Cochrane
Library

Cochrane Database of Systematic Reviews

Baclofen for alcohol use disorder (Review)

Minozzi S, Saulle R, Rösner S

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](https://doi.org/10.1002/14651858.CD012557.pub2).

www.cochranelibrary.com

Baclofen for alcohol use disorder (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	7
METHODS	8
RESULTS	10
Figure 1.	11
Figure 2.	13
Figure 3.	14
DISCUSSION	17
AUTHORS' CONCLUSIONS	18
ACKNOWLEDGEMENTS	19
REFERENCES	20
CHARACTERISTICS OF STUDIES	25
DATA AND ANALYSES	58
Analysis 1.1. Comparison 1 Baclofen vs placebo, Outcome 1 Relapse: return to any drinking at end of treatment.	60
Analysis 1.2. Comparison 1 Baclofen vs placebo, Outcome 2 Frequency of use: % days abstinence at end of treatment.	60
Analysis 1.3. Comparison 1 Baclofen vs placebo, Outcome 3 Frequency of use: % of heavy drinking days at end of treatment. ..	61
Analysis 1.4. Comparison 1 Baclofen vs placebo, Outcome 4 Amount of use: drink per drinking days at end of treatment.	61
Analysis 1.5. Comparison 1 Baclofen vs placebo, Outcome 5 Adverse events: number of participants with at least one adverse event at end of treatment.	61
Analysis 1.6. Comparison 1 Baclofen vs placebo, Outcome 6 Dropout at end of treatment.	62
Analysis 1.7. Comparison 1 Baclofen vs placebo, Outcome 7 Dropout due to adverse events.	62
Analysis 1.8. Comparison 1 Baclofen vs placebo, Outcome 8 Craving.	63
Analysis 1.9. Comparison 1 Baclofen vs placebo, Outcome 9 Anxiety.	63
Analysis 1.10. Comparison 1 Baclofen vs placebo, Outcome 10 Depression.	63
Analysis 1.11. Comparison 1 Baclofen vs placebo, Outcome 11 Adverse events: fatigue, tiredness.	64
Analysis 1.12. Comparison 1 Baclofen vs placebo, Outcome 12 Adverse events: insomnia.	64
Analysis 1.13. Comparison 1 Baclofen vs placebo, Outcome 13 Adverse events: pain (diverse).	64
Analysis 1.14. Comparison 1 Baclofen vs placebo, Outcome 14 Adverse events: vertigo, dizziness.	65
Analysis 1.15. Comparison 1 Baclofen vs placebo, Outcome 15 Adverse events: constipation.	65
Analysis 1.16. Comparison 1 Baclofen vs placebo, Outcome 16 Adverse events: somnolence, sleepiness, drowsiness or sedation.	65
Analysis 1.17. Comparison 1 Baclofen vs placebo, Outcome 17 Adverse events: muscle pain.	66
Analysis 1.18. Comparison 1 Baclofen vs placebo, Outcome 18 Adverse events: dry mouth.	66
Analysis 1.19. Comparison 1 Baclofen vs placebo, Outcome 19 Adverse events: nausea.	66
Analysis 1.20. Comparison 1 Baclofen vs placebo, Outcome 20 Adverse events: skin rash.	67
Analysis 1.21. Comparison 1 Baclofen vs placebo, Outcome 21 Adverse events: headaches.	67
Analysis 1.22. Comparison 1 Baclofen vs placebo, Outcome 22 Adverse events: paresthesia/numbness.	67
Analysis 1.23. Comparison 1 Baclofen vs placebo, Outcome 23 Adverse events: diarrhoea.	68
Analysis 1.24. Comparison 1 Baclofen vs placebo, Outcome 24 Adverse events: tinnitus.	68
Analysis 1.25. Comparison 1 Baclofen vs placebo, Outcome 25 Adverse events: muscle spasm/rigidity.	68
Analysis 1.26. Comparison 1 Baclofen vs placebo, Outcome 26 Adverse events: hyperhidrosis.	69
Analysis 1.27. Comparison 1 Baclofen vs placebo, Outcome 27 Adverse events: nasopharyngitis.	69
Analysis 1.28. Comparison 1 Baclofen vs placebo, Outcome 28 Adverse events: decrease appetite/anorexia.	69
Analysis 1.29. Comparison 1 Baclofen vs placebo, Outcome 29 Adverse events: dysgeusia/ageusia.	70
Analysis 1.30. Comparison 1 Baclofen vs placebo, Outcome 30 Adverse events: tremor.	70
Analysis 1.31. Comparison 1 Baclofen vs placebo, Outcome 31 Adverse events: weakness.	70
Analysis 1.32. Comparison 1 Baclofen vs placebo, Outcome 32 Adverse events: vomiting.	70

Analysis 1.33. Comparison 1 Baclofen vs placebo, Outcome 33 Adverse events: urinary frequency.	71
Analysis 2.1. Comparison 2 Baclofen vs acamprosate, Outcome 1 Craving.	71
APPENDICES	71
CONTRIBUTIONS OF AUTHORS	77
DECLARATIONS OF INTEREST	77
SOURCES OF SUPPORT	77
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	77
INDEX TERMS	77

[Intervention Review]

Baclofen for alcohol use disorder

Silvia Minozzi¹, Rosella Saulle¹, Susanne Rösner²

¹Department of Epidemiology, Lazio Regional Health Service, Rome, Italy. ²Forel Klinik, Ellikon an der Thur, Switzerland

Contact address: Silvia Minozzi, Department of Epidemiology, Lazio Regional Health Service, Via Cristoforo Colombo, 112, Rome, 00154, Italy. minozzi.silvia@gmail.com.

Editorial group: Cochrane Drugs and Alcohol Group.

Publication status and date: New, published in Issue 11, 2018.

Citation: 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](https://doi.org/10.1002/14651858.CD012557.pub2).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Alcohol use disorder (AUD) and alcohol-related impairments belong to the most widespread psychiatric disorders leading to specific psychophysical, affective and cognitive symptoms and consequences for psychosocial well-being and health. Alcohol consumption is increasingly becoming a problem in many developing regions and AUD prevalence is estimated at 4.1% worldwide, with highest prevalence in European countries (7.5%), and the North America (6.0%). Therapeutic approaches, including pharmacotherapy, play an important role in treating patients with AUD.

Objectives

To assess the efficacy and safety of baclofen for treating people with AUD, who are currently drinking, with the aim of achieving and maintaining abstinence or reducing alcohol consumption.

Search methods

We searched the Cochrane Drugs and Alcohol Specialised Register, CENTRAL, MEDLINE, Embase, two further databases and two clinical trials registries, conference proceedings, and the reference lists of retrieved articles. The date of the most recent search was 30 January 2018.

Selection criteria

Randomised controlled trials (RCTs) of at least four weeks' treatment duration and 12 weeks' overall study duration comparing baclofen for relapse prevention of AUD with placebo, no treatment or other treatments.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 12 RCTs (1128 participants). All studies but three recruited fewer than 100 participants. Participants had a diagnosis of alcohol dependence according the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV or the International Classification of Diseases (ICD)-10 criteria who were currently drinking. The mean age of participants was 48 years, and there were more men (69%), than women. All studies compared baclofen to placebo, except for one study that evaluated baclofen versus acamprosate. The included studies considered baclofen at different doses (range 10 mg a day to 150 mg a day). In all but one of the studies, participants in both the baclofen and placebo groups received psychosocial treatment or counselling of various intensity.

We judged most of the studies at low risk of selection, performance, detection (subjective outcome), attrition and reporting bias.

We did not find any difference between baclofen and placebo for the primary outcomes: relapse-return to any drinking (RR 0.88, 95% CI 0.74 to 1.04; 5 studies, 781 participants, moderate certainty evidence); frequency of use by percentage of days abstinent (MD 0.39, 95% CI -11.51 to 12.29; 6 studies, 465 participants, low certainty evidence) and frequency of use by percentage of heavy drinking days at the end of treatment (MD 0.25, 95% CI -1.25 to 1.76; 3 studies, 186 participants, moderate certainty evidence); number of participants with at least one adverse event (RR 1.04, 95% CI 0.99 to 1.10; 4 studies, 430 participants, high certainty evidence); the dropout rate at the end of treatment (RR 0.98, 95% CI 0.77 to 1.26, 8 studies, 977 participants, high certainty evidence) and dropout due to adverse events (RR 1.11, 95% CI 0.59 to 2.07; 7 studies, 913 participants, high certainty evidence).

We found evidence that baclofen increases amount of use (drink per drinking days), (MD 1.55, 95% CI 1.32 to 1.77; 2 studies, 72 participants, low certainty evidence).

Among secondary outcomes, there was no difference on craving (MD 1.38, 95% CI -1.28 to 4.03, 5 studies, 469 participants), and anxiety (SMD 0.07, 95% CI -0.14 to 0.28; 5 trials, 509 participants). We found that baclofen increased depression (SMD 0.27, 95% CI 0.05 to 0.48; 3 studies, 387 participants).

Concerning the specific adverse events we found that baclofen increased: vertigo (RR 2.16, 95% CI 1.24 to 3.74; 7 studies, 858 participants), somnolence/sedation (RR 1.48, 95% CI 1.11 to 1.96; 8 studies, 946 participants), paraesthesia (RR 4.28, 95% CI 2.11 to 8.67; 4 studies, 593 participants), and muscle spasms/rigidity (RR 1.94, 95% CI 1.08 to 3.48; 3 studies, 551 participants). For all the other adverse events we did not find significant differences between baclofen and placebo.

For the comparison baclofen versus acamprosate, we were only able to extract data for one outcome, craving. For this outcome, we found that baclofen increased craving compared with acamprosate (MD 14.62, 95% CI 12.72 to 16.52; 1 study, 49 participants).

Authors' conclusions

None of the primary or secondary outcomes of the review showed evidence of a difference between baclofen and placebo. The high heterogeneity among primary studies results limits the interpretation of the summary estimate, the identification of moderators and mediators of baclofen's effects on alcohol use remains a challenge for further research. Even though some results from RCTs are promising, current evidence remains uncertain regarding the use of baclofen as a first-line treatment for people with AUDs.

PLAIN LANGUAGE SUMMARY

Baclofen for alcohol use disorder

Review question

We reviewed the evidence about the effectiveness and safety of baclofen for treating people with alcohol use disorder (AUD), who are currently drinking, in order to achieve and maintain abstinence (stopping drinking), or to reduce alcohol consumption.

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

For many years, the main treatments for AUD have been psychosocial strategies, but using only psychosocial treatments has limited success. A high proportion of people with AUD do not respond to the treatment at all, and those who do respond do not stay alcohol-free in the long-term. Drugs, such as baclofen, could play an important role in treating people with AUD.

Search date

The evidence is current to January 2018.

Study characteristics

We found 12 randomised controlled trials (studies where people were allocated at random to one of two or more treatment or control groups), with 1128 participants. On average, the interventions lasted about five months, while investigators followed up participants from between 4 to 52 months. Five studies took place in the USA and one each in Australia, France, Germany, India, Israel, Italy, and the Netherlands.

The studies considered baclofen at different doses (ranging from 10 mg a day to 150 mg a day), and in some cases, the doses were increased during the treatment. None of the studies added other drugs or other treatments to the baclofen treatment. All the studies compared baclofen to placebo, except for one study that compared baclofen to acamprosate at a dose of 666.66 mg three times a day for three months.

Key results

Compared with placebo, baclofen makes little or no difference to participants who dropped out from treatment, dropped out due to adverse events (side effects), or the number of participants with at least one adverse event. Baclofen probably makes little difference to

the number of participants who start drinking again, nor to how much or how often they drink. Baclofen may make little or no difference in the percentage of days people remain alcohol-free.

Baclofen may increase the amount of use measured by number of drinks per drinking days.

We found that baclofen increased adverse events like depression, vertigo, somnolence, numbness and muscle rigidity but we did not find significant differences between baclofen and placebo for other adverse events.

Cerainty of evidence

The certainty of evidence (how much we can be confident that the evidence is reliable) was high for results about the number of participants with at least one adverse event, and about people dropping out of the studies for any reason or dropping out due to adverse events. The certainty of the evidence was moderate for results about people returning to any drinking and how many heavy drinking days they had. It was low for results about drink per drinking days and percentage of days of abstinence.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Baclofen compared to placebo for alcohol use disorder

Baclofen compared to placebo for alcohol use disorder

Patient or population: adults (18 years and older) with alcohol use disorder

Setting: outpatient setting in USA (n = 5), Australia (n = 1), France (n = 1), Germany (n = 1), India (n = 1), Israel (n = 1), Italy (n = 1), the Netherlands (n = 1)

Intervention: baclofen in any dose and route of administration

Comparison: placebo or any other pharmacological relapse prevention treatment

Outcomes	Nº of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with baclofen
Relapse return to any drinking at the end of treatment	781 (5 RCTs)	⊕⊕⊕⊖ Moderate ¹	RR 0.88 (0.74 to 1.04)	Study population 781 per 1000	94 fewer per 1000 (203 fewer to 31 more)
Frequency of use % days abstinence at the end of treatment	465 (6 RCTs)	⊕⊕⊖⊖ Low ²		The mean % days abstinence at end of treatment ranged from 36.7% to 70.9%	MD 0.39 higher (11.51 lower to 12.29 higher)
Frequency of use % of heavy drinking days at the end of treatment	186 (3 RCTs)	⊕⊕⊕⊖ Moderate ³	-	The mean frequency of use (% of heavy drinking days at end of treatment) ranged from 16.32% to 25.5%	MD 0.25 higher (1.25 lower to 1.76 higher)
Amount of use drink per drinking days at the end of treatment	72 (2 RCTs)	⊕⊕⊖⊖ Low ⁴	-	The mean amount of use (drink per drinking days at end of treatment) ranged from 2.14 drinks to 2.82 drinks	MD 1.55 higher (1.32 higher to 1.77 higher)
Adverse events number of participants with at least one side effect at the end of treatment	430 (4 RCTs)	⊕⊕⊕⊕ High	RR 1.04 (0.99 to 1.10)	Study population 785 per 1000	31 more per 1000 (8 fewer to 78 more)
Dropout at end of treatment	977 (8 RCTs)	⊕⊕⊕⊕ High	RR 0.98 (0.77 to 1.26)	Study population	

			301 per 1000	6 fewer per 1000 (69 fewer to 78 more)
Dropout due to adverse events	913 (7 RCTs)	⊕⊕⊕⊕ High	RR 1.11 (0.59 to 2.07)	Study population
			41 per 1000	8 more per 1000 (14 fewer to 47 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded one level for significant heterogeneity: $I^2 = 77\%$

²Downgraded two levels for very high heterogeneity: $I^2 = 96\%$

³Downgraded one level for imprecision: fewer than 400 participants included in the analysis

⁴Downgraded two levels for imprecision: fewer than 400 participants included in the analysis

BACKGROUND

Description of the condition

Alcohol use disorder (AUD) is a behavioural disorder characterised by dysfunctional patterns of alcohol use, leading to specific psychophysical, affective and cognitive symptoms and consequences for psychosocial well-being and health. AUD as a disease category has been introduced with the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the DSM-V (APA 2013). While the DSM-IV version (APA 2000), and International Classification of Diseases (ICD)-10 (WHO 2010), subdivide substance use disorders into dependence and a secondary category, called 'abuse' in DSM-IV and 'harmful use' in ICD-10 (Hasin 2006), the DSM-V integrates both categories into a single substance use disorder concept that ranges along a continuum from mild to severe (Hasin 2013; Rehm 2013).

AUD and alcohol-related impairments belong to the most widespread psychiatric disorders (Alonso 2004; Grant 2015). According to the WHO status report on alcohol and health (WHO 2014), the one-year prevalence of AUDs is estimated at 4.1% worldwide, with highest prevalence in European countries (7.5%), and the North America (6.0%). Statistics vary between regions, with a higher prevalence of psychoactive substance use in high-income countries compared to low- and middle-income countries (WHO 2002a). There is evidence indicating an enormous increase in alcohol use, high-risk drinking, and DSM-IV AUD in the US population during the last decade (Grant 2017). Nevertheless, with the improved industrialisation and centralisation of alcohol production, alcohol consumption is increasingly becoming a problem in many low- and middle-income countries (WHO 2002b). Irrespective of region, the prevalence of AUD is greater in men than in women (Rehm 2009), while there is evidence on converging drinking patterns between genders (White 2015).

The misuse of alcohol is one of the leading global health risk factors, causing 20% to 30% of oesophageal cancer, liver disease, epilepsy, motor vehicle accidents, homicide and other intentional injuries (WHO 2002a). Men with AUD have a threefold-higher mortality risk compared to men without AUD; in women, the risk is even higher (Roerecke 2013). In 2004, 3.8% of all global deaths and 4.6% of global disability-adjusted life-years were attributable to alcohol (Rehm 2009). The costs attributable to alcohol consumption are estimated at more than 1% of the gross domestic products in high-income and middle-income countries (Rehm 2009). At the same time, alcohol consumption is one of the major, potentially avoidable risk factors, underscoring the need for effective strategies to reduce excessive drinking and to maintain abstinence in people who are dependent on alcohol.

