scales.

Subgroups:

- patients already detoxified from at least three days and patients currently drinking
- different dosages of baclofen
- treatment duration (up to 12 weeks; more than 12 weeks).

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

3.1 Search strategy

In 2018, the CDAG published a systematic review on the effect of baclofen on achieving and maintaining abstinence or reducing alcohol consumption on people who are currently drinking or have been recently detoxified. Therefore, we searched for systematic reviews on the effectiveness of baclofen for relapse prevention and management of alcohol dependence on MEDLINE, Embase, PsycInfo, Web of Science Core Collection, Epistemonikos, Global Index Medicus (GIM) and PROSPERO from January 2018 to 14 January 2022. The detailed search strategy for each database is provided in Appendix 2a. The inclusion criteria were: systematic reviews of randomized controlled trials that assessed the effect of baclofen compared to placebo or other pharmacological intervention to achieve and maintain abstinence or reduce alcohol consumption in adults with alcohol dependence.

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 the 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 assessed the methodological quality of retrieved reviews with AMSTAR 2 checklist (https://amstar.ca/Amstar_Checklist.php).

3.5 Analysis of subgroups or subsets

No subgroup analysis was undertaken in Phase 1.

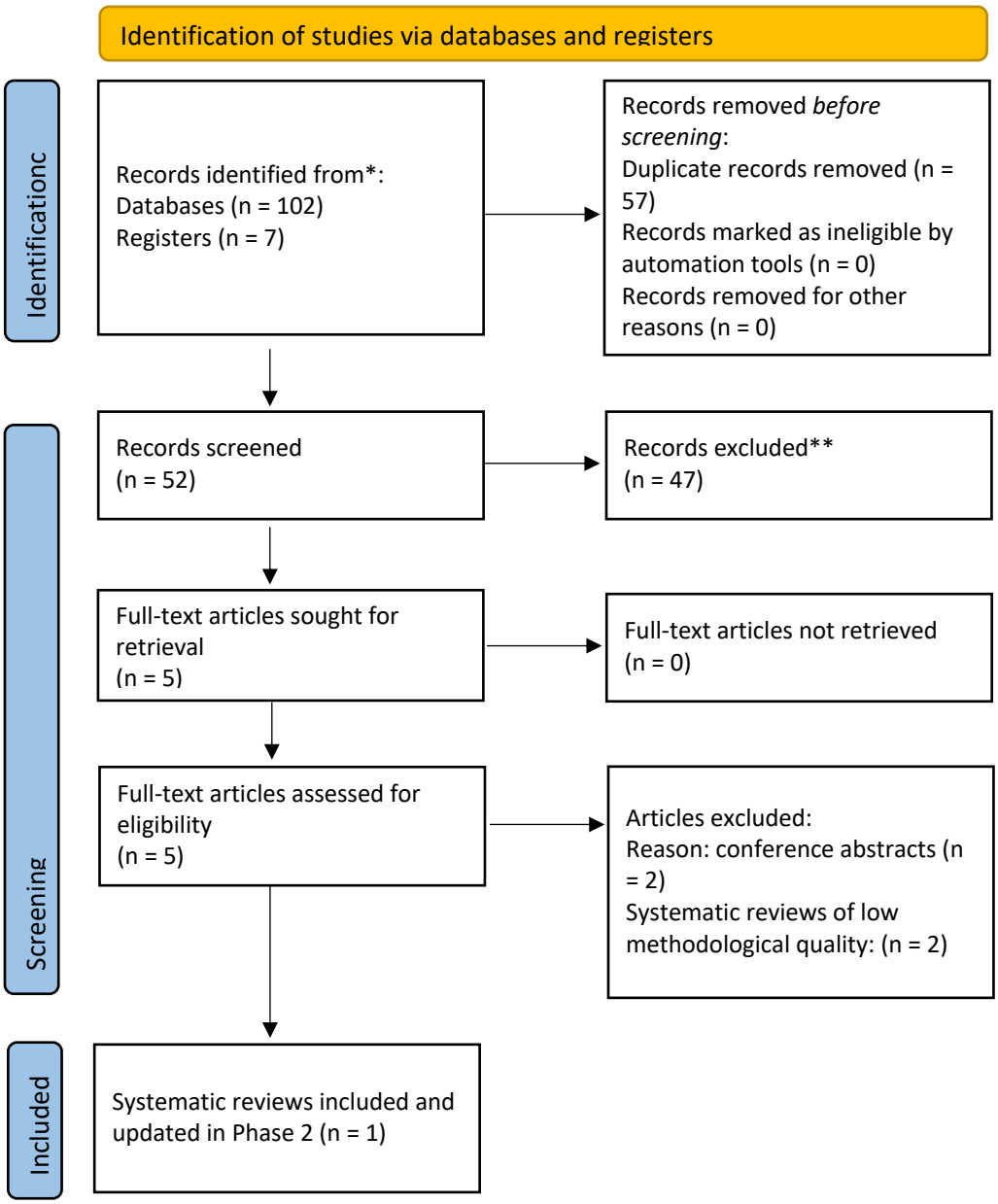
4. Results: Phase 1

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

As shown in Fig. 1, after removing duplicates, we screened 52 titles and abstracts. Five reviews were judged as potentially relevant and acquired in full text. Two were conference abstracts without usable data. We evaluated the methodological quality of the three remaining systematic reviews (Minozzi et al., 2018, Cheng 2020, Bschor 2018). Minozzi et al., 2018 was judged of high methodological quality, Bschor 2018 of low quality and Cheng 2020 of moderate quality. Furthermore, Bschor 2018 measured the effect of baclofen by pooling together all the outcomes that were judged as primary outcomes in the primary studies and measuring the standardized mean difference. This measure is not very useful nor informative from a clinical point of view. Cheng 2020 is a network meta-analysis that compared many different pharmacological and non-pharmacological intervention for alcohol dependence and included just one study on baclofen. The details of methodological quality of the retrieved reviews are shown in Appendix 2b, based on A MeaSurement Tool to Assess systematic Reviews (AMSTAR).

Therefore, we decided that the most appropriate approach would be to update the existing Cochrane review (see section 5).

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.

5. Methodology: Phase 2 – Update of Cochrane systematic review

The existing Cochrane review to be updated was: Minozzi S, Saulle R, Rösner S. Baclofen for alcohol use disorder. Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD012557. DOI: 10.1002/14651858.CD012557.pub2.

5.1 Search strategy

We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL; 2021, issue 11) via Wiley Online

Library, MEDLINE, Ovid, Embase, PsycInfo, Web of Science and CINAHL from January 2018 to 22 November 2021 without language restriction. We searched the following trials registries on 22 November 2021:

ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). Details of the search strategies are reported in Appendix 2c.

The inclusion criteria were: randomized controlled trials that assessed the effect of baclofen any dose compared to placebo or other pharmacological intervention to achieve and maintain abstinence or reduce alcohol consumption in adults with alcohol dependence.

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 was 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 the full text of potentially relevant reviews. Two authors independently extracted relevant data from the included studies.

5.3 Selection and coding of identified records

We used EndNote X7 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 et al., 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

We performed subgroup analysis for:

- people already detoxified and people currently drinking
- different dosage of baclofen
- short and long treatment duration (up to 12 weeks or longer).