The treatment of AUD was exclusively dominated by psychosocial strategies for many decades. Even though techniques from different theoretical and therapeutic backgrounds have been developed, treatment effects obtained by an exclusive application of psychosocial treatment are limited. A high proportion of patients do not respond to the interventions at all and of those who respond, few succeed in maintaining abstinence in the long term (Moos 2006). With the investigation of the neurobiological mechanism of AUD, several pharmacological agents have been examined for their potential to support people with AUD in achieving abstinence or in cutting down their alcohol consumption. Four agents are approved for pharmacological

support of relapse prevention in AUDs: the opioid antagonists naltrexone and nalmefene; the glutamate antagonist acamprosate; and the aversive agent disulfiram (Mutschler 2016). While the primary mechanism of action of the two opioid antagonists is to block alcohol-induced reward effects, acamprosate is assumed to work by restoring the balance between inhibitory and excitatory neurotransmitters (Rösner 2010a; Rösner 2010b). In contrast to naltrexone, nalmefene and acamprosate, which are assumed to modulate neurobiological mechanisms of addiction, disulfiram works by producing an aversive reaction when combined with alcohol (Mutschler 2016). Various Cochrane Reviews have investigated the effects of pharmacological interventions for the treatment of alcohol withdrawal (Amato 2010; Amato 2011; Gillman 2007; Leone 2010; Liu 2015; Minozzi 2010; Sarai 2013), and for relapse prevention in AUD (Pani 2014; Pedersen 2013; Rösner 2010a; Rösner 2010b; Vaz de Lima 2010).

Description of the intervention

Baclofen, also known as beta-4-chlorophenyl-gamma-aminobutyric acid (Steardo 1984), is an agonist of the γ -aminobutyric acid type B (GABAB) receptor and sold under the brand names Kemstro and Lioresal. The substance was originally approved for use in spasticity associated with neurological conditions and has recently emerged as a treatment of major interest for AUD (Agabio 2014; Brennan 2013; Garbutt 2010; Ponizovsky 2015). Baclofen is available in oral formulations and intrathecal solutions, the latter reserved for treatment of spasticity unresponsive to oral administration of baclofen. The recommended oral daily dose for baclofen ranges from 15 mg to 80 mg, starting from 15 mg a day and gradually increasing by 5 mg every three days (Agabio 2014). Despite high individual variation in pharmacokinetics, baclofen is rapidly absorbed from the gastrointestinal tract following oral administration. Up to 80% of an oral dose is excreted in the urine, with only a limited hepatic metabolism, making it a useful agent in people with impaired hepatic function, while renal function should be carefully assessed prior to baclofen administration (Agabio 2013; Brennan 2013). In addition, baclofen has a short half-life of three to four hours and is rapidly cleared from the blood. As a result, baclofen needs to be administered three or four times per day to maintain therapeutic effects (Schwarz Pharma 2003).

Preclinical studies have found that baclofen reduces the acquisition of alcohol-drinking behaviour and its maintenance and reinstatement in alcohol-experienced rats (Agabio 2014). Effects on reinstatement were assessed by the modification of the so-called 'alcohol deprivation effect', a rodent model for studying relapse behaviour referring to the temporary increase in voluntary alcohol intake after a period of forced abstinence from alcohol in a free-choice experiment (Martin-Fardon 2013). Furthermore, baclofen has been shown to dose-dependently reduce the number of lever-responses for alcohol and the amount of self-administered alcohol in rats under operant self-administration conditions (e.g. Maccioni 2005; Maccioni 2012). In operant self-administration experiments, a specific amount of 'work' is required to access alcohol, with predictive validity for human alcohol craving, and providing measures of alcohol consumption and the reinforcing properties of alcohol (Agabio 2014). Thereby baclofen was found to be more potent and effective in those rats seeking and taking larger amounts of alcohol (Maccioni 2012; Walker 2007).

A series of case reports found that the administration of baclofen markedly reduced alcohol intake in people affected by AUD (Agabio 2007; Ameisen 2005; Bucknam 2006; Flannery 2004; Pastor 2012). One of these reports (Ameisen 2005), described the personal history of a French physician, who conducted an original dose-finding curve with baclofen with the aim of treating his own AUD (Agabio 2014). He tested oral baclofen, starting with the 'conventional' dose of 30 mg a day and increased the daily dose of baclofen up to 270 mg after five weeks, experiencing, "complete medication-induced suppression of craving" for alcohol with alleviation of comorbid anxiety (Ameisen 2005).

While numerous case reports, case series, and open-label trials have been published, indicating the effectiveness of baclofen in people with AUD (for an overview see Brennan 2013), randomised controlled trials (RCTs) conducted to date (e.g. Addolorato 2002; Addolorato 2007; Garbutt 2010; Ponizovsky 2015), have yielded conflicting results. The diversity of findings has stimulated the discussion on potential moderators of effectiveness. Among others, severity of alcohol dependence (Agabio 2014; Hauser 2017; Leggio 2010; Maccioni 2012; Walker 2007), baclofen dosing (Addolorato 2007; Agabio 2014; Beraha 2016; Muller 2015), and comorbid anxiety (Addolorato 2002; Addolorato 2007; Agabio 2014; Muller 2015), have been discussed to moderate the effects of baclofen on alcohol consumption.

Although data are mixed regarding baclofen's efficacy in AUD, they are consistent in terms of safety if used as recommended (Brennan 2013). Extensive information on baclofen's safety is available from its widespread use for the treatment of spasticity for decades. Most adverse events are not severe, are dose-related and are transient. Sedation, somnolence, weakness, vertigo and psychological disturbances are reported as the most common adverse events (Dario 2004). The administration of low doses of baclofen is considered to be safe in people affected by AUD, while an abrupt interruption and withdrawal from higher doses of baclofen may lead to serious adverse effects (Agabio 2014; Dario 2004). While such events are rare, the lack of noted adverse events may be a result of small sample sizes and low doses of baclofen utilised in available trials (Brennan 2013). In France, where baclofen is frequently prescribed for the treatment of AUDs, an alarming increase of self-poisonings with baclofen, including suicide attempts and unintentional overdose, has been reported (e.g. Holla 2015; Pellisier 2017), leading to the advice that authorities should put forward a new policy for prescribing baclofen for this indication (Boels 2017).

How the intervention might work

The mesolimbic dopamine pathway, including dopamine cells in the ventral tegmental area projecting into the nucleus accumbens, has been shown to be crucial for drug reward and addiction (Volkow 2011; Wise 2009). Baclofen's primary mechanism of action for alcohol dependence is presumed to be the reduction of the reinforcing properties of alcohol by suppressing alcohol-stimulated dopamine release in the mesolimbic dopamine system. Agonistic effects of baclofen at GABAB receptors located in several brain areas including the mesolimbic circuit (Pitman 2014), and the ventral tegmental area, inhibit alcohol-induced firing of dopaminergic neurons and of the alcohol-stimulated dopamine release in the nucleus accumbens, resulting in the reduction of reinforcing properties of alcohol and drugs (Agabio 2014; Maccioni 2009; Young 2014). As baclofen did not affect spontaneous motor activity in rats,

baclofen's effects are shown not to be due to muscle-relaxant or sedative properties of the drug, but can rather be considered as a result of its ability to reduce the appetitive strength of alcohol (Colombo 2003). In addition, substitutional effects of baclofen to replace alcohol have been discussed (Chick 2012; Rolland 2013).

In addition, GABAB receptors are highly expressed in limbic structures involved in the mediation of anxiety, while activation of GABAB receptors in these structures might reduce anxiety (Morley 2014). Evidence from various clinical studies (Addolorato 2002; Flannery 2004; Garbutt 2010; Krupitsky 1993; Morley 2014), shows that baclofen reduced anxiety in people with AUD. Post-hoc analyses in one of the trials (Morley 2014), found that treatment with baclofen was most effective in people with comorbid anxiety. Following these lines of evidence, baclofen may also influence the subjective expression of craving and risk of relapse by suppressing anxiety associated with AUD (Morley 2014). Thus, besides dampening the reinforcing properties of alcohol through the suppression of alcohol-stimulated dopamine release in the mesolimbic dopamine system, baclofen's effects on drinking might also be due, at least in part, to the relief of anxiety symptoms (Agabio 2014).

Why it is important to do this review

While a number of pharmacological treatments have been approved for the treatment of AUD (see Background), their clinical use is limited by a number of factors. The aversive agent disulfiram has been shown to support abstinence (Jorgensen 2011), but due to its safety profile it is only a therapeutic option for selected patient groups with a high self-efficacy expectation to abstain from drinking after taking disulfiram (Mutschler 2016). Further substances like the opioid-antagonists naltrexone and nalmefene, and the glutamate antagonist, acamprosate appear to be safe and effective in people with AUD, but the strong variation in treatment response (Rösner 2010a; Rösner 2010b), indicates that patients might benefit from an extended range of treatment options that allow a further individualisation of pharmacological approaches. Baclofen as a treatment option for AUD has received much attention in recent years, initiated by pharmacological self-experimentation of Olivier Ameisen (Ameisen 2005). Even though numerous case reports and case series confirmed the effectiveness of baclofen in people with AUD, data from RCTs yield conflicting results (Brennan 2013; Ponizovsky 2015). The planned review of baclofen to achieve abstinence or to reduce alcohol consumption in people with AUD who are currently drinking, will provide a systematic integration of the available evidence for health decision makers, therapists and patients, and aims to offer illustrative measures for estimating the therapeutic benefits and risks of baclofen, while indicating gaps in knowledge and methodological demands for future clinical research.

OBJECTIVES

To assess the efficacy and safety of baclofen for treating people with AUD, who are currently drinking, with the aim of achieving and maintaining abstinence or reducing alcohol consumption

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of at least four weeks' treatment duration and 12 weeks' overall study duration, comparing baclofen with placebo, no treatment or other pharmacological treatments for achieving alcohol abstinence and reducing consumption in people with AUD. We will include studies employing a cross-over design, using data from the first active treatment stage only to remove the risk of carry-over effects.

Types of participants

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). There were no limitations on other participant characteristics such as concomitant substance use disorders or other comorbid psychiatric conditions. We also included trials with participants in methadone maintenance schemes. We excluded studies where baclofen was used to treat alcohol withdrawal.

We excluded people younger than 18 years of age and pregnant women because of the substantially different approach required for clinical management of these individuals.

Types of interventions

Experimental intervention

We included baclofen in any dose and route of administration. Studies could consider baclofen as monotherapy or in combination with further treatments provided that concomitant treatments were provided equally in both the experimental and control groups.

Control intervention

Placebo or any other pharmacological relapse prevention treatment, including acamprosate, naltrexone or nalmefene. We did not consider disulfiram as a control condition due to the psychological mediation of its effects.

Types of outcome measures

Primary 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, both subjectively or objectively assessed
- Dropouts from treatment: number of participants who did not complete the study protocol
- Dropout from treatment due to adverse events

Secondary outcomes

- Cumulative abstinence duration (the total sum of days a participant remained abstinent in the course of the study, including continuous as well as interrupted abstinence intervals)
- Craving, as measured by validated scales
- Anxiety, as measured by validated scales
- Depression, as measured by validated scales
- Frequency of most relevant adverse events

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

Search methods for identification of studies

The Cochrane Drugs and Alcohol Information Specialist conducted systematic searches for RCTs and controlled clinical studies. There were no language, publication year or publication status restrictions. The date of the search was 30 January 2018.

Electronic searches

We searched the following databases:

- Cochrane Drugs and Alcohol Group (CDAG) Specialised Register (30 January 2018; [Appendix 1](#));
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, issue 12) via onlinelibrary.wiley.com ([Appendix 2](#));
- MEDLINE via PubMed (January 1966 to 30 January 2018), using the search strategy outlined in [Appendix 3](#);
- Embase (www.elsevier.com/solutions/embase-biomedical-research; January 1974 to 30 January 2018; [Appendix 4](#));
- PsycINFO (EBSCOhost; 1800 to 30 January 2018; [Appendix 5](#));
- Web of Science (Thomson Reuters; January 2006 to 30 January 2018; [Appendix 6](#));
- CINAHL (EBSCOhost; 1982 to 30 January 2018; [Appendix 7](#)).

We searched the databases using MeSH and free-text terms relating to baclofen and alcohol dependence. We combined the PubMed search with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity-maximising version (Lefebvre 2011). We revised this strategy appropriately for each database to take account of differences in controlled vocabulary and syntax rules.

We searched the following trials registries on 30 January 2018:

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

Searching other resources

We contacted key informants and experts to request any further, potentially relevant studies and seek information about unpublished or incomplete trials. We also handsearched the reference lists of included studies and current reviews. We included all eligible studies identified by the search, irrespective of language, publication type or status.

Data collection and analysis

Selection of studies

Two authors (SM, RS) independently screened the abstracts of all publications that were obtained by the search strategy. Two authors (SM, RS) independently assessed the full text of potentially-relevant studies for inclusion. We used Covidence software ([Covidence](#)) for study selection. We resolved any disagreement by discussion; involving a third review author (SR) in case of persisting disagreements.

Data extraction and management

Two authors (RS, SM), independently extracted data. We resolved any doubts by discussion. We extracted the following information: number and characteristics of participants, setting, type of experimental and control intervention, length of follow-up, types of outcomes, country of origin, funding and conflict of interest. We used Covidence software for data extraction ([Covidence](#)).

Assessment of risk of bias in included studies

Two authors (SM, RS) independently assessed the risk of bias of the included studies. We used the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). The recommended approach for assessing risk of bias in studies included in Cochrane Reviews is a two-part tool, addressing the following specific domains: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgements we used the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions*, adapted to the addiction field. See [Appendix 8](#) for details.

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

We considered blinding of participants, personnel and outcome assessors (avoidance of performance bias and detection bias), separately for objective outcomes (e.g. dropout, duration of abstinence, relapse to use by urine or breath analysis), and subjective outcomes (e.g. patient self-reported use of substance, adverse events, craving, psychiatric symptoms).

We considered incomplete outcome data (avoidance of attrition bias), for all outcomes except for dropout from the treatment, which is very often the primary outcome measure in trials on addiction.

Measures of treatment effect

We analysed dichotomous outcomes by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed with a 95% confidence interval (CI). We analysed continuous outcomes by calculating the mean difference (MD) with 95% CI when the studies used the same instrument for assessing

the outcome. We used the standardised mean difference (SMD) when the studies used different instruments.

Unit of analysis issues

If we included multi-armed studies in the meta-analyses and one arm was considered more than once in the same comparisons (e.g. two different dosages of baclofen compared with the same control group), we combined all the relevant experimental groups into a single group and we compared it with the control to avoid double counting of participants in the control groups. For cross-over studies in meta-analyses, we planned to use data from the first period only (i.e. before cross-over), to address the risk of carry-over effects. We did not include any cross-over studies.

Dealing with missing data

For the analysis of binary outcome data (relapse), we included all randomised participants in the statistical analysis, with those who dropped out or who were lost to follow-up assigned to the relapse category. For continuous outcomes, we used data reported in the studies without any imputation of missing data.

Assessment of heterogeneity

We analysed heterogeneity by means of the I^2 statistic ([Higgins 2003](#)), and the χ^2 test. We regarded heterogeneity as substantial if the I^2 was greater than 50% or the P value lower than 0.10 for the χ^2 test for heterogeneity ([Deeks 2017](#)). Following the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2017](#)), we distinguished the following values to denote no important, moderate, substantial, and considerable heterogeneity, respectively: 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100%. If we found considerable levels of heterogeneity (i.e. 75% or above), we explored possible reasons by visually inspecting the forest plot to identify studies that might be contributing to heterogeneity.

Assessment of reporting biases

We planned to use visual inspection of funnel plots (plots of the effect estimate from each study against the sample size or effect standard error) to indicate possible publication bias if there were at least 10 studies included in the meta-analysis. We did not inspect funnel plot because we included fewer than 10 studies in the meta-analyses ([Sterne 2017](#)).

Data synthesis

We combined the outcomes from the individual trials through meta-analysis where possible (comparability of intervention and outcomes between trials), using a random-effects model, because we expected a certain degree of heterogeneity between trials. If the clinical or statistical heterogeneity between trials was too high (i.e. 75% to 100%), we considered not pooling the data.

Subgroup analysis and investigation of heterogeneity

We planned to investigate the sources of heterogeneity by performing subgroup analysis of studies for the following variables:

- different dosages of baclofen;
- participants with concomitant substance use disorders;
- participants with other comorbid psychiatric conditions.

We did not perform subgroup analyses because there were too few studies included in the meta-analyses. In particular, for the subgroup different dosages of baclofen, only one study ([Beraha 2016](#)), reported a high baclofen dose (150 mg a day), in a separate group from a low baclofen dose (30 mg a day), versus placebo, while [Muller 2015](#) reported a single group with a dosage in a range from 30 mg a day to 270 mg a day versus placebo, not stratifying results from low or high dose.

Sensitivity analysis

To incorporate our assessment of risk of bias in the review process we first plotted the intervention effect estimates stratified by risk of bias for allocation concealment (selection bias). If differences in the results were present among studies at different risks of selection bias, we planned to perform sensitivity analysis by excluding studies at high risk of bias from the analysis. We also planned to perform sensitivity analysis to assess how sensitive the results were to changes in the assumptions about missing data for relapse, assuming dropout or loss to follow-up as not relapsed. We did not perform any sensitivity analyses because there were no such cases.

Grading of evidence and 'Summary of findings' tables

We assessed the overall quality of the evidence for the following primary outcomes using the GRADE system: relapse, frequency of use, amount of use, any adverse events and dropout from treatment. The GRADE Working Group developed a system for grading the quality of evidence ([GRADE 2004](#); [Guyatt 2008](#); [Guyatt 2011](#); [Schünemann 2006](#)), which takes into account issues not only related to internal validity but also to external validity, such as directness of results.

We have presented the main findings of the review in a 'Summary of findings' table. This is a transparent and simple tabular format that provides key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes.

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

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Grading is decreased for the following reasons:

- serious (-1) or very serious (-2) study limitations for risk of bias;
- serious (-1) or very serious (-2) inconsistency between study results;
- some (-1) or major (-2) uncertainty about directness (the correspondence between the population, the intervention, or the outcomes measured in the studies actually found and those under consideration in our systematic review);
- serious (-1) or very serious (-2) imprecision of the pooled estimate;
- publication bias strongly suspected (-1).