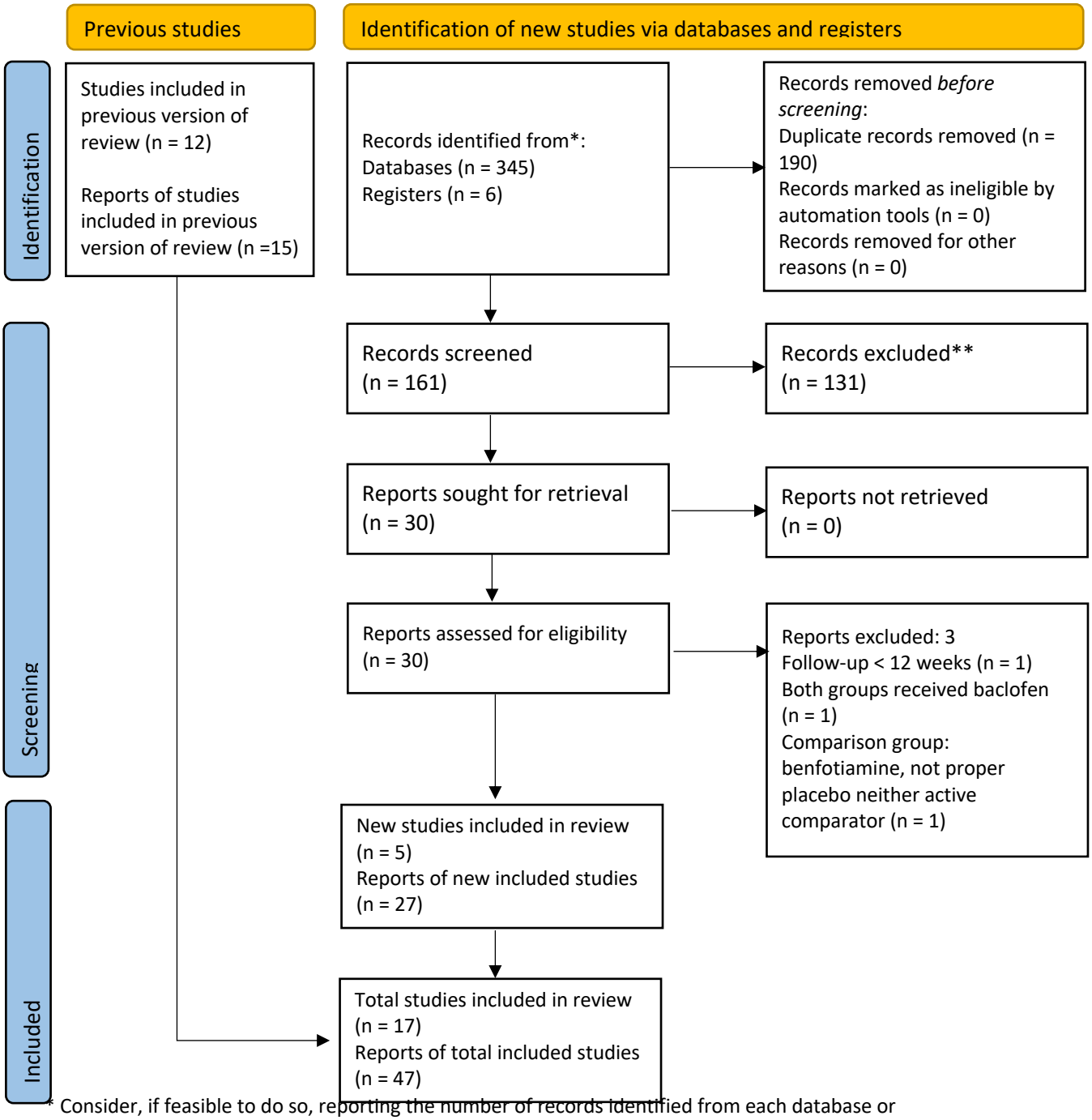
6. Results: Phase 2

6.1 Systematic reviews and/or studies identified by the search process

As shown in Fig. 2, after removing duplicates, we screened 161 titles and abstracts. Thirty records were judged as potentially relevant and were acquired in full text. Three studies were excluded as not fulfilling the inclusion criteria. Five new studies, reported in 27 reports, were finally included.

Overall, 17 studies involving a total of 1818 participants were included in this update.

Fig. 2. PRISMA 2020 flow diagram for updated 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.

6.2 Lists of studies included and excluded

Studies included in Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables/footnotes (n = 17 studies)

Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007;370(9603):1915-22. doi:10.1016/S0140-6736(07)61814-5.

Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedogni G, Caputo F, et al. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. Alcohol Alcohol. 2011;46(3):312-317.

Beraha EM, Salemink E, Goudriaan AE, Bakker A, DeJong D, Smits N, et al. Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: a multicentre randomised, double-blind controlled trial. Eur Neuropsychopharmacol. 2017;26(12):1950-9.

Garbutt JC, Kalka-Juhl L, Kampov-Polevoy AB, Wells S, Nicholas L, Gallop R, et al. Feasibility and tolerability of a combination of naltrexone and baclofen for alcohol dependence: a pilot study. Alcohol Clin Exp Res. 2010;34(6):178A.

Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res. 2010;34(11):1849-57. doi:10.1111/j.1530-0277.2010.01273.x.

Garbutt JC, Kampov-Polevoy AB, Pedersen C, Stansbury M, Jordan R, Willing L, et al. Efficacy and tolerability of baclofen in a U.S. community population with alcohol use disorder: a dose-response, randomized, controlled trial. Neuropsychopharmacology. 2021;46(13):2250-2256.

Hauser P, Fuller B, Ho SB, Thuras P, Kern S, Dieperink E. The safety and efficacy of baclofen to reduce alcohol use in veterans with chronic hepatitis C: a randomized controlled trial. Addiction. 2017;112(7):1173-83. doi:10.1111/add.13787.

Krupitskii EM, Rybakova KV, Kiselev AS, Alekseeva YV, Berntsev VA, Chekhlatyi EI, et al. Efficacy and safety of the use of baclofen in the treatment of alcohol dependent (a double-blind, randomized, placebo-controlled pilot study). Neurosci Behav Physiol. 2017;47(2):153-62. doi:10.1007/s11055-016-0379-6.

Kumar A, Sharma A, Bansal PD, Bahetra M, Gill HK, Kumar R. A comparative study on the safety and efficacy of naltrexone versus baclofen versus acamprosate in the management of alcohol dependence. Indian J Psychiatry. 2020;62(6):650-658.

Leggio L, Zywiak WH, Edwards SM, Tidey JW, SwiN RM, Kenna GA. A preliminary double-blind, placebo-controlled randomized study of baclofen effects in alcoholic smokers. Psychopharmacology. 2015;232(1):233-43. doi:10.1007/s00213-014-3652-9.

Mishra SN, Rath NM, Mishra A, Swain SP, Shukla RK. A study of comparative efficacy of baclofen vs acamprosate in reducing alcohol craving and abuse. Indian J Psychiatry. 2010;52(Suppl 1):S69.

Morley KC, Baillie A, Leung S, Addolorato G, Leggio L, Haber PS. Baclofen for the treatment of alcohol dependence and possible role of comorbid anxiety. Alcohol Alcohol. 2014;49(6):654-660. doi:10.1093/alcalc/agu062.

Morley KC, Baillie A, Fraser I, Furneaux-Bate A, Dore G, Roberts M, et al. Baclofen in the treatment of alcohol dependence with or without liver disease: multisite, randomised, double-blind, placebo-controlled trial. Br J Psychiatry. 2018;212(6):362-369.

Muller CA, Geisel O, Pelz P, Higl V, Kruger J, Stickel A, et al. High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2015;25(8):1167-1177. doi:10.1016/j.euroneuro.2015.04.002

Ponizovsky AM, Rosca P, Aronovich E, Weizman A, Grinshpoon A. Baclofen as add-on to standard psychosocial treatment for alcohol dependence: a randomized, double-blind, placebo-controlled trial with 1 year follow-up. J Subst Abuse Treat. 2015;52:24-30. doi:10.1016/j.jsat.2014.11.007.

Reynaud M, Aubin HJ, Trinquet F, Zakine B, Dano C, Dematteis M, et al. A randomized, placebo-controlled study of high-dose baclofen in alcohol-dependent patients – the ALPADIR Study. Alcohol Alcohol. 2017;52(4):439-446.

Rigal L, Sidorkiewicz S, Tréluyer JM, Perrodeau E, Le Jeunne C, Porcher R, Jaury P. Titrated baclofen for high-risk alcohol consumption: a randomized placebo-controlled trial in out-patients with 1-year follow-up. Addiction. 2020;115(7):1265-1276.

Studies excluded from GRADE tables/footnotes (n = 6 studies)

Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri M, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomised controlled study. Alcohol Alcohol. 2002;37:504-8. doi:10.1093/alcalc/37.5.504.

Flannery BA, Garbutt JC, Cody MW, Renn W, Grace K, Osborne M, et al. Baclofen for alcohol dependence: a preliminary open label study. Alcohol Clin Exp Res. 2004;28(10):1517-23. doi:10.1097/01.ALC.0000141812.06529.66.

Gupta M, Verma P, Rastogi R, Arora S, Elwadhi D. Randomized open-label trial of baclofen for relapse prevention in alcohol dependence. Am J Drug Alcohol Abuse. 2017;43(3):324-331. doi:10.1080/00952990.2016.1247792.

Kumar R, Kumar KJ, Benegal V, Roopesh BN, Ravi GS. Integrated intervention program for alcoholism improves impulsiveness and disadvantageous reward processing/risk-taking. Indian J Psychiatry. 2020;62(4):384-391.

Leggio L, Kenna G, Zywiak W, Edwards S, Fricchione S, Taveres T. Baclofen as a novel pharmacotherapy for alcohol dependence: preliminary findings from a human laboratory double-blind placebo-controlled randomized study [abstract]. Neuropsychopharmacology. 2011;36:Poster #187.

Leggio L, Zywiak WH, McGeary JE, Edwards S, Fricchione SR, ShoaK JR, et al. A human laboratory pilot study with baclofen in alcoholic individuals. Pharmacol Biochem Behav. 2013;103(4):784-91. doi:10.1016/j.pbb.2012.11.013.

Table 1. PICO Table for the updated systematic review

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
1	Baclofen vs placebo	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.	Agabio R, Saulle R, Rösner S, Minozzi S. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2022 update, Submitted for publication CD012557	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Frequency of use: measured as percentage of 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.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Amount of use: number of drinks per drinking day or drinking occasion.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Adverse events: measured by number of people with at least one adverse event, either subjectively or objectively assessed.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Dropouts from treatment: number of participants who did not complete the study protocol	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Dropout from treatment due to adverse events.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
		Use of primary substance of abuse (longest period of abstinence).	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Craving.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Anxiety.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Depression.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
2	Baclofen vs acamprosate	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.	Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Frequency of use: measured as percentage of 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.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Amount of use: number of drinks per drinking day or drinking occasion.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Adverse events: measured by number of people with at least one adverse event, either subjectively or objectively assessed.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
		Dropouts from treatment: number of participants who did not complete the study protocol.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Dropout from treatment due to adverse events.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Use of primary substance of abuse (longest period of abstinence).	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Craving.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Anxiety.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Depression.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
3	Baclofen vs naltrexone	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.	Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Frequency of use: measured as percentage of 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.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
		Amount of use: number of drinks per drinking day or drinking occasion.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Adverse events: measured by number of people with at least one adverse event, either subjectively or objectively assessed.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Dropouts from treatment: number of participants who did not complete the study protocol.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Dropout from treatment due to adverse events.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Use of primary substance of abuse (longest period of abstinence).	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Craving.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Anxiety.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.
		Depression.	- Agabio et al., 2022 update	No available recent meta-analytic evidence on this outcome (N/A). We updated the Cochrane Review by Minozzi et al., 2018.

6.3 Narrative description of studies that contributed to GRADE analysis[1]

We included 17 RCTs involving a total of 1818 participants. The mean study size was 107 participants, ranging from 30 in Leggio et al., 2015 to 320 in Reynaud et al., 2017. Six studies (Beraha et al., 2016-LD; Garbutt 2021-LD; Garbutt 2021-MD; Hauser 2017;Morley 2018-LD; Morley 2018-MD; Reynaud 2017) recruited more than 100 participants. The mean age of participants was 46.5 years, and there were more men (69.6%) than women. All studies except one recruited participants with a diagnosis of alcohol dependence according to the DSM IV or ICD 10 criteria. The study that did not require the diagnosis of alcohol dependence (Rigal 2020) recruited at high risk drinkers according to the WHO definition of at risk drinking (alcohol consumption > 40 g/day or single occasion and/or > 280 g/week for women; > 60 g/day or single occasion and/or > 420 g/week for men; WHO 2000). These participants to be included also had to voluntarily consulting a physician for their alcohol problem and expressing the desire to achieve abstinence or reducing alcohol consumption. Accordingly, we assumed that these participants met at least three criteria for AUD (alcohol consumption in higher amounts than intended; desire to cut down or control alcohol use; craving; APA 2013) and the study was included. Three studies took place in the USA (Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Garbutt 2021-LD; Garbutt 2021-MD), two studies in Australia (Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD), France (Reynaud 2017; Rigal 2020), Italy (Addolorato 2007; Addolorato 2011-LD; Addolorato 2011-MD), and India (Kumar 2020; Mishra 2010); one in Germany (Muller 2015), Israel (Ponizovsky 2015), and the Netherlands (Beraha 2016-HD; Beraha 2016-LD).

All trials excluded patients with substance use disorders by substances other than alcohol or nicotine. One trail recruited participants dependent by both alcohol and nicotine (Leggio 2015). All trials excluded participants with comorbid severe mental disorders but five studies recruited participants under stable doses of antidepressants (Beraha 2016-LD; Beraha 2016-HD; Garbutt 2010a; Garbutt 2021-LD; Garbutt 2021-MD; Morley 2018-LD; Morley 2018-MD; Reynaud 2017). Three studies recruited patients with severe liver disease (i.e. cirrhosis including Child-Pugh, hepatitis B virus-positive, hepatitis C virus-positive; Addolorato 2007; chronic HCV Hauser 2017; alcoholic liver disease Morley 2018-LD; Morley 2018-MD).

Most studies required participants to abstain from alcohol for at least three days before the beginning of the pharmacological treatment (Addolorato 2007; Addolorato 2011-LD; Addolorato 2011-MD; Beraha 2016-HD; Beraha 2016-LD; Garbutt 2010a; Krupitskii 2017; Kumar 2020; Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD; Muller 2015; Reynaud 2017). In these studies abstinence ranged from three days to 28 days (Beraha 2016-HD; Beraha 2016-LD). Seven trials recruited participants who were still drinking at the beginning of the pharmacological treatment (Garbutt 2010b1; Garbutt 2010b2; Garbutt 2021-LD; Garbutt 2021-MD; Hauser 2017; Leggio 2015; Mishra 2010; Ponizovsky 2015; Rigal 2020).

Most trials were 12 weeks long (Addolorato 2007; Addolorato 2011-LD; Addolorato 2011-MD; Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Hauser 2017; Krupitskii 2017; Leggio 2015; Mishra 2010; Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD; Muller 2015; Ponizovsky 2015) while five trials were longer than 12 weeks (16 weeks: Beraha 2016-HD; Beraha 2016-LD; Garbutt 2021-LD; Garbutt 2021-MD; 24 weeks: Kumar 2020; 26 weeks: Reynaud 2017; 48 weeks: Rigal 2020). The mean duration of the interventions was 16.1 weeks (range 12 to 48 weeks).

[1] Please note that this section includes the abstracts as taken directly from the publications.

Types of interventions

In the included studies, baclofen was administered in daily doses ranging from 30 to 300 mg. Ten trials administered low daily doses (Addolorato 2007; Addolorato 2011-LD; Beraha 2016-LD; Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Garbutt 2021-LD; Hauser 2017; Mishra 2010; Morley 2014-LD; Morley 2018-LD), eight trials medium daily doses (Addolorato 2011-MD; Garbutt 2021-MD; Krupitskii 2017; Kumar 2020; Leggio 2015; Morley 2014-MD; Morley 2018-MD; Ponizovsky 2015), and four trials high daily doses of baclofen (Beraha 2016-HD; Muller 2015; Reynaud 2017; Rigal 2020).

Most trials administered fixed doses of baclofen, starting with a daily dose of 5 mg , three times a days, and gradually increasing up to 30–80 mg/day. Four trials administered flexible doses of baclofen starting from low daily doses and progressively increasing up to 300 mg, according to the beneficial and/or unwanted effects (Beraha 2016-HD; Muller 2015; Reynaud 2017; Rigal 2020).

In all but one study (Mishra 2010), participants in both the baclofen and placebo groups received psychosocial treatment or counselling of various intensity.

Types of comparisons

Most trials compared baclofen to placebo (Addolorato 2007; Addolorato 2011-LD; Addolorato 2011-MD; Beraha 2016-HD; Beraha 2016-LD; Garbutt 2010a; Garbutt 2010b1; Garbutt 2021-LD; Garbutt 2021-MD; Hauser 2017; Krupitskii 2017; Leggio 2015; Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD; Muller 2015; Ponizovsky 2015; Reynaud 2017; Rigal 2020). Two studies compared baclofen to naltrexone (Garbutt 2010b2; Kumar 2020) and two trials compared baclofen to acamprosate (Kumar 2020; Mishra 2010).

6.4 Grading the evidence

Measures adopted by the meta-analyses conducted to evaluate the benefits and side-effects of medications.

CI: Confidence interval (measure of uncertainty of the estimate; when narrow, uncertainty is smaller, when wider, uncertainty is greater) (Higgins et al., 2021)

Hedges' *g*:* SMD (see below) in social science; according to this value, effects are ranked as "small" (0.2), "medium" (around 0.5) or "large" (above 0.8) (Higgins et al., 2021)

MD*: Mean difference of continuous outcomes (e.g. drinks per day); 0 = no difference between treatments; values > 0 and < 0 indicate changes compared to control (Higgins et al., 2021)

RR*: Risk ratio or relative risk of dichotomous outcomes (e.g. number of abstinent participants); 1 = no difference between treatments; values > 1 and < 1 indicate the increase and/or reduction of the risk (e.g. RR = 3, the event with medication is 3 times more likely than with control; RR = 0.25, medication decreases the risk of events by 75%) (Higgins et al., 2021)

SD: Standard deviation (measure of variability around the mean; low SD indicate all values close to the mean; high SD values indicate high variability) (Higgins et al., 2021)

SMD*: Standardized mean difference of continuous outcomes (MD/pooled SD) used to pool data when the studies assess the same outcome using different instruments (Higgins et al., 2021)

*Expressed with a measure of uncertainty (Higgins et al., 2021).

6.5 Evidence profiles

Table 2a: Evidence profile baclofen versus placebo
Author(s): Agabio R, Saulle R, Rosner S, Minozzi S.
Date:
Question: Should baclofen versus placebo be used to subjects with alcohol use disorders?
Setting: Outpatients
Reference: Agabio R, Saulle R, Rösner S, Minozzi S. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2023(1):CD012557. doi:10.1002/14651858.CD012557.pub3.

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Relapse: return to any drinking at end of treatment												
12	randomized trials	not serious	serious[a]	not serious	not serious	none	414/584 (70.9%)	386/473 (81.6%)	RR 0.87 (0.77 to 0.99)	106 fewer per 1000 (from 188 fewer to 8 fewer)	⨁⨁⨁◯ Moderate	
Frequency of use: % days abstinence at end of treatment												
16	randomized trials	not serious	not serious	not serious	not serious	none	696	577	-	MD 9.07 higher (3.3 higher to 14.85 higher)	⨁⨁⨁⨁ High	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of use: heavy drinking days at end of treatment												
13	randomized trials	not serious	serious[b]	not serious	not serious	none	475	365	-	SMD 0.18 lower (0.48 lower to 0.11 higher)	⨁⨁⨁◯ Moderate	
Amount of use: drink per drinking days at end of treatment												
9	randomized trials	serious[c]	not serious	not serious	not serious	none	249	143	-	MD 0.45 lower (1.2 lower to 0.3 higher)	⨁⨁⨁◯ Moderate	
Adverse events: number of participants with at least one adverse event at end of treatment												
10	randomized trials	not serious	not serious	not serious	not serious	none	265/414 (64.0%)	206/324 (63.6%)	RR 1.05 (0.99 to 1.11)	32 more per 1000 (from 6 fewer to 70 more)	⨁⨁⨁⨁ High	
Dropout at end of treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute (95% CI)		
17	randomized trials	not serious	not serious	not serious	not serious	none	295/846 (34.9%)	301/717 (42.0%)	RR 0.88 (0.74 to 1.03)	50 fewer per 1000 (from 109 fewer to 13 more)	⨁⨁⨁⨁ High	
Dropout due to adverse events												
16	randomized trials	not serious	not serious	not serious	not serious	none	56/814 (6.9%)	30/685 (4.4%)	RR 1.39 (0.89 to 2.18)	17 more per 1000 (from 5 fewer to 52 more)	⨁⨁⨁⨁ High	

[a]Downgraded of one level for inconsistency: $I^2 = 73\%$

[b]Downgraded of one level for inconsistency: $I^2 = 71\%$

[c]Downgraded of one level for risk of bias: one study at high risk for attrition and reporting bias.