We used the GRADEpro GDT ([GRADEpro GDT 2015](#)), software to prepare 'Summary of findings' tables.

RESULTS

Description of studies

Results of the search

The database searches (see [Electronic searches](#)) retrieved 858 records. Our searches of the trials registers identified 35 further records. Our screening of the reference lists of the included publications did not reveal additional RCTs. We therefore had a total of 893 records.

Once duplicates had been removed, we had a total of 469 records. We excluded 445 records based on titles and abstracts. We obtained and assessed the full texts of the remaining 24 records. We excluded four studies (see [Characteristics of excluded studies](#)), six records are awaiting classification (see [Characteristics of studies awaiting classification](#)), and we identified two ongoing studies (see [Characteristics of ongoing studies](#)).

We included 12 studies reported in 15 references.

For a further description of our screening process, see the PRISMA study flow diagram ([Figure 1](#); [Moher 2009](#)).

Figure 1. Study flow diagram

Figure 1. (Continued)

Included studies

We included 12 RCTs involving a total of 1128 participants (see [Characteristics of included studies](#)). The mean study size was 99 participants, ranging from 30 in [Leggio 2015](#) to 320 in [Reynaud 2017](#).

All studies but three ([Beraha 2016](#); [Hauser 2017](#); [Reynaud 2017](#)), recruited fewer than 100 participants. The mean age of participants was 48 years, and there were more men (69%) than women. All studies included participants with a diagnosis of alcohol dependence according the DSM IV or the ICD 10 criteria, who were currently drinking. Five studies took place in the USA and one each in Australia, France, Germany, India, Israel, Italy, and the Netherlands.

Most trials did not report comorbidity ([Garbutt 2010a](#); [Krupitskii 2017](#); [Leggio 2015](#); [Mishra 2010](#); [Morley 2014](#); [Muller 2015](#); [Ponizovsky 2015](#)); one study reported liver cirrhosis including Child-Pugh, Hepatitis B virus-positive, Hepatitis C virus-positive ([Addolorato 2007](#)); three studies reported depression and anxiety comorbidity ([Beraha 2016](#); [Garbutt 2010a](#); [Reynaud 2017](#)). One study ([Garbutt 2010b](#)), excluded patients with significant medical or psychiatric problems, including other substance dependence.

The mean duration of the interventions was 19.2 weeks (range 12 to 26 weeks). The mean duration of studies was 22.8 weeks (range 12 to 52 weeks).

Types of interventions

The included studies considered baclofen at different doses (range 10 mg a day to 270 mg a day). In [Muller 2015](#) the Baclofen dose varied from 30 mg a day to 270 mg a day. [Morley 2014](#) randomised participants in treatment to receive baclofen at 30 mg a day in one group and baclofen at 60 mg a day in another group. [Beraha 2016](#) grouped participants to receive baclofen at a low dose (30 mg a day) and at a high dose (150 mg a day).

In some cases, the dose was increased during the treatment, as in [Mishra 2010](#) (15 mg a day for the first three days and 30 mg a day subsequently for a total duration of three consecutive months), in [Addolorato 2007](#) (baclofen was given at a dose of 5 mg three times a day for the first three days; subsequently, the dose was increased to 10 mg three times per day), and in [Reynaud 2017](#) (the initial dose was provided twice a day, 10 mg morning and evening for two days, then three times a day and the dose increased by 10 mg every four days; a 17-week maintenance period at the dose reached at the end of the titration period).

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 comparison

All studies compared baclofen to placebo, except for one study ([Mishra 2010](#)), that evaluated baclofen versus acamprosate at a dose of 666.66 mg three times a day for three months. [Garbutt 2010b](#) divided participants into four groups: baclofen + placebo, baclofen + naltrexone, placebo + naltrexone, and placebo + placebo. For our analysis, we grouped participants into two groups: baclofen with or without naltrexone, placebo with or without naltrexone.

Excluded studies

We excluded four studies for various reasons: two studies because the objective of the study was not in our inclusion criteria (human laboratory study; [Leggio 2011](#); [Leggio 2013](#)); one study because its study design was not in our inclusion criteria ("uncontrolled preliminary study on 14 participants"; [Flannery 2004](#)); and one because the duration of the study was less than 12 weeks ([Addolorato 2002](#)). For more details see [Characteristics of excluded studies](#).

Studies awaiting classification

Six studies are awaiting classification. One published study reported only post hoc analyses ([Addolorato 2011](#)). We wrote to the study authors to request the results obtained from the primary analysis but they did not release them. Two are conference abstracts without enough useful data ([Farokhnia 2014](#); [Sharma 2012](#)), and the other three are protocols published on clinicaltrials.gov, where it is reported that the studies have been completed but the results have not been posted (CTRI/2016/01/006525; [Jaury 2014](#); [Morley 2013](#)). We wrote to the study authors to request the results obtained from the studies but they did not release them. See [Characteristics of studies awaiting classification](#) for more details.

Ongoing studies

Two studies are ongoing (CTRI/2011/11/002154; NCT01980706). See [Characteristics of ongoing studies](#) for more details.

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#). For a detailed description of the reasons supporting our judgment, see the 'Risk of bias' tables in the [Characteristics of included studies](#).

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): objective outcomes	Blinding of participants and personnel (performance bias): subjective outcomes	Blinding of outcome assessment (detection bias): subjective outcomes	Blinding of outcome assessment (detection bias): objective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Addolorato 2007	?	+	+	+	+	+	+	+
Beraha 2016	+	+	+	+	+	+	+	+
Garbutt 2010a	+	?	+	?	-	+	+	+
Garbutt 2010b	?	?	?	?	?	?	+	?
Hauser 2017	+	+	+	+	?	+	+	+
Krupitskii 2017	+	+	+	+	+	+	?	+
Leggio 2015	+	?	+	?	?	+	?	+
Mishra 2010	?	?	-	-	-	-	?	-
Morley 2014	+	+	+	+	?	+	-	+
Muller 2015	+	+	+	+	?	+	+	+
Ponizovsky 2015	+	?	+	+	?	+	+	+
Reynaud 2017	+	+	+	+	+	+	?	+

Allocation

Random sequence generation

We judged nine studies to be at low risk of bias; the study authors did not report any information about methods of sequence random generation for the other three studies, so we judged them to be at unclear risk of bias.

Allocation concealment

We judged seven studies to be at low risk of bias; the other five studies did not report methods of allocation concealment, so we judged them to be at unclear risk of bias.

Blinding

Performance bias

We judged 10 studies to be at low risk of bias for objective outcomes and one to be at high risk. One study did not provide information about blinding, so we judged it to be at unclear risk of bias.

We judged eight studies to be at low risk of bias for subjective outcomes and one to be at high risk. The other three studies did not report methods for blinding, so we judged them to be at unclear risk of bias.

Detection bias

For subjective outcomes, we considered four studies to be at low risk of bias and two studies to be at high risk of bias. The other six studies did not report enough information to make a judgement, so we judged them to be at unclear risk of bias.

For objective outcomes, we considered 10 studies to be at low risk of bias, one study to be at high risk of bias and one at unclear risk.

Incomplete outcome data

We deemed seven studies to be at low risk of bias and one study to be at high risk of bias. The other studies did not report numbers and reasons of dropouts or missing data for each group, so we judged them to be at unclear risk of bias.

Selective reporting

We judged 10 trials to be at low risk of bias and one study to be at high risk of bias. One study did not provide enough information, so we judged it to be at unclear risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Baclofen compared to placebo for alcohol use disorder](#)

We identified 12 randomised trials from which it was possible to extract numerical data. The only quantitative comparison was in relation to placebo (10 studies); just one study compared baclofen with acamprosate (Mishra 2010), and none of the included studies considered the effect of baclofen versus any other pharmacological treatment, including naltrexone or nalmefene.

Comparison 1: baclofen versus placebo

1.1 Relapse: return to any drinking at the end of treatment

For this outcome we found five relevant studies involving 781 participants. There was no difference between baclofen and

placebo (RR 0.88, 95% CI 0.74, to 1.04; moderate certainty evidence). This outcome had important levels of heterogeneity ($\text{Chi}^2 = 17.13$; $\text{df} = 4$; $P = 0.002$; $I^2 = 77\%$; [Analysis 1.1](#)).

1.2 Frequency of use: percentage of days abstinent at the end of treatment

For this outcome we found six relevant studies involving 465 participants. We did not find any difference between the two treatments in this comparison (MD 0.39, 95% CI -11.51 to 12.29; low certainty evidence). Heterogeneity was very high ($\text{Chi}^2 = 121.22$; $\text{df} = 5$; $P < 0.00001$; $I^2 = 96\%$; [Analysis 1.2](#)). One study with 40 participants (Garbutt 2010b), reported the main percentage of days abstinent for each group but didn't provide the SD; the mean percentage of days abstinent was 62.6% in the baclofen group and 46.1% in the placebo group.

1.3 Frequency of use: percentage of heavy drinking days at the end of treatment

We identified three studies relevant to this outcome involving 186 participants. There was no difference between baclofen and placebo (MD 0.25, 95% CI -1.25 to 1.76; moderate certainty evidence; [Analysis 1.3](#)). One study with 40 participants (Garbutt 2010b), reported the main percentage of heavy drinking days for each group but didn't provide the SD; the mean percentage of days abstinent was 13.2 % in the baclofen group and 14.4 % in the placebo group.

1.4 Amount of use: drink per drinking days at the end of treatment

We identified two studies relevant to this outcome involving 72 participants. We found evidence for this outcome that baclofen increases drink per drinking days compared with placebo (MD 1.55, 95% CI 1.32 to 1.77; low certainty evidence; [Analysis 1.4](#)).

1.5 Adverse events: number of participants with at least one side effect at the end of treatment

For this outcome we found four relevant studies involving 430 participants. We did not find evidence of a clear difference between the two treatments in this comparison (RR 1.04, 95% CI 0.99 to 1.10; high certainty evidence; [Analysis 1.5](#)).

1.6 Dropouts at the end of treatment

For this outcome we found eight relevant studies involving 977 participants. There was no difference between baclofen and placebo (RR 0.98, 95% CI 0.77 to 1.26; high certainty evidence; [Analysis 1.6](#)).

1.7 Dropout due to adverse events

For this outcome we found seven relevant studies involving 913 participants. There was no difference between baclofen and placebo (RR 1.11, 95% CI 0.59 to 2.07; high certainty evidence; [Analysis 1.7](#)).

1.8 Craving

For this outcome we found five relevant studies, with a total of 469 people. We did not find any difference between the two treatments in this comparison (MD 1.38, 95% CI -1.28 to 4.03). Heterogeneity was high ($\text{Chi}^2 = 14.40$; $\text{df} = 4.0$; $P = 0.006$; $I^2 = 72\%$; [Analysis 1.8](#)).

1.9 Anxiety

For this outcome we found five relevant studies involving 509 participants. We did not find any difference between baclofen and placebo (SMD 0.07, 95% CI -0.14 to 0.28; [Analysis 1.9](#)).

1.10 Depression

We identified three studies relevant to this outcome involving 387 participants. We found evidence that baclofen reduces depression compared with placebo (SMD 0.27, 95% CI 0.05 to 0.48; [Analysis 1.10](#)).

1.11 Adverse events: fatigue, tiredness

For this outcome we found six relevant studies involving 828 participants. There was no difference between baclofen and placebo (RR 1.24; 95% CI 0.98 to 1.56; [Analysis 1.11](#)).

1.12 Adverse events: insomnia

We identified four studies relevant to this outcome involving 577 participants. There was no difference between baclofen and placebo (RR 0.59, 95% CI 0.23 to 1.51; [Analysis 1.12](#)).

1.13 Adverse events: pain (diverse)

We identified two studies relevant to this outcome involving 86 participants. We did not find evidence of any difference between the two treatments in this comparison (RR 0.95, 95% CI 0.28 to 3.27; [Analysis 1.13](#)).

1.14 Adverse events: vertigo, dizziness

For this outcome we found seven relevant studies involving 858 participants. We found evidence that baclofen increases the frequency of vertigo when compared with placebo (RR 2.16, 95% CI 1.24 to 3.74; [Analysis 1.14](#)).

1.15 Adverse events: constipation

For this outcome we found four relevant studies involving 567 participants. There was no difference between baclofen and placebo (RR 0.93, 95% CI 0.54 to 1.58; [Analysis 1.15](#)).

1.16 Adverse events: somnolence, sleepiness, drowsiness or sedation

For this outcome we found nine relevant studies involving 986 participants. We found evidence that baclofen increased the frequency of somnolence when compared with placebo (RR 1.48, 95% CI 1.11 to 1.96; [Analysis 1.16](#)).

1.17 Adverse events: muscle pain

For this outcome we found four relevant studies involving 593 participants. There was no difference between baclofen and placebo (RR 0.94, 95% CI 0.39 to 2.26; [Analysis 1.17](#)).

1.18 Adverse events: dry mouth

We identified three studies relevant to this outcome with 509 participants. For this outcome, we found that baclofen increased the frequency of dry mouth compared with placebo (RR 2.68, 95% CI 0.77 to 9.32; [Analysis 1.18](#)).

1.19 Adverse events: nausea

For this outcome we found four relevant studies, with a total of 577 participants. There was no difference between baclofen and placebo (RR 1.19, 95% CI 0.61 to 2.30; [Analysis 1.19](#)).

1.20 Adverse events: skin rash

We identified three studies relevant to this outcome with 251 participants. We did not find any difference between the two treatments in this comparison (RR 2.59, 95% CI 0.78 to 8.55; [Analysis 1.20](#)).

1.21 Adverse events: headaches

We identified seven studies relevant to this outcome, with a total of 821 participants. We did not find a difference between the two treatments in this comparison (RR 1.23, 95% CI 0.84 to 1.81; [Analysis 1.21](#)).

1.22 Adverse events: paraesthesia/numbness

We identified four studies relevant to this outcome, with a total of 593 participants. We found that baclofen increases the frequency of paraesthesia (RR 4.28, 95% CI 2.11 to 8.67; [Analysis 1.22](#)).

1.23 Adverse events: diarrhoea

We identified two studies relevant to this outcome, with a total of 495 people. We did not find any difference between the two treatments in this comparison (RR 0.64, 95% CI 0.31 to 1.31; [Analysis 1.23](#)).

1.24 Adverse events: tinnitus

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find any difference between the two treatments in this comparison (RR 1.78, 95% CI 0.16 to 20.05). Heterogeneity was high ($\chi^2 = 8.36$; $df = 1.0$; $P = 0.004$; $I^2 = 88\%$; [Analysis 1.24](#)).

1.25 Adverse events: muscle spasm/rigidity

We identified three studies relevant to this outcome, with a total of 551 participants. We found that baclofen increases the frequency of muscle spasm (RR 1.94, 95% CI 1.08 to 3.48; [Analysis 1.25](#)).

1.26 Adverse events: hyperhidrosis

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find any difference between the two treatments in this comparison (RR 2.00, 95% CI 0.86 to 4.63; [Analysis 1.26](#)).

1.27 Adverse events: nasopharyngitis

We identified three studies relevant to this outcome, with a total of 551 participants. We did not find any difference between the two treatments in this comparison (RR 0.71, 95% CI 0.23 to 2.23). Heterogeneity was high ($\chi^2 = 7.36$; $df = 2.0$; $P = 0.03$; $I^2 = 73\%$; [Analysis 1.27](#)).

1.28 Adverse events: decreased appetite/anorexia

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find any difference between the two treatments in this comparison (RR 1.02, 95% CI 0.49 to 2.12; [Analysis 1.28](#)).

1.29 Adverse events: dysgeusia/ageusia

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find any difference between the two treatments in this comparison (RR 2.29, 95% CI 0.44 to 11.94. Heterogeneity was high ($\text{Chi}^2 = 2.99$; $\text{df} = 1.0$; $P = 0.08$; $I^2 = 67\%$; [Analysis 1.29](#)).

1.30 Adverse events: tremor

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find difference between the two treatments in this comparison (RR 0.87, 95% CI 0.46 to 1.65; [Analysis 1.30](#)).

1.31 Adverse events: weakness

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find any difference between the two treatments in this comparison (RR 1.07, 95% CI 0.60 to 1.92; [Analysis 1.31](#)).

1.32 Adverse events: vomiting

We identified two studies relevant to this outcome, with a total of 495 participants. We did not find any difference between the two treatments in this comparison (RR 0.97, 95% CI 0.50 to 1.88; [Analysis 1.32](#)).

1.33 Adverse events: urinary frequency

We identified three studies relevant to this outcome, with a total of 265 participants. We did not find any difference between the two treatments in this comparison (RR 1.64, 95% CI 0.35 to 7.63; [Analysis 1.33](#)).

Comparison 2: baclofen versus acamprosate

This comparison has only one outcome.

2.1 Craving

We identified one study relevant to this outcome, with a total of 49 participants. We found that baclofen increased craving compared with acamprosate (MD 14.62, 95% CI 12.72 to 16.52; [Analysis 2.1](#)).

DISCUSSION

Summary of main results

We included a total of 12 RCTs with 1128 participants and a minimum duration of 12 weeks in the review. Eleven of the 12 RCTs compared baclofen with placebo, and the other RCT compared baclofen with acamprosate. Meta-analyses did not find significant superiority of baclofen compared to placebo for any drinking outcome at the end of treatment (certainty of evidence low and moderate). In addition, we found no significant difference between baclofen and placebo for dropout, dropout due to adverse events (high-certainty evidence), number of participants with at least one adverse event, craving and anxiety, while depression was even higher in the baclofen than in the placebo group.