Table 2a1. Baclofen versus placebo: Subgroup analyses for different doses (low, medium and high), duration of treatment (12 weeks; longer than 12 weeks), and detoxified versus non-detoxified participants

#	Primary outcome	N studies	N participants	Risk ratio/MD/SMD	Heterogeneity	P	GRADE/ Test for subgroup differences
1	Relapse: return to any drinking at end of treatment (all studies)	12	1.057	RR = 0.87 (0.77, 0.99)	I^2 = 73%	*P* = 0.03	Moderate
	• Low doses	6	463	RR = 0.82 (0.64, 1.04)	I^2 = 85%	*P* = 0.10	
	• Medium doses	3	129	RR = 0.73 (0.37, 1.45)	I^2 = 82%	*P* = 0.37	Chi^2 = 0.54, df = 2 (*P* = 0.77), I^2 = 0%
	• High doses	3	465	RR = 0.90 (0.71, 1.15)	I^2 = 58%	*P* = 0.40	
	○ 12-week	7	466	RR = 0.63 (0.40, 1.00)	I^2 = 89%	*P* = 0.05	Chi^2 = 3.40, df = 1 (*P* = 0.07), I^2 = 70.5%
	○ Longer than 12 weeks	5	591	RR = 0.98 (0.93, 1.03)	I^2 = 0%	*P* = 0.43	
	▪ Detoxified	9	757	RR = 0.73 (0.55, 0.95)	I^2 =76%	*P* = 0.02	Chi^2 = 4.94, df = 1 (*P* = 0.03), I^2 = 79.8%
	▪ Non-detoxified	3	300	RR = 1.00 (0.94, 1.06)	I^2 = 0%	*P* = 0.90	
2	Frequency of use: % days abstinence at end of treatment (all studies)	16	1.273	MD = 9.07 (3.30, 14.85)	I^2 = 66%	*P* = 0.002	High
	• Low doses	8	583	MD = 10.59 (0.77, 20.41)	I^2 =64%	*P* = 0.03	
	• Medium doses	5	225	MD = 7.14 (-3.10, 17.38)	I^2 = 52%	*P* = 0.17	Chi^2 = 0.42, df = 2 (*P* = 0.81), I^2 = 0%
	• High doses	3	465	MD = 11.09 (4.39, 17.80)	I^2 = 6%	*P* = 0.001	

#	Primary outcome	N studies	N participants	Risk ratio/MD/SMD	Heterogeneity	P	GRADE/ Test for subgroup differences
	○ 12-week	11	682	MD = 10.90 (3.17, 18.62)	I^2 = 70%	*P* = 0.006	Chi² = 0.29, df = 1 (*P* = 0.59), I^2 = 0%
	○ Longer than 12 weeks	5	591	MD = 8.05 (1.09, 15.01)	I^2 = 18%	*P* = 0.02	
	▪ Detoxified	10	549	MD = 11.79 (3.22, 20.29)	I^2 = 54%	*P* = 0.007	Chi² = 0.96, df = 1 (*P* = 0.33), I^2 = 0%
	▪ Non-detoxified	6	724	MD = 6.03 (-1.59, 13.64)	I^2 = 70%	*P* = 0.12	
3	Frequency of use: % of heavy drinking days at end of treatment (all studies)	13	840	SMD = -0.18 (-0.48, 0.11)	I^2 = 71%	*P* = 0.22	Moderate
	• Low doses	6	278	SMD = 0.10 (-0.15, 0.34)	I^2 = 0%	*P* = 0.44	Chi² = 4.59, df = 2 (*P* = 0.10), I^2 = 56.4%
	• Medium doses	6	242	SMD = -0.47 (-1.15, 0.20)	I^2 = 83%	*P* = 0.17	
	• High doses	1	320	SMD = -0.21 (-0.43, 0.01)	NA	*P* = 0.06	
	○ 12-week	10	400	SMD = -0.07 (-0.27, 0.13)	I^2 = 0%	*P* = 0.51	Chi² = 0.64, df = 1 (*P* = 0.42), I^2 = 0%
	○ Longer than 12 weeks	3	440	SMD = -0.54 (-1.68, 0.60)	I^2 = 95%	*P* = 0.35	
	▪ Detoxified	8	296	SMD = -0.08 (-0.32, 0.16)	I^2 = 0%	*P* = 0.52	Chi² = 0.56, df = 1 (*P* = 0.45), I^2 = 0%
	▪ Non-detoxified	5	544	SMD = -0.34 (-0.98, 0.30)	I^2 = 89%	*P* = 0.30	

#	Primary outcome	N studies	N participants	Risk ratio/MD/SMD	Heterogeneity	P	GRADE/ Test for subgroup differences
4	Amount of use: drink per drinking days at end of treatment (all studies)	9	392	MD = -0.45 (-1.20, 0.30)	I^2 = 31%	*P* = 0.24	Moderate
	• Low doses	5	242	MD = -0.06 (-1.33, 1.22)	I^2 = 46%	*P* = 0.93	
	• Medium doses	4	150	MD = -0.64 (-1.95, 0.68)	I^2 = 27%	*P* = 0.34	Chi² = 0.39, df = 1 (*P* = 0.53), I^2 = 0%
	• High doses	-	-	-	-	-	
	○ 12-week	7	272	MD = -0.36 (-1.29, 0.57)	I^2 = 46%	*P* = 0.45	Chi² = 0.02, df = 1 (*P* = 0.90), I^2 = 0%
	○ Longer than 12 weeks	2	120	MD = -0.49 (-2.31, 1.32)	I^2 = 0%	*P* = 0.59	
	▪ Detoxified	7	272	MD = -0.36 (-1.29, 0.57)	I^2 = 46%	*P* = 0.45	Chi² = 0.02, df = 1 (*P* = 0.90), I^2 = 0%
	▪ Non-detoxified	2	120	MD = -0.49 (-2.31, 1.32)	I^2 = 0%	*P* = 0.59	
5	Adverse events: number of participants with at least one adverse event at the end of treatment (all studies)	10	738	RR = 1.05 (0.99, 1.11)	I^2 = 0%	*P* = 0.08	High
	▪ Low doses	5	260	RR = 1.23 (0.92, 1.64)	I^2 = 0%	*P* = 0.16	
	▪ Medium doses	4	162	RR = 0.90 (0.63, 1.28)	I^2 = 0%	*P* = 0.55	Chi² = 1.93, df = 2 (*P* = 0.38), I^2 = 0%
	▪ High doses	1	316	RR = 1.05 (0.99, 1.11)	NA	*P* = 0.10	
	○ 12-week	7	302	RR =0.99 (0.70, 1.39)	I^2 = 0%	*P* = 0.95	

#	Primary outcome	N studies	N participants	Risk ratio/MD/SMD	Heterogeneity	P	GRADE/ Test for subgroup differences
	○ Longer than 12 weeks	3	436	RR =1.05 (1.00, 1.11)	I^2 = 0%	*P* = 0.07	Chi^2 = 0.12, df = 1 (*P* = 0.72), I^2 = 0%
	▪ Detoxified	7	578	RR = 1.05 (0.99, 1.11)	I^2 = 0%	*P* = 0.10	Chi^2 = 0.15, df = 1 (*P* = 0.70), I^2 = 0%
	▪ Non-detoxified	3	160	RR = 1.11 (0.84, 1.45)	I^2 = 0%	*P* = 0.47	
6	Dropout at the end of treatment (all studies)	17	1563	RR = 0.88 (0.74, 1.03)	I^2 = 18%	*P* = 0.12	High
	▪ Low doses	8	564	RR = 0.96 (0.70, 1.32)	I^2 = 16%	*P* = 0.80	Chi^2 = 2.97, df = 2 (*P* = 0.23), I^2 = 32.6%
	▪ Medium doses	5	214	RR = 1.03 (0.65, 1.61)	I^2 = 19%	*P* = 0.91	
	▪ High doses	4	785	RR = 0.76 (0.67, 0.87)	I^2 = 0%	P < 0.0001	
	○ 12-week	11	652	RR = 0.98 (0.73, 1.31)	I^2 = 13%	*P* = 0.88	Chi^2 = 2.03, df = 1 (*P* = 0.15), I^2 = 50.8%
	○ Longer than 12 weeks	6	911	RR = 0.78 (0.69, 0.88)	I^2 = 0%	*P* < 0.0001	
	▪ Detoxified	12	879	RR = 0.87 (0.71, 1.07)	I^2 = 0%	*P* = 0.19	Chi^2 = 0.12, df = 1 (*P* = 0.72), I^2 = 0%
	▪ Non-detoxified	5	684	RR = 0.93 (0.69, 1.28)	I^2 = 52%	*P* = 0.67	
7	Dropout due to adverse events (all studies)	16	1499	RR = 1.39 (0.89, 2.18)	I^2 = 0%	*P* = 0.14	High
	▪ Low doses	8	564	RR = 1.81 (0.61, 5.32)	I^2 = 0%	*P* = 0.28	

#	Primary outcome	N studies	N participants	Risk ratio/MD/SMD	Heterogeneity	P	GRADE/ Test for subgroup differences
	▪ Medium doses	4	150	RR = 6.11 (0.82, 45.25)	I^2 = 0%	*P* = 0.08	Chi^2 = 2.54, df = 2 (*P* = 0.28), I^2 = 21.4%
	▪ High doses	4	785	RR = 1.21 (0.68, 2.13)	I^2 = 13%	*P* = 0.52	
	○ 12-week	10	588	RR =3.00 (0.93, 9.66)	I^2 = 0%	*P* = 0.07	Chi^2 = 1.93, df = 1 (*P* = 0.17), I^2 = 48.1%
	○ Longer than 12 weeks	6	911	RR =1.22 (0.76, 1.98)	I^2 = 0%	*P* = 0.41	
	▪ Detoxified	12	879	RR =1.08 (0.59, 1.98)	I^2 = 0%	*P* = 0.80	Chi^2 = 1.45, df = 1 (*P* = 0.23), I^2 = 31.2%
	▪ Non-detoxified	4	6620	RR =1.87 (0.97, 3.61)	I^2 = 0%	*P* = 0.06	

Table 2b. Evidence profile baclofen versus acamprosate
Author(s): Agabio R, Saulle R, Rosner S, Minozzi S.
Date:
Question: Should baclofen versus acamprosate be used to subjects with alcohol use disorders?
Setting: Outpatients
Reference List: Agabio R, Saulle R, Rösner S, Minozzi S. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2023(1):CD012557. doi:10.1002/14651858.CD012557.pub3.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baclofen	acamprosate	Relative (95% CI)	Absolute (95% CI)		
Relapse: return to any drinking at end of treatment												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	15/30 (50.0%)	12/30 (40.0%)	RR 1.25 (0.71 to 2.20)	100 more per 1000 (from 116 fewer to 480 more)	⨁◯◯◯ Very low	
Adverse events: number of participants with at least one adverse event at end of treatment												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	5/30 (16.7%)	8/30 (26.7%)	RR 0.63 (0.23 to 1.69)	99 fewer per 1000 (from 205 fewer to 184 more)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baclofen	acamprosate	Relative (95% CI)	Absolute (95% CI)		
Dropout at end of treatment												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	5/30 (16.7%)	9/30 (30.0%)	RR 0.56 (0.21 to 1.46)	132 fewer per 1000 (from 237 fewer to 138 more)	⨁◯◯◯ Very low	
Dropout due to adverse events												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/30 (0.0%)	1/30 (3.3%)	RR 0.33 (0.01 to 7.87)	22 fewer per 1000 (from 33 fewer to 229 more)	⨁◯◯◯ Very low	

[a] Downgraded one level for risk of bias: One study at high risk of performance, detection, and attrition bias and at unclear risk of selection bias.
[b] Downgraded two levels for imprecision: less than 100 events.

Table 2c: Evidence Profile Baclofen versus naltrexone
Author(s): Agabio R, Saulle R, Rosner S, Minozzi S.
Date:
Question: Should baclofen versus naltrexone be used to subjects with alcohol use disorders?
Setting: Outpatients
Reference List: Agabio R, Saulle R, Rösner S, Minozzi S. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2023(1):CD012557. doi:10.1002/14651858.CD012557.pub3.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Naltrexone	Relative (95% CI)	Absolute (95% CI)		
Relapse: return to any drinking at end of treatment.												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	15/30 (50.0%)	6/30 (20.0%)	RR 2.50 (1.12 to 5.56)	300 more per 1000 (from 24 more to 912 more)	⨁◯◯◯ Very low	
Adverse events: number of participants with at least one adverse event at end of treatment												
2	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	6/40 (15.0%)	18/40 (45.0%)	RR 0.35 (0.15 to 0.80)	293 fewer per 1000 (from 383 fewer to 90 fewer)	⨁◯◯◯ Very low	
Dropout at end of treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Naltrexone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	5/30 (16.7%)	5/30 (16.7%)	RR 1.00 (0.32 to 3.10)	0 fewer per 1000 (from 113 fewer to 350 more)	⨁◯◯◯ Very low	

[a] Downgraded one level for risk of bias: One study at high risk of performance, detection, and attrition bias
[b]Downgraded two levels due to imprecision: less than 100 events

Key for the categories of quality of evidence: ⨁⨁⨁⨁ (High), ⨁⨁⨁◯ (Moderate), ⨁⨁◯◯ (Low), ⨁◯◯◯ (Very low). Examples are provided in the table.
[2]Recommendation: two 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.

6.6 Additional evidence not mentioned in GRADE tables

We did not include Leggio et al., 2015 (30 participants) in meta-analyses and GRADE table because its results were substantially different from the other studies and were responsible of the high heterogeneity in some results. Participants included in this study were both nicotine and alcohol dependent, the study had the aim to obtain both smoking and drinking abstinence and the study was conducted in a laboratory setting.

Relapse: return to any drinking at the end of treatment: RR -0.53, 95% CI: -3.11 to 2.05
Frequency of use: percentage of days abstinent at the end of treatment: MD -19.00, 95% CI: -21.18 to -16.82.
Frequency of use: percentage of heavy drinking days at the end of treatment: MD -2.00, 95% CI: -13.22 to 9.22).
Amount of use: drink per drinking days at the end of treatment: MD -0.53, 95% CI: -3.11 to 2.05
Adverse events: number of participants with at least one side-effect at the end of treatment: RR 1.15, 95% CI: 0.91 to 1.44
Dropouts at the end of treatment: RR 0.50, 95% CI: 0.11 to 2.33.

7. From evidence to recommendations

7.1 Summary of findings

Table 3. Summary of findings table

GRADE table	Source	Outcome	Number of studies	Effects	Certainty of evidence
GRADE table 1 baclofen vs placebo	Agabio et al., 2023. Baclofen for alcohol use disorder. Cochrane Review.	Relapse: return to any drinking at end of treatment	12 (1057 participants)	RR 0.87 (95% CI: 0.77 to 0.99) Compared to placebo, baclofen probably decreases the risk to relapse to any drinking	⊕⊕⊕◯ Moderate[a]
		Frequency of use: % days abstinence at end of treatment	16 (1253 participants)	MD 9.07 (95% CI: 3.3 to 14.85) Compared to placebo, baclofen increases the % of days abstinent	⊕⊕⊕⊕ High
		Frequency of use: heavy drinking days at end of treatment	13 (840 participants)	SMD -0.18 (95% CI: -0.48 to 0.11) Compared to placebo, baclofen probably does not reduce heavy drinking days	⊕⊕⊕◯ Moderate[b]
		Amount of use: drink per drinking days at end of treatment	8 (392 participants)	MD -0.45 (95% CI: -1.2 to 0.3) Compared to placebo, baclofen probably does not reduce the number of drinks per drinking days	⊕⊕⊕◯ Moderate[c]
		Adverse events: number of participants with at least one adverse	10 (738 participants)	RR 1.05 (95% CI: 0.99 to 1.11) Compared to placebo, baclofen does not increase the number of participants	⊕⊕⊕⊕ High

GRADE table	Source	Outcome	Number of studies	Effects	Certainty of evidence
		event at end of treatment		with at least one adverse event at the end of treatment	
		Dropout end of treatment	17 (1563 participants)	RR 0.88 (95% CI: 0.74 to 1.03) Compared to placebo, baclofen does not increase the number of participants who dropout at the end of treatment	⨁⨁⨁⨁ High
		Dropout due to adverse events	16 (1499 participants)	RR 1.39 (95% CI: 0.89 to 2.18) Compared to placebo, baclofen does not increase the number of dropouts due to adverse events	⨁⨁⨁⨁ High

[a]Downgraded of one level for inconsistency: I^2 = 73%
[b]Downgraded of one level for inconsistency: I^2 = 71%
[c]Downgraded of one level for risk of bias: one study at high risk for attrition and reporting bias.

GRADE table	Source	Outcome	Number of studies	Effects	Certainty of evidence
GRADE table 2 baclofen vs acamprosate	Agabio et al., 2022. Baclofen for alcohol use disorder. Cochrane Review.	Relapse: return to any drinking at end of treatment	1 (60 participants)	RR 1.25 (95% CI: 0.71 to 2.20) It is uncertain whether baclofen and acamprosate differ in the return to any drinking	⊕◯◯◯ Very low[a,b]
		Adverse events: number of participants with at least one adverse event at end of treatment	1 (60 participants)	RR 0.63 (95% CI: 0.23 to 1.69) It is uncertain whether baclofen and acamprosate differ in the number of participants with at least one adverse event at the end of treatment	⊕◯◯◯ Very low[a,b]
		Dropout end of treatment	1 (60 participants)	RR 0.56 (95% CI: 0.21 to 1.46) It is uncertain whether baclofen and acamprosate differ in the dropout at the end of treatment	⊕◯◯◯ Very low[a,b]
		Dropout due to adverse events	1 (60 participants)	RR 0.33 (95% CI: 0.01 to 7.87) It is uncertain whether baclofen and acamprosate differ in the dropout due to adverse events at the end of treatment	⊕◯◯◯ Very low[a,b]

[a] Downgraded one level for risk of bias: one study at high risk of performance, detection, and attrition bias and at unclear risk of selection bias.
[b]Downgraded two levels for imprecision: less than 100 events.