In comparison to placebo, baclofen increased the frequency of vertigo, somnolence, dry mouth, paraesthesia and muscle spasms. For all the other adverse events we did not find significant differences between baclofen and placebo.

For the comparison between baclofen and acamprosate, only one outcome was available, showing higher craving scores under baclofen compared to acamprosate; however, this result was based on one study of 49 participants, so should be interpreted with caution.

In addition, various outcomes had a high level of heterogeneity, reflecting the dichotomous nature of primary evidence (with the majority of RCTs missing significance contrasted by a small subset of trials with proof of efficacy), and indicating the need to identify potential sources of heterogeneity (see also [Quality of the evidence](#)).

Overall completeness and applicability of evidence

The diversity of the outcomes used to assess effectiveness in the included studies, diversity that, in many cases, limited the possibility of pooling the results, reflects the fact that various outcomes are established in alcoholism research with no clear superiority for one outcome compared to another in terms of validity or clinical relevance.

There is high variability in the trials considered in the review, for baclofen dosing, titration schedules, compliance, and duration of treatment. Additionally, we defined inclusion criteria in a non-restrictive way, so that samples would reflect a mix of different participant characteristics in terms of comorbidity and baseline alcohol use.

Nevertheless, heterogeneity of summary effects indicates that differences across effect sizes are likely due to sources other than sampling error, suggesting the impact of moderators and mediators that influence baclofen's effects on drinking outcomes. As subgroup analyses to investigate the impact of patient characteristics were not applicable due to the limited number of RCTs (see [Methods](#)), we qualitatively reviewed studies and 'Risk of bias' tables (see [Characteristics of included studies](#)), to identify differences between studies with and without proof of efficacy.

However, none of the considered variables could provide consistent explanations for the differences. While it has been suggested that baclofen may have more impact on higher severity of alcohol dependence by preclinical ([Maccioni 2012](#); [Walker 2007](#)), and clinical evidence ([Agabio 2014](#); [Leggio 2010](#)), [Hauser 2017](#) did not find an effect of baclofen on drinking when accounting for baseline alcohol use. Among reasons that may contribute to the discrepancy of findings, differences in baclofen dosing are among the most discussed issues ([Agabio 2014](#)). Indeed, maximum baclofen dosing was lower in some studies with non-significant results (e.g. [Garbutt 2010a](#); [Hauser 2017](#); [Ponizovsky 2015](#)), compared to those with significant findings ([Addolorato 2007](#); [Muller 2015](#)), while therapeutic response was shown not to differ between the low- and high-dose participants, as shown by subgroup analyses in one trial ([Beraha 2016](#)). In addition, the hypothesis that abstinence-maintaining effects in alcohol-dependent participants are mediated by the suppression of comorbid anxiety ([Agabio 2014](#); [Addolorato 2002](#); [Addolorato 2007](#)), a hypothesis consistent with the role of the GABAB receptor in the neural circuits of anxiety ([Cryan 2005](#)), was not confirmed by a recent trial ([Muller 2015](#)). Random error due to heterogeneity among the study sites may have lowered effect sizes for the opioid-antagonist naltrexone in multicentre studies ([Feinn 2005](#)), but non-significant effects have also been observed in single-centre studies on baclofen as well

(e.g. [Garbutt 2010a](#); [Krupitskii 2017](#); [Ponizovsky 2015](#)). In addition, further potential moderators of efficacy that could serve as a reason for contrasting results such as drinking status at baseline (abstinent versus actively drinking), or treatment setting (inpatient versus outpatient) do not systematically differ between RCTs with and without proof of efficacy.

The identification of moderators and mediators of efficacy by future research will not only be crucial for determining the therapeutic potential of baclofen, but also to assess the applicability of meta-analytic results to different frame conditions of baclofen use in clinical practice.

Data on adverse events from RCTs are more consistent, but unlikely to cover all conditions in routine care. Evidence from RCTs shows adverse events of baclofen that are of mild and transient nature such as vertigo, somnolence and dry mouth. Nevertheless, the review does not allow conclusions on the safety of baclofen taken outside the recommended dose range or in specific patient subgroups, such as individuals with suicidal ideation (e.g. [Holla 2015](#); [Pellissier 2017](#)).

Levels of the heterogeneity indicate that the summary effects shown in the meta-analyses of the review are not generalisable over all studied conditions and are likely to be affected by variables like sample, setting, or design. Our qualitative review of selected sample characteristics, treatment and design features, did not yield systematic differences between studies with and without proof of efficacy. Accordingly, available evidence could not provide consistent explanations for the diversity of findings.

Quality of the evidence

Applying the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), we judged most of the RCTs to have a low risk of selection, performance, detection (subjective outcome), attrition and reporting bias.

While the systematic application of criteria for assessing bias risks allowed us to rate the quality of studies and outcomes, it did not identify sources of bias that could explain the contrasting findings on the primary level of evidence. One potential threat of bias that concerns all RCTs applying inert placebo is the unmasking of blinding - a methodological limitation that has been shown to be associated with an overestimation of effects for antidepressant substances ([Moncrieff 2004](#)). Even though baclofen and placebo were of identical appearance in most RCTs, perceptible differences between treatment groups such as adverse events can reveal participants' affiliation to treatment conditions. Thus, from a theoretical perspective, we could not definitely exclude the possibility that proof of efficacy in some trials is attributable to an overestimation of effects caused by an unmasking of treatment allocation.

All in all, we rated the certainty of evidence as high for the outcomes dropouts, participants with at least one adverse event, and dropout due to adverse events; moderate for relapse to any drinking, percentage of heavy drinking days; and as low for number of drinks per drinking days and percent days abstinent. Reasons for downgrading were inconsistency among study results for the outcomes relapse and percentage of days abstinent, showed by high or very high heterogeneity among study results or imprecision because of few or very few participants included in the analysis

for the outcome percentage of heavy drinking days at end of treatment, and drink per drinking days.

Potential biases in the review process

To lower the risk of bias in the review process, two review authors independently screened abstracts, assessed full texts, rated risk of bias for included studies and extracted data from primary studies. None of the review authors has any personal, scientific or financial conflicts of interest or expected advantages from significant results in terms of reviewer decisions or raising funds, lowering the risk for confirmation bias ([Nickerson 1998](#)), and significance bias ([Kagereki 2016](#)). We could not inspect funnel plots for risk of possible publication bias due to the small number of studies included in the meta-analyses; however, we wrote to the authors of published studies and searched on [ClinicalTrials.gov](#) and [ICTRP](#) to search for unpublished studies to minimise the risk of publication bias.

Agreements and disagreements with other studies or reviews

Overall, most conclusions of the review are in line with previous reviews, emphasising the inconsistency of results and the necessity for further research (e.g. [Agabio 2014](#); [Brennan 2013](#); [Lesouef 2014](#)). While the review corresponds with further meta-analyses ([Lesouef 2014](#); [Rose 2018](#)), by missing significance for frequency measures of alcohol use, it did not confirm the significance of effects for continuous abstinence ('return to any drinking'). While [Lesouef 2014](#) identified a significant 2.8-fold increase of the chance of maintaining abstinence under baclofen compared to placebo (RR 2.79 95% CI 1.79 to 4.34, 3 RCTs, 65 participants), and [Rose 2018](#) a 2.7-fold increase (OR 2.67 95% CI 1.03 to 6.93; 6 RCTs, 590 participants), effects on abstinence in the review at hand missed significance. At the same time, the discrepancy between findings is mainly attributable to differences in the dates of search and the criteria for including RCTs in the meta-analytic integrations. The present review also considered newer RCTs with weaker effects (e.g. [Beraha 2016](#); [Hauser 2017](#); [Krupitskii 2017](#); [Reynaud 2017](#)), but defined a duration of 12 weeks as a criteria of inclusion. We chose a minimum of 12 weeks' treatment to allow an adequate implementation of the intervention, but this led to the exclusion of a study with a comparatively large positive treatment effect ([Addolorato 2002](#)).

AUTHORS' CONCLUSIONS

Implications for practice

None of the primary or secondary outcomes of the review showed evidence of a difference between baclofen and placebo. Baclofen was similar to placebo in both maintaining continuous abstinence and in reducing drinking frequency or drinking amount. Evidence from meta-analytic integrations of primary evidence does not indicate positive effects of baclofen in the treatment of alcohol use disorder (AUD), and does not support the use of baclofen as a first-line treatment for people with AUD. Even though some results from randomised controlled trials (RCTs) are promising, current evidence remains uncertain regarding the use of baclofen as a first-line treatment for people with AUD. Nevertheless, the heterogeneity of summary effects and their susceptibility to marginal changes in the primary data illustrates the preliminary character of efficacy conclusions and the need for

further research targeting moderators of efficacy and specific bias risks (see [Implications for research](#)).

Implications for research

For exploring the inconsistency of effects shown in the review, factors like dosing schedules, treatment setting, severity of AUD and drinking status at the beginning of treatment might be potential mediators of efficacy. One factor requiring special attention in future studies is the titration of dose to obtain an optimal therapeutic response. Due to the high inter-individual variation of effective doses ([Thompson 2017](#)), titration regimes might be advantageous compared to fixed dosing of baclofen in future studies. In addition, to ensure an adequate implementation of treatment and a sufficient 'fairness of testing', participants' compliance should be monitored to ensure that dosing schedules are implemented as foreseen in the study protocol.

One potential threat to bias that needs to be further addressed by research is the unmasking of blinding in the course of treatment. Even though quality of blinding is ensured by various measures

of bias control, such as allocation concealment and blinding of participants and personnel, adverse events can potentially reveal a participant's affiliation to treatment conditions in the course of treatment. The use of active placebo mimicking adverse events of baclofen could prevent an overestimation of effects through response bias, placebo effects or differential attrition ([Hróbjartsson 2014](#)). If inert placebo is used, testing of blinding integrity by querying participants about their assumed group allocation would be a simple method that allows at least a retrospective assessment of blinding integrity ([Wilsey 2016](#)).

Thus, the further exploration of baclofen's profile of efficacy and safety and the identification of moderators and mediators of baclofen's effects on alcohol use remains a challenge for further research.

ACKNOWLEDGEMENTS

Parts of this review were generated using RevMan HAL v 4.0 (schizophrenia.cochrane.org/revman-hal-v4).

REFERENCES

References to studies included in this review

Addolorato 2007 {published data only}

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](https://doi.org/10.1016/S0140-6736(07)61814-5)]

Beraha 2016 {published data only}

Beraha EM, Salemin E, Goudriaan AE, Bakker A, De Jong 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. *European Neuropsychopharmacology* 2017;**26**(12):1950-9.

Garbutt 2010a {published data only}

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. *Alcoholism, Clinical and Experimental Research* 2010;**34**(11):1849-57. [DOI: [10.1111/j.1530-0277.2010.01273.x](https://doi.org/10.1111/j.1530-0277.2010.01273.x)]

Garbutt 2010b {published data only}

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. *Alcoholism: Clinical and Experimental Research* 2010;**34**(6):178A.

Hauser 2017 {published data only}

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](https://doi.org/10.1111/add.13787)]

Krupitskii 2017 {published data only}

* 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). *Neuroscience and Behavioral Physiology* 2017;**47**(2):153-62. [DOI: [10.1007/s11055-016-0379-6](https://doi.org/10.1007/s11055-016-0379-6)]

Krupitsky EM, Rybakova KV, Kiselev AS, Alexeeva YV, Berntsev VA, Chekhlatyi EI, et al. Double blind placebo controlled randomized pilot clinical trial of baclofen (Baclosan®) for alcohol dependence. *Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova* 2015;**115**(6):53-62. [DOI: [10.17116/jnevro20151156153-62](https://doi.org/10.17116/jnevro20151156153-62)]

Leggio 2015 {published data only}

Bollinger J, Edwards SM, Zywiak WK, Tidey JW, Swift RM, Kenna GA, et al. A double-blind, placebo-controlled randomized pilot study of the effects of baclofen on alcohol-tobacco co-use and alcohol cue-reactivity in alcoholic smokers. *Clinical and Translational Science* 2014;**7**(3):265.

* Leggio L, Zywiak WH, Edwards SM, Tidey JW, Swift 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](https://doi.org/10.1007/s00213-014-3652-9)]

Mishra 2010 {published data only}

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 Journal of Psychiatry* 2010;**52**:S69.

Morley 2014 {published data only}

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 and Alcoholism* 2014;**49**(6):654-60. [DOI: [10.1093/alcalc/agu062](https://doi.org/10.1093/alcalc/agu062)]

Muller 2015 {published data only}

* 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. *European Neuropsychopharmacology* 2015;**25**(8):1167-77. [DOI: [10.1016/j.euroneuro.2015.04.002](https://doi.org/10.1016/j.euroneuro.2015.04.002)]

Muller CA, Geisel O, Pelz P, Higl V, Kruger J, Stickel A, et al. Individually titrated high-dose baclofen for the treatment of alcohol dependence (BACLAD study)-a randomized controlled trial. *European Psychiatry* 2015;**30**(S1):1611. [DOI: [10.1016/S0924-9338\(15\)31243-8](https://doi.org/10.1016/S0924-9338(15)31243-8)]

Ponizovsky 2015 {published data only}

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. *Journal of Substance Abuse Treatment* 2015;**52**:24-30. [DOI: [10.1016/j.jsat.2014.11.007](https://doi.org/10.1016/j.jsat.2014.11.007)]

Reynaud 2017 {published data only}

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 and Alcoholism* 2017;**52**(4):439-46.

References to studies excluded from this review

Addolorato 2002 {published data only}

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 & Alcoholism* 2002;**37**:504-8.

Flannery 2004 {published data only}

Flannery BA, Garbutt JC, Cody MW, Renn W, Grace K, Osborne M, et al. Baclofen for alcohol dependence: a preliminary open-label study. *Alcoholism, Clinical and Experimental Research* 2004;**28**(10):1517-23.

Leggio 2011 {published data only}

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 2013 {published data only}

Leggio L, Zywiak WH, McGeary JE, Edwards S, Fricchione SR, Shoaff JR, et al. A human laboratory pilot study with baclofen in alcoholic individuals. *Pharmacology, Biochemistry, and Behavior* 2013;**103**(4):784-91. [DOI: [10.1016/j.pbb.2012.11.013](https://doi.org/10.1016/j.pbb.2012.11.013)]

References to studies awaiting assessment

Addolorato 2011 {published data only}

* 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 and Alcoholism (Oxford, Oxfordshire)* 2011;**46**(3):312-7. [DOI: [10.1093/alcalc/agr017](https://doi.org/10.1093/alcalc/agr017)]

Addolorato G, Leggio L, on behalf of all authors. Response to Ameisen. *Alcohol and Alcoholism (Oxford, Oxfordshire)* 2011;**46**(4):504-5. [DOI: [10.1093/alcalc/agr061](https://doi.org/10.1093/alcalc/agr061)]

CTRI/2016/01/006525 {published data only}

CTRI/2016/01/006525. Role of baclofen and topiramate in alcoholism. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=13646 2016.

Farokhnia 2014 {published data only}

Farokhnia M, Edwards SM, Bollinger J, Amodio J, Zywiak WH, Tidey JW. Baclofen as a pharmacotherapy for the treatment of concurrent alcohol and nicotine dependence: a double-blind, placebo-controlled, randomized trial. *Neuropsychopharmacology* 2014;**39**:S340. [DOI: [10.1038/npp.2014.281](https://doi.org/10.1038/npp.2014.281)]

Farokhnia M, Edwards SM, Bollinger J, Amodio J, Zywiak WH, Tidey JW, et al. Corrigendum: T76. Baclofen as a pharmacotherapy for the treatment of concurrent alcohol and nicotine dependence: a double-blind, placebo-controlled, randomized trial (*Neuropsychopharmacology* (2014) 39 (S291-S472) DOI: [10.1038/npp.2014.281](https://doi.org/10.1038/npp.2014.281)). *Neuropsychopharmacology* 2015;**40**(6):1560.

Jaury 2014 {published data only}

Jaury PH. Baclofen for the treatment of alcohol drinkers (Bacloville). *Alcoholism: Clinical and Experimental Research* 2014;**38**:215a.

Morley 2013 {published data only}

Morley KC, Leung S, Baillie A, Haber PS. The efficacy and biobehavioural basis of baclofen in the treatment of alcoholic liver disease (BacALD): study protocol for a randomised controlled trial. *Contemporary Clinical Trials* 2013;**36**(2):348-55. [DOI: [10.1016/j.cct.2013.08.002](https://doi.org/10.1016/j.cct.2013.08.002)]

Sharma 2012 {published data only}

Sharma V, Sharma R, Chaturvedi M, Bharadwaj B. A dose-response effect of baclofen in reducing daily alcohol intake in alcohol-dependent subjects. *Journal of Gastroenterology and Hepatology* 2012;**27**:263. [DOI: [10.1111/jgh.12006](https://doi.org/10.1111/jgh.12006)]

References to ongoing studies

CTRI/2011/11/002154 {published data only}

CTRI/2011/11/002154. Efficacy and safety of baclofen GRS for treatment of alcohol dependence, a 12 week study. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3752 (first received 21 November 2011).

NCT01980706 {published data only}

NCT01980706. Efficacy and safety of high dose baclofen for alcohol dependence. clinicaltrials.gov/show/NCT01980706 (first received November 11, 2013).

Additional references

Agabio 2007

Agabio R, Marras P, Addolorato G, Carpinello B, Gessa GL. Baclofen suppresses alcohol intake and craving for alcohol in a schizophrenic alcohol-dependent patient: a case report. *Journal of Clinical Psychopharmacology* 2007;**27**(3):319-20.

Agabio 2013

Agabio R, Preti A, Gessa GL. Efficacy and tolerability of baclofen in substance use disorders: a systematic review. *European Addiction Research* 2013;**19**(6):325-45.