GRADE table	Source	Outcome	Number of studies	Effects	Certainty of evidence
GRADE table 3 baclofen vs naltrexone	Agabio et al., 2022. Baclofen for alcohol use disorder. Cochrane Review.	Relapse: return to any drinking at end of treatment	1 (60 participants)	RR 2.50 (95% CI: 1.12 to 5.56) It is uncertain whether baclofen and neltrexone differ in the return to any drinking	⨁◯◯◯ Very low[a,b]
		Adverse events: number of participants with at least one adverse event at end of treatment	2 (80 participants)	RR 0.35 (95% CI: 0.15 to 0.80) It is uncertain whether baclofen and naltrexone differ in the number of participants with at least one adverse event at the end of treatment	⨁◯◯◯ Very low[a,b]
		Dropout end of treatment	1 (60 participants)	RR 1.00 (95%CI: 0.32 to 3.10) It is uncertain whether baclofen and naltrexone differ in the dropout at the end of treatment	⨁◯◯◯ Very low[a,b]

[a] Downgraded one level for risk of bias: one study at high risk of performance, detection, and attrition bias.
[b] Downgraded two levels due to imprecision: less than 100 events.

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 (i.e. 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 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	
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	Baclofen vs Placebo (at the end of treatment): Effect: • Probably decreases the risk to relapse to any drinking (106 fewer per 1000; Moderate certainty) • Increases the % of days abstinent (9.07% abstinent days more; High certainty) No effect:	Subgroup analysis Baclofen vs placebo (at the end of treatment): • Reduce return to any drinking for detoxified patients • Increases the % of days abstinent for low/high dosages, 12 weeks/longer than 12 weeks duration of treatment, and for detoxified patients • Reduces dropouts from treatment in high dosages

Criteria, questions	Judgement	Research evidence	Additional considerations
		• Probably does not reduce heavy drinking days (Moderate certainty) • Probably does not reduce the number of drinks per drinking days (Moderate certainty) • Does not increase the number of participants who dropout (High certainty) Baclofen vs acamprosate (at the end of treatment): • It is uncertain whether baclofen and acamprosate differ in the return to any drinking (Very low certainty) • It is uncertain whether baclofen and acamprosate differ in the dropout (Very low certainty) Baclofen vs Naltrexone (at the end of treatment): • It is uncertain whether baclofen and naltrexone differ in the return to any drinking (Very low certainty)	and in studies with duration of treatment longer than 12 weeks

Criteria, questions	Judgement	Research evidence	Additional considerations
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	Baclofen vs Placebo (at the end of treatment): • Does not increase the number of participants with at least one adverse event (High certainty) • Does not increase the number of dropouts due to adverse events (High certainty) Baclofen vs Acamprosate (at the end of treatment): • It is uncertain whether baclofen and acamprosate differ in the number of participants with at least one adverse event (Very low certainty) • It is uncertain whether baclofen and acamprosate differ in the dropout due to adverse events (Very low certainty) Baclofen vs Naltrexone (at the end of treatment): • It is uncertain whether baclofen and naltrexone	Subgroup analysis Baclofen VS placebo (at the end of treatment): • Reduces dropouts from treatment in high dosages and in studies with duration of treatment longer than 12 weeks • No difference was identified for adverse events or dropouts due to adverse events for dosages, duration, or detoxification status

Criteria, questions		Judgement	Research evidence	Additional considerations
			differ in the number of participants with at least one adverse event (Very low certainty) • It is uncertain whether baclofen and naltrexone differ in the dropout (Very low 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	See above: • Moderate or high for Baclofen vs placebo • Very low for Baclofen vs Acamprosate/Naltrexone	
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 each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ **Probably no important uncertainty or variability**	No reviews that examined values were identified.	

Criteria, questions		Judgement	Research evidence	Additional considerations
		☐ No important uncertainty or variability		
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	Baclofen showed better effectiveness for patients after management of withdrawal syndrome (post-detoxification) when compared to those using alcohol (non-detoxified), but no differences identified for low/high dosages or duration of treatment. For other outcomes (dropouts from treatment), duration of treatment longer than 12 weeks showed effect, but no other difference was identified for adverse events or dropouts due to adverse events for dosages, duration of treatment or detoxification status.	
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 require or save?	☐ Large costs ☐ Moderate costs ☒ **Negligible costs and savings** ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	Baclofen is available in generic form and is inexpensive.	

Criteria, questions		Judgement	Research evidence	Additional considerations
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**	We are aware of one study showing that chlordiazepoxide is more cost-effective than baclofen (Reddy et al., 2014). However, there is no comparison to no treatment, treatment as usual or other interventions.	
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? • 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?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies ☒ **No included studies**	No reviews examining cost-effectiveness identified	

Criteria, questions	Judgement	Research evidence	Additional considerations
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 prioritize 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	There is some limited evidence suggesting sex can be a mediator in response to baclofen treatment, potentially with better effect among females (Garbut et al., 2021; Morley et al., 2022;) There is some limited evidence suggesting sex can be a mediator in response to baclofen treatment, potentially with better effect among females (Garbut et al., 2021; Morley et al., 2022). Gronholm et al., 2023 qualitative review. homelessness, poverty, lack of education and stigma contributed to people not seeking treatment. Education: Basic issues like knowledge of where to seek treatment and low literacy challenged access to care. Finances: People who need treatment also might consider that treatment-	

Criteria, questions		Judgement	Research evidence	Additional considerations
			seeking process may lead to lost wages and possible disapproval from the employers. Stigma: Treatment seeking, especially in designated facilities, makes patients easily identifiable and results in them facing discrimination by other members of the society or being tracked by law enforcement. Stigma was of a greater concern among women and acted as a significant barrier of treatment seeking. Opioid use disorder and AUD: While barriers related to medications were seemingly more important barriers for treatment seeking for opioid use disorders, socio-environmental factors played a vital role in the case of treatment seeking of individuals with alcohol use disorders.	
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: Australia, France, Germany, Italy, Netherlands, USA. There is no clear understanding on feasibility in low-resource settings. There is both variability and uncertainty in the feasibility of	

Criteria, questions	Judgement	Research evidence	Additional considerations
		baclofen for relapse prevention of alcohol dependence. Baclofen is not available in all countries and is not registered for the use of alcohol dependence. Most of the studies (except one from India) done in high income countries. There is no clear understanding on feasibility in low-resource settings. There is both variability and uncertainty in the feasibility of baclofen for relapse prevention of alcohol dependence. Baclofen is not available in all countries and is not registered for the use of alcohol dependence. Gronholm et al., 2023 qualitative review. Barriers included fragmented health services and people not thinking that they have any health problems. These barriers in addition to the once listed above can have an effect on how and if people seek the treatment and if they continue to visit the health-care facilities for treatment. In addition: feasibility considerations include:	

Criteria, questions	Judgement	Research evidence	Additional considerations
		• Acceptability of interventions for stakeholders • Health worker workload, competency – requires training, refreshers, supervision; networking with others in same role. • Availability of a task-sharing workforce; • Participant education and literacy requires verbal explanations/tasks; • Logistical issues, e.g. mobile populations, affordability of travel to receive care, lack of private space; • Limited resources/mental health budget.	
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?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies**	Gronholm et al., 2023. *A number of considerations were noted which would impact the right to health and access to health care.

Criteria, questions	Judgement	Research evidence	Additional considerations
• 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?	☐ Don't know	E.g. stigma and discrimination were identified as barriers that affect the help-seeking among service users. Lack of confidentiality is another factor that can deter people from accessing care or receiving confidential and safe mental health care. A range of stigma-related concerns were flagged up: • Social stigma and exclusion due to substance use. • Fear of being seen in designated health facilities. • Facing discrimination by other members of society. • Concerns around being tracked by law enforcement. Mitigating steps proposed by the review: • Awareness activities to reduce the stigma towards those with substance use disorders. • Training health personnel to obtain additional skills and empower them to provide care. Care for patients with substance use disorder to also include provision of empathetic support and supportive communication. Training on communication and professional factors of service delivery (like confidentiality, positive outlook of	

Criteria, questions	Judgement	Research evidence	Additional considerations
		future, linkages of care) would probably reduce the stigma and make a health care system more palatable. Financial issues around the treatment can also be a barrier that limits access to those who need to seek help. Mitigating steps proposed by the review: • low-cost scalable solutions to make treatment available to different parts of the country would be helpful to make care accessible to a more people (using telemedicine and telehealth as one of the options). • draw attention of the administrators to the need to allocate sufficient resources and funding for substance use disorder services, so that the individuals with substance use, their families and the society can benefit and access the treatments.	

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 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

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World Health Organization. WHO handbook for guideline development, 2nd ed. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/145714).

World Health Organization. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP), version 2.0. Geneva: World Health Organization; 2016 (https://iris.who.int/handle/10665/250239).

Appendix 1. mhGAP guideline update – Notes on process for identifying the required level of evidence review 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 (2014)*.[1]

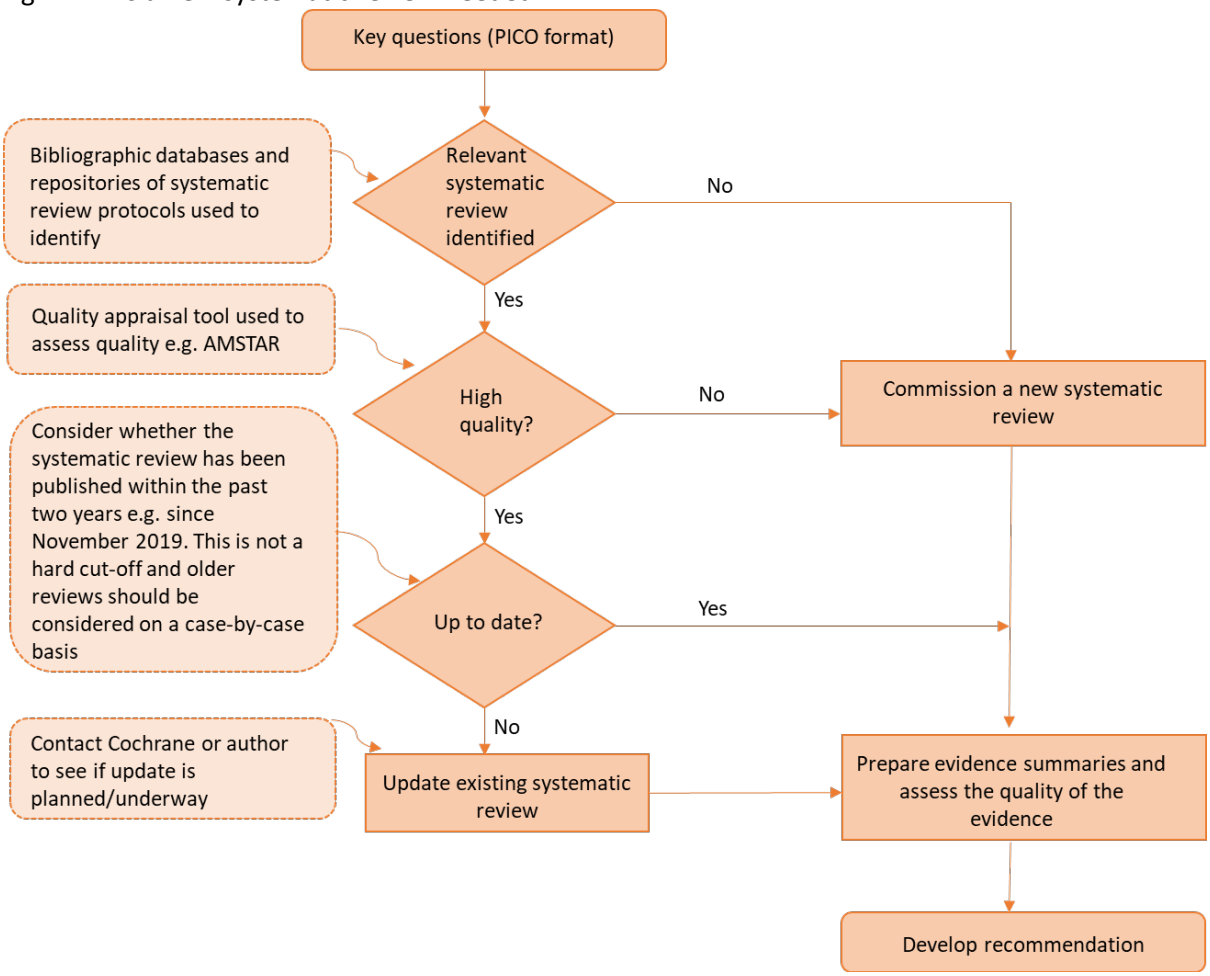
Three main categories of evidence review are proposed in this document:

- 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.
- 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.
- 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.

Fig. A1-1 below details the process to identify which level of evidence review is required to support the evidence retrieval process for a PICO.

[1] Available at: https://apps.who.int/iris/handle/10665/145714

Fig. A1-1: 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, CENTRAL, CINAHL, 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 Fig. A1-1, 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:

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

Appendix 2a. Search terms used to identify systematic reviews (Phase 1)

Ovid MEDLINE(R)
Searched: from January 2018 to 14 January 2022 (20 results)

1 exp Alcoholism/
2 ((alcohol$ or drink$) adj5 (abstinen$ 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$)).mp.
3 1 or 2
4 exp Baclofen/ or baclofen.mp.
5 3 and 4
6 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
7 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
8 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
9 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
10 (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
11 (handsearch* or hand search*).ti,ab,kf,kw.
12 (handsearch* or hand search*).ti,ab,kf,kw.
13 (meta regression* or metaregression*).ti,ab,kf,kw.
14 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
15 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
16 (cochrane or (health adj2 technology assessment) or evidence report).jw.
17 (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
18 (outcomes research or relative effectiveness).ti,ab,kf,kw.
19 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.
20 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 5 and 20
22 limit 21 to yr="2018 -Current"

Ovid Embase
Searched: from January 2018 to 14 January 2022 (47 results)

1 exp alcoholism/
2 exp drinking behavior/
3 alcohol.mp.
4 (abuse* or addict* or dependen* or disorder* or drink* or consumption or treatment).ti,ab.
5 3 and 4
6 1 or 2 or 5
7 exp baclofen/ or baclofen.mp.
8 6 and 7
9 "systematic review"/ or meta analysis/
10 "meta analysis (topic)"/
11 "systematic review (topic)"/
12 biomedical technology assessment/
13 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.

14 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
15 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
16 (data synthes* or data extraction* or data abstraction*).ti,ab.
17 (handsearch* or hand search*).ti,ab.
18 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
19 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
20 (meta regression* or metaregression*).ti,ab.
21 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
22 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab.
23 (cochrane or (health adj2 technology assessment) or evidence report).jw.
24 (comparative adj3 (efficacy or effectiveness)).ti,ab.
25 (outcomes research or relative effectiveness).ti,ab.
26 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
27 9 or 10 or 11 or 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
28 8 and 27
29 limit 28 to yr="2018 -Current"

Ovid PsycInfo
Searched: from January 2018 to January Week 2 2022 (13 results)
1 exp Alcoholism/
2 ((alcohol$ or drink$) adj5 (abstinen$ 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$)).mp.
3 1 or 2
4 Baclofen/ or baclofen.mp.
5 3 and 4
6 "systematic review"/ or meta analysis/
7 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
8 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
9 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
10 (data synthes* or data extraction* or data abstraction*).ti,ab.
11 (handsearch* or hand search*).ti,ab.
12 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
13 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
14 (meta regression* or metaregression*).ti,ab.
15 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
16 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab.
17 (cochrane or (health adj2 technology assessment) or evidence report).jw.
18 (comparative adj3 (efficacy or effectiveness)).ti,ab.
19 (outcomes research or relative effectiveness).ti,ab.

20 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
21 or/6-20
22 5 and 21
23 limit 22 to yr="2018 -Current"

13 results from Web of Science Core Collection for:
Publication year: 2018-2022
(TS=(systematic* NEAR/3 (review* OR overview*) OR "meta-analysis")) AND TS=(alcohol* AND baclofen)

9 results from Epistemonikos for
Publication year: 2018-2022
Publication type: Systematic Review
baclofen and alcohol

2 results from the Global Index Medicus (GIM)
tw:(baclofen AND alcohol) AND (year_cluster:[2018 TO 2022])

Appendix 2b. Methodological quality of the retrieved reviews (Phase 1)

	AMSTAR checklist -items	Author & publication year	Author & publication year	Author & publication year
		Minozzi et al., 2018	Bschor 2018	Cheng 2020
1	Did the research questions and inclusion criteria for the review include the components of PICO?	y	y	y
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	y	y	y
3	Did the review authors explain their selection of the study designs for inclusion in the review?	y	y	y
4	Did the review authors use a comprehensive literature search strategy?	y	y	y
5	Did the review authors perform study selection in duplicate?	y	y	y
6	Did the review authors perform data extraction in duplicate?	y	y	y
7	Did the review authors provide a list of excluded studies and justify the exclusions?	y	n	partial y
8	Did the review authors describe the included studies in adequate detail?	y	partial y	partial y
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	y	y	y
10	Did the review authors report on the sources of funding for the studies included in the review?	y	n	n
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	y	n	y
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	y	y	y
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	y	y	y
14	Did the review authors provide a satisfactory explanation for, and discussion of, any	y	y	y

	heterogeneity observed in the results of the review?			
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	y	y	n
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	y	y	y
	Overall rating	HIGH	LOW	MODERATE

AMSTAR: A MeaSurement Tool to Assess systematic Reviews.