Agabio 2014

Agabio R, Colombo G. GABAB receptor ligands for the treatment of alcohol use disorder: preclinical and clinical evidence. *Frontiers in Neuroscience* 2014;**8**:140. [DOI: [10.3389/fnins.2014.00140](https://doi.org/10.3389/fnins.2014.00140)]

Alonso 2004

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica. Supplementum* 2004;**420**:21-7.

Amato 2010

Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 3. [DOI: [10.1002/14651858.CD005063.pub3](https://doi.org/10.1002/14651858.CD005063.pub3)]

Amato 2011

Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: [10.1002/14651858.CD008537.pub2](https://doi.org/10.1002/14651858.CD008537.pub2)]

Ameisen 2005

Ameisen O. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-

dose baclofen: a self-case report of a physician. *Alcohol and Alcoholism (Oxford, Oxfordshire)* 2005;**40**(2):147-50.

APA 1980

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd Edition. Washington, DC: American Psychiatric Association, 1980.

APA 1987

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

APA 2000

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition. Washington, DC: American Psychiatric Association, 2000.

APA 2013

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. Washington, DC: American Psychiatric Association, 2013.

Boels 2017

Boels D, Victorri-Vigneau C, Grall-Bronnec M, Touré A, Garnier A, Turcant A, et al. Baclofen and alcohol-dependent patients: a real risk of severe self-poisoning. *Basic & Clinical Pharmacology & Toxicology* 2017;**121**(4):353-9.

Brennan 2013

Brennan JL, Leung JG, Gagliardi JP, Rivelli SK, Muzyk AJ. Clinical effectiveness of baclofen for the treatment of alcohol dependence: a review. *Clinical Pharmacology* 2013;**5**:99-107. [DOI: [10.2147/CPAA.S32434](https://doi.org/10.2147/CPAA.S32434)]

Bucknam 2006

Bucknam W. Suppression of symptoms of alcohol dependence and craving using high-dose baclofen. *Alcohol and Alcoholism* 2006;**2**(42):158-60.

Chick 2012

Chick J, Nutt DJ. Substitution therapy for alcoholism: time for a reappraisal?. *Journal of Psychopharmacology* 2012;**26**(2):205-12.

Colombo 2003

Colombo G, Vacca G, Serra S, Brunetti G, Carai MA, Gessa GL. Baclofen suppresses motivation to consume alcohol in rats. *Psychopharmacology* 2003;**167**(3):221-4.

Covidence [Computer program]

Veritas Health Innovation. Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 30 January 2018.

Cryan 2005

Cryan JF, Kaupmann K. Don't worry 'B' happy!: a role for GABA(B) receptors in anxiety and depression. *Trends in Pharmacological Sciences* 2005;**26**:36-43.

Dario 2004

Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. *Drug Safety* 2004;**27**(11):799-818.

Deeks 2017

Deeks JJ, Higgins JP, Altman DG (editors) on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Feinn 2005

Feinn R, Kranzler HR. Does effect size in naltrexone trials for alcohol dependence differ for single-site vs. multi-center studies?. *Alcoholism, Clinical and Experimental Research* 2005;**29**(6):983-8.

Garbutt 2010

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. *Alcoholism, Clinical and Experimental Research* 2010;**34**(11):1849-57.

Gillman 2007

Gillman MA, Lichtigfeld F, Young T. Psychotropic analgesic nitrous oxide for alcoholic withdrawal states. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: [10.1002/14651858.CD005190.pub2](https://doi.org/10.1002/14651858.CD005190.pub2)]

GRADE 2004

GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(19):1490-4.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 30 January 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Grant 2015

Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: results From the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry* 2015;**72**(8):757-66.

Grant 2017

Grant BF, Chou SP, Saha TD, Pickering RP, Kerridge BT, Ruan WJ, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry* 2017;**74**(9):911-23.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7560):924-6.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines 1. Introduction-GRADE evidence profiles and

summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**:383-94.

Hasin 2006

Hasin D, Hatzenbuehler ML, Keyes K, Ogburn E. Substance use disorders: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases, tenth edition (ICD-10). *Addiction* 2006;**101**(Suppl 1):59-75.

Hasin 2013

Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *American Journal of Psychiatry* 2013;**170**(8):834-51.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Higgins 2017

Higgins JP, Altman DG, Sterne JA (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Holla 2015

Holla B, Gowda GS, Prabhu L, Baby S, Viswanath B, Chand P, et al. High doses of baclofen as suicide attempt in patients with alcohol use disorders - a serious concern. *Asian Journal of Psychiatry* 2015;**17**:99-100.

Hróbjartsson 2014

Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *International Journal of Epidemiology* 2014;**43**(4):1272-83.

Jorgensen 2011

Jorgensen CH, Pedersen B, Tonnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcoholism, Clinical and Experimental Research* 2011;**35**:1749-58.

Kagereki 2016

Kagereki E, Gakonyo J, Simila H. Significance bias: an empirical evaluation of the oral health literature. *BMC Oral Health* 2016;**16**(1):53.

Krupitsky 1993

Krupitsky EM, Burakov AM, Ivanov VB, Krandashova GF, Lapin IP, Grinenko AJ, et al. Baclofen administration for the treatment

of affective disorders in alcoholic patients. *Drug and Alcohol Dependence* 1993;**33**(2):157-63.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Leggio 2010

Leggio L, Garbutt JC, Addolorato G. Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS & Neurological Disorders Drug Targets* 2010;**9**:33-44.

Leone 2010

Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database of Systematic Reviews* 2010, Issue 2. [DOI: [10.1002/14651858.CD006266.pub2](https://doi.org/10.1002/14651858.CD006266.pub2)]

Lesouef 2014

Lesouef N, Bellet F, Mounier G, Beyens MN. Efficacy of baclofen on abstinence and craving in alcohol-dependent patients: a meta-analysis of randomized controlled trials. *Therapie* 2014;**69**(5):427-35.

Liu 2015

Liu J, Wang LN. Baclofen for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2015, Issue 4. [DOI: [10.1002/14651858.CD008502.pub4](https://doi.org/10.1002/14651858.CD008502.pub4)]

Maccioni 2005

Maccioni P, Serra S, Vacca G, Orrù A, Pes D, Agabio R, et al. Baclofen-induced reduction of alcohol reinforcement in alcohol-preferring rats. *Alcohol* 2005;**36**(3):161-8.

Maccioni 2009

Maccioni P, Colombo G. Role of the GABA(B) receptor in alcohol-seeking and drinking behavior. *Alcohol* 2009;**43**(7):555-8.

Maccioni 2012

Maccioni P, Zaru A, Loi B, Lobina C, Carai MA, Gessa GL, et al. Comparison of the effect of the GABAB receptor agonist, baclofen, and the positive allosteric modulator of the GABAB receptor, GS39783, on alcohol self-administration in 3 different lines of alcohol-preferring rats. *Alcoholism, Clinical and Experimental Research* 2012;**36**(10):1748-66.

Martin-Fardon 2013

Martin-Fardon R, Weiss F. Modeling relapse in animals. *Current Topics in Behavioral Neurosciences* 2013;**13**:403-32.

Minozzi 2010

Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 3. [DOI: [10.1002/14651858.CD006754.pub4](https://doi.org/10.1002/14651858.CD006754.pub4)]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Medicine* 6;7:e1000097. [DOI: [10.1371/journal.pmed1000097](https://doi.org/10.1371/journal.pmed1000097)]

Moncrieff 2004

Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: [10.1002/14651858.CD003012.pub2](https://doi.org/10.1002/14651858.CD003012.pub2)]

Moos 2006

Moos RH, Moos BS. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006;101(2):212-22.

Mutschler 2016

Mutschler J, Grosshans M, Soyka M, Rösner S. Current findings and mechanisms of action of disulfiram in the treatment of alcohol dependence. *Pharmacopsychiatry* 2016;49(4):137-41.

Nickerson 1998

Nickerson RS. Confirmation bias: a ubiquitous phenomenon in many guises. *Review of General Psychology* 1998;2(2):175-220.

Pani 2014

Pani PP, Trogu E, Pacini M, Maremmani I. Anticonvulsants for alcohol dependence. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: [10.1002/14651858.CD008544.pub2](https://doi.org/10.1002/14651858.CD008544.pub2)]

Pastor 2012

Pastor A, Jones D, Currie J. High-dose baclofen for treatment-resistant alcohol dependence. *Journal of Clinical Psychopharmacology* 2012;32:266-8.

Pedersen 2013

Pedersen B, Askgaard G, Oppedal K. Disulfiram for alcohol use disorder. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: [10.1002/14651858.CD010487](https://doi.org/10.1002/14651858.CD010487)]

Pellissier 2017

Pellissier F, de Haro L, Cardona F, Picot C, Puskarczyk E, Saporì JM, et al. Self-poisoning with baclofen in alcohol-dependent patients: national reports to French Poison Control Centers, 2008-2013. *Clinical Toxicology* 2017;55(4):275-84.

Pitman 2014

Pitman KA, Puil E, Borgland SL. GABA(B) modulation of dopamine release in the nucleus accumbens core. *European Journal of Neuroscience* 2014;40(10):3472-80.

Rehm 2009

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009;373(9682):2223-33.

Rehm 2013

Rehm J, Marmet S, Anderson P, Gual A, Kraus L, Nutt DJ, et al. Defining substance use disorders: do we really need more than heavy use?. *Alcohol and Alcoholism* 2013;48(6):633-40.

Roerecke 2013

Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. *Addiction* 2013;108(9):1562-78.

Rolland 2013

Rolland B, Bordet R, Deheul S, Cottencin O. Baclofen for alcohol-dependence: anticraving or partial substitution?. *Journal of Clinical Psychopharmacology* 2013;33(2):280-1.

Rose 2018

Rose AK, Jones A. Baclofen: its effectiveness in reducing harmful drinking, craving, and negative mood. A meta-analysis. *Addiction* 2018;113(8):1396-406.

Rösner 2010a

Rösner S, Hackl-Herrwerth A, Leucht S, Leherer P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: [10.1002/14651858.CD004332.pub2](https://doi.org/10.1002/14651858.CD004332.pub2)]

Rösner 2010b

Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: [10.1002/14651858.CD001867.pub3](https://doi.org/10.1002/14651858.CD001867.pub3)]

Sarai 2013

Sarai M, Tejani AM, Chan AHW, Kuo IF, Li J. Magnesium for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: [10.1002/14651858.CD008358.pub2](https://doi.org/10.1002/14651858.CD008358.pub2)]

Schwarz Pharma 2003

Schwarz Pharma. Kemstro® (oral baclofen tablets) package insert. Schwarz Pharma, Monheim, Germany 2003.

Schünemann 2006

Schünemann HJ, Jaeschke R, Cook D, Bria W, El-Solh A, Ernst A. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *American Journal of Respiratory and Critical Care Medicine* 2006;174(5):605-14.

Steardo 1984

Steardo L, Leo A, Marano E. Efficacy of baclofen in trigeminal neuralgia and some other painful conditions. A clinical trial. *European Neurology* 1984;23(1):51-5.

Sterne 2017

Sterne JAC, Egger M, Moher D, Boutron I (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Thompson 2017

Thompson A, Owens L, Richardson P, Pirmohamed M. Systematic review: baclofen dosing protocols for alcohol use disorders used in observational studies. *European Neuropsychopharmacology* 2017;**27**(11):1077-89.

Vaz de Lima 2010

Vaz de Lima FB, Andriolo RB, da Silveira DX. Dopaminergic antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: [10.1002/14651858.CD003352.pub4](https://doi.org/10.1002/14651858.CD003352.pub4)]

Volkow 2011

Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. *Proceedings of the National Academy of Sciences USA* 2011 Sep 13;**108**(37):15037-42.

Walker 2007

Walker BM, Koob GF. The gamma-aminobutyric acid-B receptor agonist baclofen attenuates responding for ethanol in ethanol-dependent rats. *Alcoholism, Clinical and Experimental Research* 2007;**31**(1):11-8.

White 2015

White A, Castle IJ, Chen CM, Shirley M, Roach D, Hingson R. Converging patterns of alcohol use and related outcomes among females and males in the United States, 2002 to 2012. *Alcoholism, Clinical and Experimental Research* 2015;**39**(9):1712-26.

WHO 1992

World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Geneva (Switzerland): World Health Organization, 1992.

WHO 2002a

World Health Organization. The world health report 2002 – Reducing risks to health, promoting healthy life. Geneva: WHO2002.. The World Health Report 2002 – reducing risks, promoting healthy life. Geneva: WHO, 2002.

WHO 2002b

World Health Organization. Alcohol in developing societies: a public health approach. Geneva: WHO, 2002.

WHO 2010

World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 4th Edition. Geneva: World Health Organization, 2010.

WHO 2014

World Health Organization. Global status report on alcohol and health. Geneva: World Health Organization, 2014.

Wilsey 2016

Wilsey B, Deutsch R, Marcotte TD. Maintenance of blinding in clinical trials and the implications for studying analgesia using cannabinoids. *Cannabis and Cannabinoid Research* 2016;**1**(1):139-48.

Wise 2009

Wise RA. Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. *Trends in Neurosciences* 2009;**32**(10):517-24.

Young 2014

Young KA, Franklin TR, Roberts DC, Jagannathan K, Suh JJ, Wetherill RR, et al. Nipping cue reactivity in the bud: baclofen prevents limbic activation elicited by subliminal drug cues. *Journal of Neuroscience* 2014;**34**(14):5038-43.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Addolorato 2007

Methods	Study design: RCT
	Study grouping: parallel-group
Participants	Baseline characteristics
	Baclofen
	<ul style="list-style-type: none"> Age (years): median 49.0 (IQR 43.0–61.0) Gender: male 32 (76%) Sample size: 42 Race: NR Marital status: 27 (64%) married Educational level: 12 (29%); education > 13 years Current use: OCDS scores, OCDS total: median 28.0 (IQR 23.0-32.0)

Baclofen for alcohol use disorder (Review)

Addolorato 2007 (Continued)

- Comorbidity: Child-Pugh score median 90 (IQR 80-110); hepatitis B virus-positive 10 (24%); hepatitis C virus-positive 12 (29%)

Placebo

- Age (years): median 49.0 (IQR 4.0-60.0)
- Gender: male 29 (69%)
- Sample size: 42
- Race: NR
- Marital status: 24 (57%) married
- Educational level: 9 (21%) education > 13 years
- Current use: OCDS scores OCDS total median 25.0 (IQR 22.0-29.0)
- Comorbidity: Child-Pugh score: median 90 (IQR 8.0-11.0); hepatitis B virus-positive 10 (24%); hepatitis C virus-positive 12 (29%)

Inclusion criteria: age-range 18-75 years; diagnosis of alcohol dependence according to DSM-IV criteria; diagnosis of liver cirrhosis; an alcohol intake of ≥ 2 heavy drinking d/week on average (men ≥ 5 drinks/d; women ≥ 4 drinks/d) and an average overall consumption of ≥ 21 drinks/week for men and ≥ 14 drinks/week for women during the 4 weeks before enrolment (1 standard drink = 12 g absolute alcohol); and presence of a referred family member able to assist with drug administration and monitoring

Exclusion criteria: severe heart or lung disease; abnormal renal function, hepatorenal syndrome, or both; malignant disease; metabolic diseases; hepatic encephalopathy; treatment with interferon or corticosteroids within the past 60 days; psychopathological illness treated with psychoactive drugs; epilepsy; and addiction to drugs other than nicotine

Interventions	<p>Intervention characteristics</p> <p>Baclofen (participants = 42) + counselling</p> <ul style="list-style-type: none"> • Dose: for the first 3 days, baclofen was given at a dose of 5 mg, 3 times/d; subsequently, the dose was increased to 10 mg 3 times/d • Duration of treatment: 12 consecutive weeks • Length of follow-up: 16 weeks <p>Placebo (participants = 42) + counselling</p> <ul style="list-style-type: none"> • Dose: N/A • Duration of treatment: 12 weeks • Length of follow up: 16 weeks
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Proportion of participants achieving and maintaining alcohol abstinence • Total abstinence duration • Cumulative abstinence duration (as the total number of days abstinent from alcohol) • Alcohol relapse (as a daily alcohol intake of > 4 drinks or an overall consumption of ≥ 14 drinks/week during at least 4 weeks) • Alcohol lapse (as any episode of alcohol consumption not classified as relapse) • Adverse events attributable to drug withdrawal <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Difference in craving measures between groups (craving level was ascertained by the Italian version of the OCDS). • Measurement of liver enzymes and biological markers of alcohol abuse (i.e. amounts of aspartate aminotransferase, alanine aminotransferase, γ glutamyl transpeptidase, and total bilirubin; international normalised ratio; and mean cellular volume), concentrations in blood of creatinine and ammonia

Addolorato 2007 (Continued)

Identification

Sponsorship source: Italian Ministry for University, Scientific and Technological Research (MURST), and by the European Research Advisory Board (ERAB)

Country: Italy

Setting: Institute of Internal Medicine of the Catholic University in Rome, Italy (which has both a liver unit and an alcohol addiction unit)

Author's name: Dr Giovanni Addolorato

Institution: Institute of Internal Medicine, Catholic University of Rome

Email: giovanni.addolorato@unicatt.it

Address: Largo A Gemelli 8, I-00168 Rome, Italy

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was balanced with blocks." Quote: "eligible patients who provided informed consent were randomly allocated either oral baclofen or placebo."
Allocation concealment (selection bias)	Low risk	Quote: "were randomly allocated either oral baclofen or placebo. The randomisation sequence was generated by the pharmacist who prepared drug and placebo. Randomisation was balanced with blocks. The pharmacist did not have any further role in the study."
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. To maintain masking, the randomisation code was concealed in a safe box in the pharmacy. For the duration of the study (including also the 4 weeks of follow-up), the pharmacist or another employee of the same pharmacy could be contacted at any time to open the safe box in the case of a specific emergency." Quote: "Placebo tablets were identical in size, colour, shape, and taste to baclofen."
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. To maintain masking, the randomisation code was concealed in a safe box in the pharmacy. For the duration of the study (including also the 4 weeks of follow-up), the pharmacist or another employee of the same pharmacy could be contacted at any time to open the safe box in the case of a specific emergency." Quote: "Placebo tablets were identical in size, colour, shape, and taste to baclofen."
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. To maintain masking, the randomisation code was concealed in a safe box in the pharmacy. For the duration of the study (including also the 4 weeks of follow-up), the pharmacist or another employee of the same pharmacy could be contacted at any time to open the safe box in the case of a specific emergency."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. To maintain masking, the randomisation code was concealed in a safe

Baclofen for alcohol use disorder (Review)

Addolorato 2007 (Continued)

objective outcomes		box in the pharmacy. For the duration of the study (including also the 4 weeks of follow-up), the pharmacist or another employee of the same pharmacy could be contacted at any time to open the safe box in the case of a specific emergency."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We assumed for this analysis that all patients who terminated treatment before the end of the study had relapsed." Quote: "Our analysis was done by intention to treat, insomuch that we assumed every patient took the drug allocated to them and counted them in that group."
Selective reporting (reporting bias)	Low risk	Study protocol available; results reported for all the primary and secondary outcomes described in the protocol

Beraha 2016

Methods	Study design: RCT Study grouping: parallel-group
Participants	<p>Baseline characteristics</p> <p>Baclofen: HD baclofen (participants = 58); LD baclofen (participants = 31)</p> <ul style="list-style-type: none"> Age (years): HD mean 45.8 (SD 9.2); LD mean 44.7 (SD 11.3) Gender: male HD 41 (70.7%); LD 20 (64.5%) Sample size: 89 Race: NR Marital status: HD 36 (62.1%); LD 17 (54.9%) married Educational level: NR Current use: HD mean 147.0 (SD 84.9); LD mean 132.5 (SD 85.2) alcohol (g/d); Comorbidity: HD mean 19.6 (SD 10.0%); LD mean 22.0 (SD 11.3%) Beck Depression Inventory. HD mean 49.7 (SD 12.4), LD mean 52.1 (SD 9.5) SpielbergerState-TraitInventory Duration of alcohol abuse (years): HD mean 18.8 (SD 10.7); LD mean 21.5 (SD 13.1) Number of previous detoxifications: HD mean 1.1 (SD 1.6); LD mean 1.8 (SD 2.9) <p>Placebo: (participants = 62)</p> <ul style="list-style-type: none"> Age (years): 49.0 (4.0–60.0) Gender: male 29 (69) Sample size: 42 Race: NR Marital status: 24 (57) married Educational level: 9 (21) Education > 13 years Current use: OCDS scores OCDS total: 25.0 (22.0–29.0) Comorbidity: HD mean 19.6 (SD10.0), LD mean 22.0 (SD11.3) Beck Depression Inventory. HD mean 49.7 (SD 12.4); LD mean 52.1 (SD 9.5) SpielbergerState-TraitInventory Duration of alcohol abuse (years): mean 19.0 (SD 11.5) Number of previous detoxifications: mean 2.0 (SD 3.6) <p>Inclusion criteria: aged 18-70 years; DSM-IV AD-diagnosis; breath alcohol concentration < 0.5% at the screening visit (informed consent); an average alcohol consumption of ≥ 14 units for women and ≥ 21 units for men/week over a consecutive 30-day period in the 90-day period before the start of the study and ≥ 2 heavy drinking days (women ≥ 5 units; men ≥ 6 units) in the past 90 days; a minimum of 96 h</p>

Beraha 2016 (Continued)

and a maximum of 21 d of abstinence prior to the start of the study medication; sufficient Dutch language skills; provision of a contact person in the event of loss of contact.

Exclusion criteria: current severe axis I disorder (other than depression, anxiety, and bipolar disorder); any primary diagnosis of substance dependence other than alcohol dependence (nicotine dependence was allowed); severe physical illnesses (e.g. Parkinson's disease, gastric ulcer, duodenal ulcer, cerebrovascular disease, respiratory insufficiency, hepatic or renal insufficiency, epilepsy); antihypertensive medication; risk of suicide; cognitive impairment interfering with the understanding of the study; current or recent (3 months before start of the study), pharmacological treatment for AD (i.e. acamprosate, naltrexone, disulfiram, ortopiramate); pregnancy or breast feeding; > 7 d inpatient treatment for SUD in the 30 days before the start of the study; and use of baclofen in the past 30 days.

Interventions	<p>Intervention characteristics</p> <p>Baclofen HD baclofen (participants = 58); LD baclofen (participants = 31) + CBT</p> <ul style="list-style-type: none"> Dose: baclofen HD group: ≤ 150 mg/d; baclofen LD group: 30 mg/d Duration of treatment: 16 weeks (6 weeks titration and 10 weeks of HD or LD baclofen) Length of follow-up: trial consisted of a 6-week titration phase and a 10-week HD phase, where the dose was stabilised <p>Placebo (participants = 62) + CBT</p> <ul style="list-style-type: none"> Dose: N/A Duration of treatment: 16 weeks; trial consisted of a 6-week titration phase and a 10-week HD phase, where the dose was stabilised Length of follow up: 16 weeks
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Time to first relapse in the HD phase (10 weeks) and the complete medication period (16 weeks): relapse was defined as the first HDD, i.e. alcohol intake of > 5 (women) or > 6 (men) standard drinks per occasion, following a lapse (any alcohol intake) <p>Secondary outcomes</p> <ul style="list-style-type: none"> TAC: assessed for participants who terminated the study Number of HDDs during treatment Proportion of participants relapsed, proportion of participants continuously abstinent throughout the study period and cumulative abstinence duration (abstinence was defined as breath alcohol concentration of 0.00, negative self-report at every visit, and % carbohydrate deficient transferrin within a normal range at the end of the study) Dropout rate: defined as participants who terminated treatment before the end of the study due to other reasons than relapse. Safety and tolerability of the study medication Changes in craving, anxiety, depression, and % CDT at the end of the HD phase
Identification	<p>Sponsorship source: funding for this study was provided by a private donation through the University of Amsterdam Fund (AUF7344)</p> <p>Country: The Netherlands</p> <p>Setting: SolutionS Center, Voorthuizen, The Netherlands; U-Center, Epen, The Netherlands; The Home Clinic, Weesp, The Netherlands; Roder Sana Addiction Treatment, Oirschot, The Netherlands</p> <p>Author's name: Dr Esther M. Beraha</p> <p>Institution: Addiction Development and Psychopathology (ADAPT) Laboratory, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands</p> <p>Email: R.W.H.J.Wiers@uva.nl (R.W.Wiers)</p>

Beraha 2016 (Continued)

Address: Addiction Development and Psychopathology Lab, Department of Psychology, University of Amsterdam, Nieuwe Achtergracht 129 B, 1018 WS Amsterdam, The Netherlands

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization (blocks of 6; pre-stratification by gender and centre) was conducted by the Clinical Research Unit of the AMC and patients were assigned to one of the three groups via an electronic database after baseline assessment"
Allocation concealment (selection bias)	Low risk	Quote: "Only the study pharmacist had access to the randomization list and had no further role in the trial"
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Stated as double-blind; quote: "The study medication was manufactured, packaged, and labelled by Tiofarma and stored and provided by the pharmacy of the AMC. Baclofen and placebo were provided in identical 10 mg tablets and supplied in containers with 24, 42, 63, 147, or 168 tablets."
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Stated as double-blind; quote: "The study medication was manufactured, packaged, and labelled by Tiofarma and stored and provided by the pharmacy of the AMC. Baclofen and placebo were provided in identical 10 mg tablets and supplied in containers with 24, 42, 63, 147, or 168 tablets."
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	Quote: "The investigators and responsible physicians remained blind with regard to the study medication during the whole study period."
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Quote: "The investigators and responsible physicians remained blind with regard to the study medication during the whole study period."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Analyses were done by intention to treat, counting pills every visit and assuming that patients took the drugs they were given". Comment: only 3 participants were lost at follow-up in the baclofen group (3%)
Selective reporting (reporting bias)	Low risk	Study protocol available; results reported for all the primary and secondary outcomes reported in the protocol

Garbutt 2010a

Methods	Study design: RCT Study grouping: parallel-group
Participants	Baseline characteristics Baclofen <ul style="list-style-type: none"> Age (years): mean 47.5 ($\pm$ 7.6 SD) Gender: male 22 (55%) Sample size: 40

Baclofen for alcohol use disorder (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Garbutt 2010a (Continued)

- Race: 95% white
- Marital status: NR
- Educational level: college degree 32%
- Current use: drinks/drinking day: mean 7.3 ($\pm$ 3.2 SD)
- Comorbidity: Zung Self-Rating Depression (max = 80): 35.4 ($\pm$ 8.1 SD); Spielberger state anxiety (max = 80): mean 34.1 ($\pm$ 10.8 SD); Spielberger trait anxiety (max = 80): mean 38.3 ($\pm$ 8.7 SD)

Placebo

- Age (years): mean 50.3 ($\pm$ 7.2 SD)
- Gender: male 22 (55%)
- Sample size: 40
- Race: 7% white
- Marital status: NR
- Educational level: college degree 37%
- Current use: drinks/drinking day: mean 6.9 ($\pm$ 3.2 SD)
- Comorbidity: Zung Self-Rating Depression (max = 80): mean 37.0 ($\pm$ 10.5 SD); Spielberger state anxiety: mean 38.5 ($\pm$ 12.7 SD); Spielberger trait anxiety (max = 80): mean 42.1 ($\pm$ 11.4 SD)

Inclusion criteria: meeting DSM-IV criteria for current alcohol dependence; $\geq$ 2 heavy drinking d/week (heavy drinking defined for men as $\geq$ 5 standard drinks/d and for women as $\geq$ 4 standard drinks/d) on average during the 4 weeks prior to screening; ability to understand and sign written informed consent; ability to refrain from alcohol for 3 days prior to the randomisation visit

Exclusion criteria: clinically significant medical disease that might interfere with the evaluation of the study medication or presence of a safety concern (e.g. cirrhosis, kidney impairment, unstable hypertension, diabetes mellitus, seizure disorder); clinically significant psychiatric illness including any psychotic disorder, bipolar disorder, or severe depression; suicidal ideation; concurrent use of any psychotropic medication including antidepressants mood stabilisers, antipsychotics, anxiolytics, stimulants, or hypnotics with the exception that stable doses of antidepressants for 2 months prior to screening was permitted (6 men and 17 women were on antidepressants); concurrent use of anti-convulsants, insulin, or oral hypoglycemics; aspartate aminotransferase (AST), alanine transaminase (ALT), or gamma-glutamyl transferase (GGT) level $>$ 3 times the ULN, bilirubin $>$ ULN, or serum creatinine $>$ ULN. Additional exclusionary criteria included: positive urine toxicology screen with the exception of cannabis. Individuals with positive cannabis screens were excluded only if they had a history of cannabis dependence. Pregnant women and women of childbearing potential who did not practice a medically acceptable form of birth control (oral or depot contraceptive, or barrier methods such as diaphragm or condom with spermicidal) were excluded, as were individuals requiring inpatient treatment or more intense outpatient treatment for their alcohol dependency

Interventions	Intervention characteristics
	<p>Baclofen (participants = 40)</p> <ul style="list-style-type: none"> • Dose: 30 mg/d • Duration of treatment: 12 weeks of treatment and utilising 8 sessions of BRENDA, a low-intensity psychosocial intervention • Length of follow-up: 12 weeks <p>Placebo (participants = 40)</p> <ul style="list-style-type: none"> • Dose: N/A • Duration of treatment: 12 weeks of treatment and utilising 8 sessions of BRENDA, a low-intensity psychosocial intervention • Length of follow up: 12 weeks
Outcomes	Primary outcomes
	<ul style="list-style-type: none"> • Percent of HDDs

Garbutt 2010a (Continued)

Secondary outcomes

- Percent abstinent days
- Craving
- Anxiety
- Depression
- Safety, tolerability, and pill compliance

Identification

Sponsorship source: National Institute of Alcohol Abuse and Alcoholism Grant R21 AA015392 and by GCRC Grant RR00046 and CTSA grant UL1RR025747 from the National Institutes of Health

Country: North Carolina (USA)

Setting: Department of Psychiatry and the Bowles Center for Alcohol Studies (JCG, ABKP, LKJ, BAF), University of North Carolina (outpatients)

Author's name: James C. Garbutt

Institution: Department of Psychiatry and the Bowles Center for Alcohol Studies

Email: jc_garbutt@med.unc.edu

Address: Chapel Hill, CB#7160, Chapel Hill, NC 27599-7160

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was implemented stratifying on gender, based on a computerized random number generator where assignment to baclofen or placebo was randomly ordered within gender."
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Only stated that study was double-blind. Outcome unlikely to be biased by lack of, or inadequate blinding.
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Only stated that study was double-blind: no further description provided
Blinding of outcome assessment (detection bias) subjective outcomes	High risk	Quote: "Medical monitoring was conducted by study physicians and consisted of taking vital signs, recording use of concomitant medication(s), and in-depth side effect monitoring using an Adverse Events Form that included common baclofen side effects (e.g., drowsiness, sedation, fatigue)" Comment: not stated whether the outcome assessor was blinded; common side effects of baclofen easily recognisable
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Quote: "Medical monitoring was conducted by study physicians and consisted of taking vital signs, recording use of concomitant medication(s), and in-depth side effect monitoring using an Adverse Events Form that included common baclofen side effects (e.g., drowsiness, sedation, fatigue)"

Garbutt 2010a (Continued)

Comment: not stated whether the outcome assessor was blinded, but objective outcomes unlikely to be biased by lack or incomplete blinding

Incomplete outcome data (attrition bias) All outcomes	Low risk	20% and 27.5% of participants lost at follow-up from placebo and baclofen groups. But reasons balanced between groups and most unlikely to be related to the intervention or the outcome
Selective reporting (reporting bias)	Low risk	Study protocol not available; results reported for all the declared outcomes in the methods section

Garbutt 2010b

Methods	<p>Study design: randomised phase 1 study</p> <p>Study grouping: parallel-group</p> <p>Masking: quadruple (participant, care provider, investigator, outcomes assessor)</p>
Participants	<p>Baseline characteristics</p> <p>40 men and women aged 25-60 years meeting DSM-IV criteria for current alcohol dependence.</p> <p>Inclusion criteria: admitted to University of North Carolina Hospitals for a medical detoxification from alcohol; receiving benzodiazepines for detoxification or recruited from the general population; average ≥ 2 HDDs per/week (≥ 5 drinks/d for men or ≥ 4 drinks/d for women); average overall consumption of ≥ 21 drinks/week (men) and ≥ 14 drinks/week (women) during the 4 weeks prior to admission or screening; ≤ 3 months of abstinence in the previous year; able to understand and sign written informed consent; willingness to engage in treatment and motivation to achieve abstinence or to greatly reduce alcohol consumption; stable residence and able to identify an individual who could locate them if needed; must have the logistical ability to come to each weekly study visit for 12 weeks in Chapel Hill, NC, USA</p>
Interventions	<p>Intervention characteristics</p> <p>Baclofen + placebo naltrexone + behavior therapy (participants = 10)</p> <ul style="list-style-type: none"> Dose: baclofen 10 mg 3 times/d; placebo naltrexone 50 mg/d; behaviour therapy 9 sessions Duration of treatment: baclofen/naltrexone 12 weeks Length of follow-up: 12 weeks <p>Baclofen + naltrexone + behavior therapy (participants = 10)</p> <ul style="list-style-type: none"> Dose: baclofen 10 mg 3 times/d; naltrexone 50 mg/d; behaviour therapy, 9 sessions Duration of treatment: baclofen/naltrexone 12 weeks Length of follow-up 12 weeks <p>Placebo baclofen + naltrexone + behavioral therapy (participants = 10)</p> <ul style="list-style-type: none"> Dose: placebo baclofen 10 mg 3 times/d; naltrexone 50 mg/d; behaviour therapy 9 sessions Duration of treatment: baclofen/naltrexone 12 weeks Length of follow-up 12 weeks <p>Placebo characteristics</p> <p>Placebo baclofen + placebo naltrexone + behavior therapy (participants = 10)</p> <ul style="list-style-type: none"> Dose: placebo baclofen 10 mg 3 times/d; placebo naltrexone 50 mg/d; behaviour therapy 9 sessions Duration of treatment: baclofen/naltrexone 12 weeks

Garbutt 2010b (Continued)

- Length of follow-up:12 weeks

Outcomes	Primary outcomes <ul style="list-style-type: none">• This is an exploratory study to gain experience with the combination of baclofen + naltrexone• pilot data on cytokine levels• Recruitment and retention of study participants Secondary outcomes <ul style="list-style-type: none">• Compliance with study visits• Compliance with follow-up	
Identification		
Notes	The pilot study is a protocol published on ClinicalTrials.gov , where it is reported that the study has been completed without results being posted. Preliminary results have been reported in a conference proceeding.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) objective outcomes	Unclear risk	Stated as double-blind, double-dummy without further details
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Stated as double-blind, double-dummy without further details
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Stated as double-blind, double-dummy without further details
Blinding of outcome assessment (detection bias) objective outcomes	Unclear risk	Stated as double-blind, double-dummy without further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals from the study
Selective reporting (reporting bias)	Unclear risk	Study protocol not available; data available only from conference proceedings