Appendix 2c. Details of the search strategies (Phase 2)

CDAG Specialised Register (via CRSLive)
Searched : from 2018 to 22 November 2021 (11 results)
baclofen (all fields)

Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Online Library) 2021, issue 11 (46 results)
#1 MeSH descriptor: [Alcohol-Related Disorders] explode all trees
#2 MeSH descriptor: [Alcohol Drinking] explode all trees
#3 (alcohol and (abuse* or addict* or dependen* or disorder* or drink* or consumption or treatment)):ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Baclofen] explode all trees
#6 "baclofen" (Word variations have been searched)
#7 Lioresal:ti,ab,kw (Word variations have been searched)
#8 #5 or #6 or #7
#9 #4 and #8 with Publication Year from 2018 to present, in Trials

MEDLINE (via Ovid)
Searched : fom January 2018 to 22 November (82hits)

1. exp Alcoholism/
2. ((alcohol$ or drink$) adj5 (abstinen$ 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$)).mp.
3. 1 or 2
4. exp Baclofen/ or baclofen.mp.
5. 3 and 4
6. limit 5 to yr="2018 -Current"

Embase (via Ovid)
From January 2018 to 22 November 2021 (78 hits)

1. exp alcoholism/
2. exp drinking behavior/
3. alcohol.mp.
4. (abuse* or addict* or dependen* or disorder* or drink* or consumption or treatment).ti,ab.
5. 3 and 4
6. 1 or 2 or 5
7. exp baclofen/ or baclofen.mp.
8. 6 and 7
9. exp randomized controlled trial/
10. exp randomization/
11. exp double blind procedure/
12. exp single blind procedure/
13. random$.tw.
14. 9 or 10 or 11 or 12 or 13

15. (animal or animal experiment).sh.
16. human.sh.
17. 15 and 16
18. 15 not 17
19. 14 not 18
20. exp clinical trial/
21. (clin$ adj3 trial$).tw.
22. exp crossover procedure/
23. exp double blind procedure/
24. exp controlled clinical trial/
25. (placebo or assign* or allocat* or volunteer* or random* or factorial* or crossover).ti,ab.
26. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
27. 20 or 21 or 22 or 23 or 24 or 25
28. 27 not 18
29. 19 or 28
30. 8 and 29

PsycInfo (via Ovid)
from January 2018 to 22 November (82 hits)

1. exp Alcoholism/
2. (alcohol$ or drink$) adj5 (abstinen$ 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$)).mp.
3. 1 or 2
4. exp Baclofen/ or baclofen.mp.
5. 3 and 4
6. limit 5 to yr="2018 -Current"

Web of Science
From January 2018 to 22 November 2021 (62 hits)

1. TOPIC: (((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$)))
2. TOPIC: (baclofen)
3. TOPIC: (randomi* OR randomly OR trial*)
4. #3 AND #2 AND #1

CINAHL (via Ebsco)
from January 2018 to 22 November 2021 (25 results)

1. MH "Alcoholism"

2. TX (alcohol N3 (drink* or abus* or misus* or risk* or consum* or withdraw* or intoxicat* or detox* or treat* or therap* or excess* or reduc* or cessation or intervention))
3. TX(overdos* or intoxicat* or abstinen* or withdraw* or relaps*)
4. TX (drink* N3 (heavy or heavily or hazard* or binge or harmful))
5. MH "Clinical Trials+"
6. PT Clinical trial
7. TI clinic* N1 trial* or AB clinic* N1 trial*
8. TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
9. AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
10. TI randomi?ed control* trial* or AB randomi?ed control* trial*
11. MH "Random Assignment"
12. TI random* allocat* or AB random* allocat*
13. MH "Placebos"
14. TI placebo* or AB placebo*
15. MH "Quantitative Studies"
16. S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
17. baclofen
18. S1 OR S2 OR S3
19. S16 AND S17 AND S18

Appendix I. Search terms used to identify systematic reviews

PubMed

1# Depression
"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR “depress*”[tiab] OR “dysthymi*”[tiab] OR “mood disorder*”[tiab] OR “affective disorder*”[tiab] OR “dysphoric disorder*”[tiab]

2# Antidepressants
"Antidepressive Agents"[Mesh:NoExp] OR "Serotonin Uptake Inhibitors"[Mesh] OR "Antidepressive Agents, Tricyclic" [Mesh] OR "Fluoxetine"[Mesh] OR "Citalopram"[Mesh] OR "Sertraline"[Mesh] OR "Nortriptyline"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Serotonin Uptake Inhibitors" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "antidepressiv*"[tiab] OR "anti-depressiv*"[tiab] OR antidepressant*[tiab] OR "anti-depressant*"[tiab] OR thymoleptic*[tiab] OR thymoanaleptic*[tiab] OR "Serotonin Reuptake Inhibitor*"[tiab] OR "Serotonin Re-uptake Inhibitor*"[tiab] OR "Serotonin uptake Inhibitor*"[tiab] OR “serotonin specific reuptake inhibitor*”[tiab] OR “serotonin specific re-uptake inhibitor*”[tiab] OR SSRI*[tiab] OR TCA[tiab] OR TCAs[tiab] OR alaproclate [tiab] OR Citalopram [tiab] OR Celexa [tiab] OR Cipramil [tiab] OR Escitalopram [tiab] OR Lexapro [tiab] OR Cipralex [tiab] OR Fluoxetine [tiab] OR Prozac [tiab] OR Sarafem [tiab] OR Fluvoxamine [tiab] OR Luvox [tiab] OR Faverin [tiab] OR Paroxetine [tiab] OR Paxil [tiab] OR Seroxat [tiab] OR Sertraline [tiab] OR Zoloft [tiab] OR Lustral [tiab] OR Vilazodone [tiab] OR Viibryd [tiab] OR femoxetine [tiab] OR indalpine [tiab] OR Zimeldine [tiab] OR Amitriptyline [tiab] OR Elavil [tiab] OR Endep [tiab] OR Amitriptylinoxide [tiab] OR Amioxid [tiab] OR Ambivalon [tiab] OR Equilibrin [tiab] OR Clomipramine [tiab] OR Anafranil [tiab] OR Desipramine [tiab] OR Norpramin [tiab] OR Pertofrane [tiab] OR Dibenzepin [tiab] OR Noveril [tiab] OR Victoril [tiab] OR Dimetacrine [tiab] OR Istonil [tiab] OR Dosulepin [tiab] OR Prothiaden [tiab] OR Doxepin [tiab] OR Adapin [tiab] OR Sinequan [tiab] OR Imipramine [tiab] OR Tofranil [tiab] OR Lofepramine [tiab] OR Lomont [tiab] OR Gamanil [tiab] OR Melitracen [tiab] OR Dixeran [tiab] OR Melixeran [tiab] OR Trausabun [tiab] OR Nitroxazepine [tiab] OR Sintamil [tiab] OR Nortriptyline [tiab] OR Pamelor [tiab] OR Aventyl [tiab] OR Noxiptiline [tiab] OR Agedal [tiab] OR Elronon [tiab] OR Nogedal [tiab] OR Opipramol [tiab] OR Insidon [tiab] OR Pipofezine [tiab] OR Azafen [tiab] OR Azaphen [tiab] OR Protriptyline [tiab] OR Vivactil [tiab] OR Trimipramine [tiab] OR Surmontil [tiab] OR Amoxapine [tiab] OR Asendin [tiab] OR cericlamine [tiab] OR dapoxetine [tiab] OR ifoxetine [tiab] OR litoxetine [tiab] OR lubazodone [tiab] OR moxifetin [tiab] OR nomelidine [tiab] OR norcitalopram [tiab] OR norfluoxetine [tiab] OR seproxetine [tiab] OR norsertraline [tiab] OR omiloxetine [tiab]

3# SR + MA filter
("Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR metaanaly*[tiab] OR meta-analy*[tiab] or metanaly*[tiab] OR "Systematic Review" [Publication Type] OR systematic[sb] OR meta-analysis[Filter] OR systematicreview[Filter] OR "Cochrane Database Syst Rev"[Journal] or prisma[tiab] OR “preferred reporting items”[tiab] OR prospero[tiab] OR ((systemati*[ti] OR umbrella[ti] OR “structured literature”[ti]) AND (review[ti] OR overview[ti])) OR “systematic review”[tiab] OR “umbrella review”[tiab] OR “structured literature review”[tiab] OR “systematic qualitative review”[tiab] OR “systematic quantitative review”[tiab] OR “systematic search and review”[tiab] OR “systematized review”[tiab] OR “systematised review”[tiab] OR “systemic review”[tiab] OR “systematic literature review”[tiab] OR “systematic integrative literature review”[tiab] OR “systematically review”[tiab] OR “scoping literature review”[tiab] OR “scoping review”[tiab] OR “systematic critical

review”[tiab] OR “systematic integrative review”[tiab] OR “systematic evidence review”[tiab] OR “systematic integrative literature review”[tiab] OR “systematic mixed studies review”[tiab] OR “systematized literature review”[tiab] OR “systematic overview”[tiab] OR “Systematic narrative review”[tiab] OR “narrative review”[tiab] OR metasynthes*[tiab] OR meta-synthes*[tiab]) NOT ("Comment" [Publication Type] OR "Letter" [Publication Type] OR "Editorial" [Publication Type] OR (("Animals"[Mesh] OR "Models, Animal"[Mesh]) NOT "Humans"[Mesh]))

Timeframe
2019-2022

Appendix II. Decision tree used to evaluate the risk of bias (ROB) in GRADE

- No data available for risk of bias → serious

- When vast majority (> 60%) of trials are **low risk** → not serious
- When low risk is between 50–60%:
  - High risk < 25% → not serious
  - High risk > 25% → serious

- When vast majority (> 60%) is **high risk** → very serious
- When high risk is between 50-60%:
  - Low risk < 25% → very serious
  - Low risk > 25% → serious

- When vast majority is **unclear risk** (> 60%) → serious
- When unclear risk is between 50–60%:
  - High risk < 25% → not serious
  - High risk > 25% → serious

- If unclear/high/low risk are all < 50%:
  - High risk < 25% → not serious
  - High risk > 25% → serious