Hauser 2017

Methods	Study design: RCT
---------	--------------------------

Baclofen for alcohol use disorder (Review)

Hauser 2017 (Continued)

Study grouping: parallel-group

Participants	Baseline characteristics
	<p>Baclofen</p> <ul style="list-style-type: none"> Age (years): mean 55.7 (SD 7.1) Gender: male 85 (96.5%) Sample size: 88 Race:white: 52 (60.5%); African American 29 (33.7%); Native American 1 (1.2%); Hawaiian/Pacific Islander 1 (1.2%); unknown 3 (3.5%) Marital status: NR Educational level: NR Current use: Structured Clinical Interview for DSM-IV (SCID): Abuse: 13 (14.8%); Dependence: 75 (85.2%); AUDIT-C: mean 8.50 (SD 2.41); No. days abstinent (prior 2 weeks): mean 5.4 (SD 4.6) No. of drinks per week: mean 30.0 (SD 23.4); Drinking days per week: mean 4.3 (SD 2.3). Drinks per drinking day: mean 7.12 (SD 3.79). Positive Urine drug screen: Cannabis 23.7% (18/76); Cocaine 1.3% (1/76); Methamphetamine 2.6% (2/76); Benzodiazepines 3.9% (3/76); Multiple drugs 15.8% (12/76). Comorbidity: BSI: mean 52.24 (SD 43.30); BDI-II: mean 15.30 (SD 10.35); PCL-C: mean 38.83 (SD 15.75); OCDS total: mean 20.55 (SD 9.54) <p>Placebo</p> <ul style="list-style-type: none"> Age (years): mean 57.5 (SD 6.9) Gender: male 92 (100%) Sample size: 92 Race: white 50 (54.3%); African American 35 (38.0%) Native American 2 (2.2%); Hawaiian/Pacific Islander 1 (1.1%); unknown 4 (4.3%) Marital status: NR Educational level: college degree: NR Current use: SCID: Abuse 12 (13.0%); Dependence 80 (87.0%); AUDIT-C: mean 8.22 (SD 2.47); No. days abstinent (prior 2 weeks): mean 5.0 (SD 4.4); No. of drinks per week: mean 33.6 (SD 24.5); Drinking days per week: mean 4.5 (SD 2.2); Drinks per drinking day: mean 7.65 (SD 4.51). Positive Urine drug screen: Cannabis 27.8% (22/79); Cocaine 3.8% (3/79); Methamphetamine 7.6% (6/79); Benzodiazepines 1.3% (1/79); Multiple drugs 10.1% (8/79). Comorbidity: BSI: mean 42.81 (SD 35.62); BDI-II: mean 13.00 (SD 9.73); PCL-C: mean 35.80 (SD 16.35); OCDS total: mean 19.50 (SD 9.65). <p>Inclusion criteria: men or women, veterans ages ≥ 18 years; chronic HCV diagnosis with confirmed vi-raemia by polymerase chain reaction (PCR); an AUD (abuse or dependence) according to the DSM-IV or DSM-IV-TR, using the Structured Clinical Interview for the DSM-IV-TR, or SCID; and ongoing alcohol use as defined by > 7 standard drinks /week for each of the preceding 2 weeks or 1 HDD/week for each of the preceding 2 weeks (HDD: > 4 drinks in 1 day for men and > 3 drinks in 1 day for women). There were no requirements for any period of abstinence before entry into the study.</p> <p>Exclusion criteria: presence of DSM-IV-TR (SCID) cocaine, methamphetamine or opioid dependence within the past 6 months; concurrent use of ondansetron, disulfiram, topiramate, naltrexone, acamprosate, buprenorphine or methadone; any metabolic kidney condition affecting renal function, including haemodialysis, renal replacement or peritoneal dialysis; and any known pre-existing medical conditions that could interfere with participation in the protocol, such as known cognitive impairment, dementia, encephalopathy from liver disease, acute psychiatric instability (significant psychosis, mania, or elevated risk for suicide).</p>
Interventions	Intervention characteristics
	<p>Baclofen (participants = 88) + BBCET</p>

Hauser 2017 (Continued)

- Dose: 30 mg (10 mg three times/d)
- Duration of treatment: 12 weeks
- Length of follow-up: 12 weeks

Placebo (participants = 92) + BBCET

- Dose: N/A
- Duration of treatment: 12 weeks
- Length of follow up: 12 weeks

Concurrent with dispensing study medication, study personnel provided BBCET, which is a standardised 15-min psychosocial treatment intervention that emphasises medication adherence as a crucial element to change alcohol use behavior

Outcomes	Primary outcomes <ul style="list-style-type: none">• Abstinence from alcohol (percentage of days abstinent) Secondary outcomes <ul style="list-style-type: none">• Complete abstinence between weeks 4 and 12 of the study• Percentage of veterans who achieved no heavy drinking between weeks 4 and 12 of the study• Craving, symptoms of anxiety and depression and post-traumatic stress disorder (PTSD)• Measurements of biomarkers of alcohol use (including ethyl glucuronide (EtG), ethyl sulfate (EtS) and percentage of carbohydrate deficient transferrin (% CDT))	
Identification	Sponsorship source: the work was supported by the U.S. Department of Veteran Affairs (VA) Clinical Sciences Research and Development Service- VA Merit Country: USA Setting: outpatients setting in four VA medical centres with established hepatology clinics (VA Long Beach, VA Minneapolis, VA Portland and VA San Diego) Author's name: Peter Hauser Institution: Division of Mental Health, Long Beach VA Medical Center, Long Beach, CA, USA Email: peter.hauser2@va.gov Address: Long Beach VA Medical Center, 300 Oceangate, Suite 700, Long Beach, CA 90802, USA	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Consented patients were randomized to oral baclofen 30 mg (10 mg three times per day) or placebo at each site 1 : 1 using random assignment software administered by the central site"
Allocation concealment (selection bias)	Low risk	Quote: "The blocked randomization sequence code was concealed from research staff. The research pharmacy at each site kept the randomization code in sequential sealed envelopes and provided study medication to research staff who then distributed study medication to participants."
Blinding of participants and personnel (performance bias)	Low risk	Stated as double-blind; quote: "Study medication and placebo were placed in identical capsules"

Hauser 2017 (Continued)

objective outcomes

Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Stated as double-blind; quote: "Study medication and placebo were placed in identical capsules"
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Information not reported
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Information not reported but objective outcomes unlikely to be biased by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the analysis
Selective reporting (reporting bias)	Low risk	Study protocol not available; results reported for all the declared outcomes in the methods section

Krupitskii 2017

Methods	Study design: RCT Study grouping: parallel-group
Participants	Baseline characteristics Baclofen <ul style="list-style-type: none"> • Age (years): 46.00 ± 2.43 • Gender: 12 (75%) men • Sample size: 16 • Race: NR • Marital status: NR • Educational level: 5 (31.25%) intermediate; 11 (68.75%) higher • Current use: type of alcohol consumption: bingeing 10, 62.50%; constant 4, 25.00%; intermittent 2, 12.50% • Comorbidity: NR Placebo <ul style="list-style-type: none"> • Age (years): 44.00 ± 2.12 • Gender: 14 (87.5%) men • Sample size: 16 • Race: NR • Marital status: NR • Educational level: 7 (43.75%) intermediate; 10 (62.5%) higher • Current use: type of alcohol consumption: bingeing 11, 68.75%; constant 2, 12.5%; intermittent 3, 18.75% • Comorbidity: NR Inclusion criteria: patients of different genders aged 18–65 years with negative tests for alcohol in exhaled air, ICD-10 diagnoses of alcohol dependence, and abstinence from alcohol consumption for at

Krupitskii 2017 (Continued)

least 7 days (recovered alcohol withdrawal syndrome). An additional inclusion criterion for women was the absence of ongoing pregnancy and agreement to use adequate contraception during study participation. All participants included in the study had to provide a telephone number for qualitative follow-up assessment (compliance with weekly clinic visits).

Exclusion criteria: marked organic brain disease, marked somatic pathology (liver, kidney, cardiovascular, nervous system pathology), psychotic states, or history of severe mental illness (schizophrenia, epilepsy, manic-depressive psychosis, etc.), any additional chemical dependency other than on alcohol and tobacco, and use of any other medication or psychotherapy for alcohol dependence (including so-called placebo therapy ('chemical protection'), 'coding', etc

Interventions	Intervention characteristics Baclofen (participants = 16) + CBT <ul style="list-style-type: none">• Dose: 50 mg/d (25 mg in the morning and evening)• Duration of treatment: 12 weeks• Length of follow-up: 12 weeks placebo (participants = 16) + CBT <ul style="list-style-type: none">• Dose: N/A• Duration of treatment: 12 weeks• Lenght of follow up: 12 weeks	
Outcomes	Primary outcomes <ul style="list-style-type: none">• Remission (alcohol consumption): assessed using the Clinical Global Impression scale Secondary outcomes <ul style="list-style-type: none">• Assessment of the levels of alcohol attraction (craving): assessed with OCDS, Pennsylvania, and visual analogue scales• Depression (assessed with Montgomery-Asberg Depression Scale) and anxiety (assessed with Hamilton and Spielberger scales)• γ-glutamyltransferase (GGT) activity and compliance with medication (urine riboflavin)	
Identification	Sponsorship source: Pharmaceutical Company Akrikhin Country: Russia Setting: Department of Narcology, Bekhterev St. Petersburg Science Research Psychoneurological Institute Author's name: E.M. Krupitskii Institution: Bekhterev St. Petersburg Research Psychoneurological Institute Email: kruenator@gmail.com. Address: Bekhterev St. Petersburg Research Psychoneurological Institute, St. Petersburg, Russia	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using a random number generator running in Excel."

Krupitskii 2017 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Agents (baclofen, placebo) were placed in numbered containers and issued to patients in double-blind conditions at each weekly visit for three months such that they always had a three-week supply of agent (in case of missing 1–2 visits). Randomization codes were kept at the institute and could be opened at any moment in case of emergency."
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Stated as double-blind, quote: "The institute pharmacists, working with the pharmaceuticals company Bios (St. Petersburg), ground baclofen tablets and prepared baclofen capsules (25 mg) and externally identical placebo capsules (starch). Both baclofen capsules and placebo were supplemented with 50 mg of riboflavin as fluorescent marker of drug ingestion"
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Stated as double-blind, quote: "The institute pharmacists, working with the pharmaceuticals company Bios (St. Petersburg), ground baclofen tablets and prepared baclofen capsules (25 mg) and externally identical placebo capsules (starch). Both baclofen capsules and placebo were supplemented with 50 mg of riboflavin as fluorescent marker of drug ingestion"
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	Quote: "Investigators, physicians, and other staff taking part in the study, like the patients, were unaware of which treatment group they were in"
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Quote: "Investigators, physicians, and other staff taking part in the study, like the patients, were unaware of which treatment group they were in"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear data reported about dropout from the study
Selective reporting (reporting bias)	Low risk	Study protocol not available; results reported for all the declared outcomes in the methods section

Leggio 2015

Methods	Study design: RCT Study grouping: parallel-group
Participants	Baseline Characteristics Baclofen <ul style="list-style-type: none"> • Age (years): 47.9 ± 9.9 • Gender: 67% (male) • Sample size: (%): American Indian 13; Asian 0; white 20; African-American 40; multiracial or others 27 • Race: NR • Marital status: NR • Educational level: NR • Current use: HDDs: mean 78.0 ± 27.3; ADS score: mean 15.8 ± 8.4 • Comorbidity: NR Placebo <ul style="list-style-type: none"> • Age (years): 44.7 ± 7.0 • Gender: 73 % (male)

Leggio 2015 (Continued)

- Sample size: (%): American Indian 0; Asian 7; white 67; African-American 27; multiracial or others 0
- Race: NR
- Marital status: NR
- Educational level: NR
- Current use: HDDs: mean 70.5 ± 26.7; ADS score: mean 13.5 ± 7.5
- Comorbidity: NR

Inclusion criteria: participants were alcohol-dependent heavy-drinking and heavy-smoking individuals: aged 18-75 years; DSM-IV diagnoses of both alcohol and nicotine codependency, with heavy use of alcohol (men ≥ 5 SDUs, women ≥ 4 SDUs, a day on average) and cigarettes (≥ 10 cigarettes per day on average) during the last 90 d before screening; interested in receiving treatment for both drinking and smoking (either reducing or stopping both substances; or reducing one substance and stopping the other).

Exclusion criteria: current (i.e. past year) DSM-IV diagnosis of dependence on any psychoactive substance other than alcohol and nicotine; lifetime DSM-IV diagnosis of schizophrenia, bipolar disorder, or other psychosis; past year diagnosis of major depression, anxiety disorders, and eating disorders; risk of suicide (e.g. active plan or recent attempt in last year); positive urine drug screen at baseline for any illegal substance other than marijuana; significant alcohol withdrawal symptoms, as assessed by a Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar) score > 10; history of hospitalisation for alcohol intoxication delirium, alcohol withdrawal delirium or seizure; participation in any research study for alcoholism and/or smoking treatment within 3 months prior to signing the consent document; pharmacological treatment with naltrexone, acamprosate, topiramate, disulfiram, nicotine replacement, bupropion, and varenicline within 1 month prior to randomisation; current use of psychotropic medications or medications that interfere with the metabolism of Baclofen, history of allergy to Baclofen or medical contraindications to take Baclofen; severe medical diseases, such as cancer, cirrhosis, chronic kidney failure, and chronic neurological disorders; and women who were of child bearing potential and not practicing effective birth control

Interventions	<p>Intervention characteristics</p> <p>Baclofen (participants = 15) + Medical Management (personalised education regarding alcohol and smoking, helped participants to develop and implement a plan to reduce/stop alcohol and smoking, motivated participants for medication adherence)</p> <ul style="list-style-type: none"> • Dose: 80 mg/d • Duration of treatment: 12 weeks • Length of follow-up: 16 weeks <p>Placebo (participants = 15) + Medical Management (personalised education regarding alcohol and smoking, helped participants to develop and implement a plan to reduce/stop alcohol and smoking, motivated participants for medication adherence)</p> <ul style="list-style-type: none"> • Dose: N/A • Duration of treatment: 12 weeks • Length of follow up: 16 weeks
Outcomes	<p>Primary outcomes/secondary outcomes (no distinction)</p> <ul style="list-style-type: none"> • Drinking and smoking co-use as abstinence from alcohol-tobacco co-use • Duration of abstinence from alcohol or tobacco
Identification	<p>Sponsorship source: supported by a grant from the ABMRF/The Foundation for Alcohol Research (PI: Leggio). The human laboratory cue-reactivity substudy was supported by an NIH grant jointly funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) (R03AA020169; PI: Leggio). Both grants were awarded to Dr. Leggio, while he was at Brown University. Dr. Leggio's current work is supported by the NIAAA Division of Intramural Clinical and Biological Research and the NIDA Intramural Research Program</p> <p>Country: USA</p>

Leggio 2015 (Continued)

Setting: Brown University Center for Alcohol and Addiction Studies (CAAS) and Roger Williams Medical Center (RWMC), Providence, RI

Author's name: Lorenzo Leggio

Institution: Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health

Email: lorenzo.leggio@nih.gov

Address: 10 Center Drive (10CRC/15330) MSC1108; Room 1-5429, Bethesda, MD 20892-1108, USA

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At week 01 visit, eligible participants were randomized to BACL or PLA using a 3-urn variable procedure ,
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Quote: "BACL at 80 mg/day (20 mg, q.i.d.), or PLA was placed into blister packs as opaque capsules containing drug and 25 mg riboflavine" Comment: outcome unlikely to be biased by lack or inadequate blinding
Blinding of participants and personnel (performance bias) subjective outcomes	Unclear risk	Quote: "BACL at 80 mg/day (20 mg, q.i.d.), or PLA was placed into blister packs as opaque capsules containing drug and 25 mg riboflavine" Comment: study described as double-blind. No further information provided about blindness a part opaque capsules
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Quote: "BACL at 80 mg/day (20 mg, q.i.d.), or PLA was placed into blister packs as opaque capsules containing drug and 25 mg riboflavine" Comment: study described as double-blind; no further information provided about blinding a part the use of opaque capsules
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Quote: "BACL at 80 mg/d (20 mg, q.i.d.), or PLA was placed into blister packs as opaque capsules containing drug and 25 mg riboflavine " Comment: study described as double-blind. Outcome unlikely to be biased by lack or inadequate blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "while 30 individuals were eligible and randomized; 24 completed the study (Supplemental Fig. 1)." Comment: 20% dropout. Number of participants who dropped out from each group not reported. The figure (Figure 1), reporting participants lost to follow-up and those who completed the study is unreadable in the supplementary file so that it's impossible to give a judgments on this.
Selective reporting (reporting bias)	Low risk	Study protocol available. Results reported for all the primary and secondary outcomes declared in the protocol

Mishra 2010

Methods	Study design: RCT Study grouping: parallel-group
Participants	Baseline characteristics Baclofen <ul style="list-style-type: none"> • Age (years): mean 41.28 ± 6.83 • Gender: NR • Sample size: 25 • Race: NR • Marital status (married): 16 (64%) • Educational level (> 10 years of education): 13 (52%) • Current use: NR • Comorbidity: NR Acamprosate <ul style="list-style-type: none"> • Age (years): mean 42.08 ± 7.07 • Gender: NR • Sample size: 24 • Race: NR • Marital status (married): 16 (68%) • Educational level (> 10 years of education): 15 (63%) • Current use: NR • Comorbidity: NR Inclusion criteria: aged 18-70 years; diagnosis of current AD according to the (ICD-10) criteria; last alcohol intake reported to have taken place in the 24 h preceding observation; presence of a key relative Exclusion criteria: presence of severe liver, kidney, heart or lung diseases requiring urgent medical attention; currently under treatment for any mental disorder with psychotic drugs; any dependence to drug other than nicotine; age > 70 years
Interventions	Intervention characteristics Baclofen (participants = 25) <ul style="list-style-type: none"> • Dose: 15mg/d for the first 3 d and 30 mg/d subsequently for a total duration of 3 consecutive months • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks Acamprosate (participants = 24) <ul style="list-style-type: none"> • Dose: 666.66 mg 3 times/d for 3 consecutive months • Duration of treatment: 12 weeks • Length of follow up: 12 weeks
Outcomes	Primary outcome/secondary outcome (no distinction) <ul style="list-style-type: none"> • % of participants in abstinence • Craving score • Obsessive and compulsive drinking score • Safety and tolerability
Identification	Sponsorship source: NR

Mishra 2010 (Continued)

Country: India

Setting: outpatients

Author's name: Suvendu N Mishra

Institution: IMS & SUM Hospital, Bhubaneswar. Mental Health Institute, Dept of Psychiatry SCB Medical college, Cuttack

Email: dr.sar07@gmail.com

Address: Mental Health Institute, SCB Medical college, Cuttack

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) objective outcomes	High risk	Participants given written informed consent, subsequently randomised into 2 groups to receive either open-label baclofen or acamprosate
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Participants given written informed consent, subsequently randomised into 2 groups to receive either open-label baclofen or acamprosate
Blinding of outcome assessment (detection bias) subjective outcomes	High risk	Participants given written informed consent, subsequently randomised into 2 groups to receive either open-label baclofen or acamprosate
Blinding of outcome assessment (detection bias) objective outcomes	High risk	Participants given written informed consent, subsequently randomised into 2 groups to receive either open-label baclofen or acamprosate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not reported
Selective reporting (reporting bias)	High risk	Study protocol not available. Primary and secondary outcomes not reported in the method section. Some results on specific outcomes were partially reported (e.g. for abstinence: "A significantly higher number of patients who achieved and maintained abstinence throughout the experiment were found in the group of patients treated with baclofen compared with acamprosate."

Morley 2014

Methods

Study design: RCT

Morley 2014 (Continued)

Study grouping: parallel-group

Participants	<p>Baseline characteristics</p> <p>Baclofen</p> <ul style="list-style-type: none"> • Age (years): mean 47 • Gender: male 10, 35.5% • Sample size: 28 • Race: NR • Marital status: NR • Educational level: NR • Current use (drinks per drinking days): 15.20 • Comorbidity: NR • Current use (HDDs/week): 4.35 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years): mean 46 • Gender: male 9, 64% • Sample size: 14 • Race: NR • Marital status: NR • Educational level: NR • Current use (drinks per drinking days): 14.30 • Comorbidity: NR • Current use (HDDs/week): 4.31 <p>Inclusion criteria: men and women aged 18-60; DSM-IV criteria for current alcohol dependence; ability to understand and provide written informed consent; abstinence from alcohol for at least 3 days prior to randomisation and resolution of any withdrawal symptoms; desire to achieve abstinence or to reduce alcohol consumption; evidence of a stable residence; proof of an individual who could locate participant if needed</p> <p>Exclusion criteria: clinically significant medical diseases that might interfere with the evaluation of the study medication or present a safety concern (e.g. kidney impairment, unstable hypertension, hypotension, diabetes mellitus, seizure disorder); clinically significant psychiatric illness (e.g. psychotic disorder, bipolar disorder, severe depression); suicidal ideation or concurrent SUD other than nicotine or cannabis, concurrent use of any psychotropic medication (participants who had been on a stable dose of selective serotonin reuptake inhibitors (SSRIs) for 2 months were still considered eligible); concurrent use of anticonvulsants, insulin or oral hypoglycaemic; women who were pregnant or breast-feeding; participation in any clinical trial within the last 60 days; use of alcohol pharmacotherapy within the last 60 d; court-mandated participation in alcohol treatment or pending incarceration</p>
Interventions	<p>Intervention characteristics</p> <p>Baclofen (participants = 28) + up to 9 sessions of BRENDA, a low-intensity psychosocial intervention</p> <ul style="list-style-type: none"> • Dose: group 1: 30 mg/d; group 2: 60 mg/d • Duration of treatment: 12 weeks • Length of follow up: 12 weeks <p>Placebo (participants = 14) + up to 9 sessions of BRENDA, a low-intensity psychosocial intervention</p> <ul style="list-style-type: none"> • Dose: N/A • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks
Outcomes	Primary outcomes

Baclofen for alcohol use disorder (Review)

Morley 2014 (Continued)

- Time to relapse (defined as ≥ 4 standard drinks on a single occasion for women, ≥ 5 standard drinks for men. Standard drinks defined as 10 g of alcohol)
- Time to consumption of any alcohol (lapse)
- Self-reported amount of alcohol consumed expressed as the number of average drinks per drinking day, number of abstinent days, number of HDDs (defined as ≥ 4 drinks for women, ≥ 5 drinks for men)

Secondary outcomes

- Improvement in cravings for alcohol and clinically evident state anxiety detected at baseline

Identification

Sponsorship source: trial was funded by a New South Wales Health Drug and Alcohol grant (PH, AB, KM). Conflict of interest statement. None declared

Country: Australia

Setting: outpatients

Author's name: Morley K.C.

Institution: NHMRC Centre of Research Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, University of Sydney, Sydney, NSW, Australia

Email: kirsten.morley@sydney.edu.au

Address: University of Sydney, Sydney, NSW 2006, Australia

Notes
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were allocated 1:1:1 as per a computer-generated randomization sequence conducted by the hospital clinical trials pharmacist."
Allocation concealment (selection bias)	Low risk	Quote: "Participants were allocated 1:1:1 as per a computer-generated randomization sequence conducted by the hospital clinical trials pharmacist."
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Quote: "participants in the (a) baclofen 30 mg/day group took a dose of 5 mg, three times a day, for the first 3 days, a dose of 10 mg, three times a day, on Days 4–81, and finally a dose of 5 mg, three times a day, for the last 3 days; (b) baclofen 60 mg/day group took a dose of 5 mg, three times a day, for the first 3 days, a dose of 10 mg, three times a day on Days 4–7, a dose of 20 mg, three times a day, on Days 8–77, a dose of 10 mg three times a day on Days 78–81, and finally a dose of 5 mg, three times a day, for the last 3 days. The placebo pills, which were identical in appearance, were also titrated upward and downward to maintain the double blind."
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Quote: "participants in the (a) baclofen 30 mg/day group took a dose of 5 mg, three times a day, for the first 3 days, a dose of 10 mg, three times a day, on Days 4–81, and finally a dose of 5 mg, three times a day, for the last 3 days; (b) baclofen 60 mg/day group took a dose of 5 mg, three times a day, for the first 3 days, a dose of 10 mg, three times a day on Days 4–7, a dose of 20 mg, three times a day, on Days 8–77, a dose of 10 mg three times a day on Days 78–81, and finally a dose of 5 mg, three times a day, for the last 3 days. The placebo pills, which were identical in appearance, were also titrated upward and downward to maintain the double blind."
Blinding of outcome assessment (detection bias)	Unclear risk	Information not reported

Morley 2014 (Continued)

subjective outcomes

Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Information not reported; objective outcomes unlikely to be biased by lack or incomplete blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Twenty-eight (67%) patients out of the enrolled 42 completed the follow-up interviews (up to Week 12–16)." Quote: "There were no significant differences between groups on study retention ($\chi^2 = 1.5$, $P = 0.47$) or medication compliance rates ($\chi^2 = 0.77$, $P = 0.68$), the number of BRENDA sessions attended ($F = 1.93$, $P = 0.826$) or days on medication ($F = 1.04$, $P = 0.36$). Time-survival analysis revealed that the treatment retention rates did not significantly differ between randomized groups over the follow-up assessments ($\chi^2 = 1.21$, $P = 0.55$)."
Selective reporting (reporting bias)	Low risk	Study protocol available. 2 primary outcomes not listed in the protocol were reported in the full publication (time to relapse, time to lapse); however authors found no significant difference for any of these outcomes. Comment: selective reporting bias judged unlikely

Muller 2015

Methods	Study design: RCT Study grouping: parallel-group
Participants	Baseline characteristics Baclofen <ul style="list-style-type: none"> • Age (years): mean 47.4 (SD 7) • Gender: male 20, 71.4% • Sample size: 28 • Race: NR • Marital status (married): 5 (17.9%) • Educational level (university degree): 4 (14.3%) • Current use (alcohol consumption/d (g) before inclusion: mean 206.2 (SD 94.1) • Comorbidity: NR • Current use years of hazardous alcohol consumption; mean 13.9 (SD 10.1) Placebo <ul style="list-style-type: none"> • Age (years): mean 45.6 (SD 7) • Gender: male 19 (67.9%) • Sample size: 28 • Race: NR • Marital status (married): 11(39.3) • Educational level (university degree): 10 (35.7%) • Current use (alcohol consumption/d (g) before inclusion: mean 191.6 (SD 94.8) • Comorbidity: NR • Current use (years of hazardous alcohol consumption; mean: 11.5 (SD 7.3) Inclusion criteria: aged ≥ 18 and < 65 years; diagnosis of AD according to ICD-10 and DSM-IV-TR; alcohol consumption of ≥ 2 HDDs/week on average (men ≥ 5 drinks/d; women < 4 drinks/day; 1 standard

Muller 2015 (Continued)

drink = 12 g absolute alcohol) and an average overall alcohol intake of ≥ 21 drinks/week (men) and ≥ 14 drinks/week (women) during the 4 weeks before detoxification; completed in- or outpatient detoxification before randomisation; last alcohol consumption within 7–21 d before randomisation; sufficient German language skills

Exclusion criteria: neurological conditions; current treatment with psychotropic drugs that could affect study outcome (i.e. sedatives, alcohol relapse prevention such as acamprosate, disulfiram, naltrexone, antidepressants, antipsychotics, anticonvulsants); epilepsy or epileptiform convulsions; pregnancy and/or currently breastfeeding; intolerance to baclofen; terminal renal failure; alanine amino-transferase (ALAT) or aspartate aminotransferase (ASAT) values 5 times the ULN, bilirubin 41.9 mg/dL, International Normalized Ratio 41.6; gastrointestinal ulcers; and treatment mandated by a legal authority

Interventions	<p>Intervention characteristics</p> <p>baclofen (participants = 28) + up to 9 Medical Management sessions that focus on psychoeducation and enhancement of motivation and adherence</p> <ul style="list-style-type: none"> Dose: 30–270 mg/d Duration of treatment: 12 weeks HD phase Length of follow up: 12 weeks <p>Placebo (participants = 28) + up to 9 Medical Management sessions that focus on psychoeducation and enhancement of motivation and adherence</p> <ul style="list-style-type: none"> Dose: N/A Duration of treatment: 12 weeks HD phase Length of follow-up: 12 weeks
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Total abstinence and cumulative abstinence duration during the HD phase. Abstinence was defined as negative subjective report plus negative breathalyzer test as well as a level of carbohydrate-deficient transferrin (CDT) within the normal range, or, if increased, lower compared to the baseline level <p>Secondary outcomes</p> <ul style="list-style-type: none"> Safety and tolerability of the study drug Dropout rate (termination of treatment before study end) Changes in psychiatric assessments compared to baseline (Hamilton Anxiety Rating Scale, Hamilton Depression Scale, Visual Analogue Scale of Craving and OCDS)
Identification	<p>Sponsorship source: the work was supported by the German Research Foundation (DFG; Cluster of Excellence EXC 257)</p> <p>Country: Germany</p> <p>Setting: outpatients</p> <p>Author's name: Christian A. Müllera</p> <p>Institution: Department of Psychiatry, Campus Charité Mitte, Charité, Universitätsmedizin Berlin</p> <p>Email: ch.mueller@charite.de</p> <p>Address: Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany</p>
Notes	
Risk of bias	
Bias	<p>Authors' judgement Support for judgement</p>

Muller 2015 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned at the baseline visit to double-blind treatment with baclofen or placebo in a 1:1 ratio according to a computer-generated randomization list (in blocks of 4; stratification with regard to sex)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization list was kept by the biometrician and the study pharmacist who prepared the study medication packages. The study pharmacist did not have any further role in the trial. Sealed envelopes containing study medication details were kept at the outpatient unit to be opened by a staff member in case of a study drug-related emergency. During the whole study, no unblinding was necessary."
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Stated as double-blind. Participants received baclofen or placebo in identical capsules in a dose of 5 mg 3 times/d
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Stated as double-blind treatment. Participants received baclofen or placebo in identical capsules in a dose of 5 mg 3 times/d
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Information not reported
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Information not reported but objective outcomes unlikely to be biased by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few lost at follow-up (7%), balanced between groups
Selective reporting (reporting bias)	Low risk	Study protocol not available; results reported for all the outcomes declared in the methods section

Ponizovsky 2015

Methods	Study design: RCT Study grouping: parallel-group
Participants	Baseline characteristics Baclofen: <ul style="list-style-type: none"> • Age (years): mean 42.6 ± 9.6 • Gender: male 24 (75%) • Sample size: 32 • Race (immigrants): 66% • Marital status: 48% • Educational level (years) : mean 11.5 ± 1.2 • Current use (duration of harmful alcohol consumption (years): mean 15.1 • Comorbidity: NR • Current use (% HDDs during the 6 weeks before the enrolment): 66% • Current use (drink per drinking days): mean 7.4 ± 1.5

Baclofen for alcohol use disorder (Review)

Ponizovsky 2015 (Continued)

Placebo

- Age (years): mean 44.7 ± 8.7
- Gender: male 24 (75%)
- Sample size: 32
- Race (immigrants): 59%
- Marital status: 59%
- Educational level (years): mean 11.7 ± 3.7
- Current use (duration of harmful alcohol consumption (years): mean 14.1
- Comorbidity: NR
- Current use (% heavy drinking days during the 6 weeks before the enrolment): 69%
- Current use (drink per drinking days): mean 8.2 ± 1.6

Inclusion criteria: aged 18-60 years; 2) had an ICD- 10 diagnosis of AD; had sought treatment to stop alcohol consumption; had an alcohol intake of ≥ 2 HDDs/week (men ≥ 5 drinks/d; women ≥ 4 drinks/d) and average overall consumption of ≥ 21 drinks/week (men) and ≥ 14 drinks/week (women) during the month preceding recruitment (1 standard drink = 12 g absolute alcohol); < 6 total abstinent days (ABS) per month on average; and had a reliable family member able to help with drug administration and monitoring. The study population could be defined as mild alcohol use disorder according to DSM 5 criteria

Exclusion criteria: a detoxification treatment for acute alcohol withdrawal syndrome (requiring hospitalisation) during the month before randomisation, chronic use of psychotropic medication before randomisation, dependence on psychoactive substances other than nicotine, liver cirrhosis, acute alcohol psychosis, severe depression, organic brain syndromes, pregnancy and lactation

Interventions
Intervention characteristics

Baclofen (participants = 32) + standard psychosocial intervention (motivational interviewing, education and therapy)

- Dose: For the first 3 days, baclofen 15 mg/day was administered in 3 divided doses; then baclofen dosage was increased to 50 mg/day in 2 divided doses (taken at 9 AM and 4 PM). During the last 3 days of the treatment protocol, the dose of baclofen was again decreased to 15 mg/day in 3 divided doses.
- Duration of treatment: 12 weeks
- Length of follow-up: 52 weeks

Placebo (participants = 32) + standard psychosocial intervention (motivational interviewing, education and therapy)

- Dose: identical table in the same frequency
- Duration of treatment: 12 weeks
- Length of follow up: 52 weeks

Outcomes
Primary outcomes

- Proportion of heavy drinking days (% HDD)
- Proportion of total abstinent days (% ABS)
- Assessed at week 6 (T1), week 12 (T2) of the medication period and at week 26 (T3) and week 52 (T4) of the follow-up period (these proportions were calculated on the basis of (1) a participant's self-report of alcohol intake as the mean number of standard drinks per day for each period by the Time Line Follow-Back)

Secondary outcomes

- Craving (OCDS), depression (abridged BDI), emotional distress (General Health Questionnaire (GHQ-12))
- Self-efficacy (General Self-Efficacy Scale (GSES))
- Perceived social support (Multidimensional Scale of Perceived Social Support (MSPSS))

Ponizovsky 2015 (Continued)

- Quality of life at T1, T2, T3 and T4 (Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q))

Identification	<p>Sponsorship source: study was supported by Israeli Anti-Drug Authority Grant #535-28. A.M. Ponizovsky was supported in part by the Ministry of Immigrant Absorption</p> <p>Country: Israel</p> <p>Setting: outpatients</p> <p>Author's name: Ponizovsky A.M.</p> <p>Institution: Research Unit, Mental Health Services, Ministry of Health, Jerusalem, Israel</p> <p>Email: alexpon8@gmail.com</p> <p>Address: Ministry of Health 39 Yirmiyahu St. POBox 1176 Jerusalem 9446724 Israel</p>
----------------	--

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by the pharmacist who prepared drug and placebo by using a random number generator, with the only restriction that the groups should be of equal size."
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Stated as double-blind, quote: "Placebo tablets were identical in all organoleptic characteristics to baclofen"
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Stated as double-blind, quote: "Placebo tablets were identical in all organoleptic characteristics to baclofen"
Blinding of outcome assessment (detection bias) subjective outcomes	Unclear risk	Not reported whether the outcome assessor was blinded
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Not reported whether the outcome assessor was blinded, but objective outcomes unlikely to be biased by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All outcome variables for patients who discontinued treatment before the end of the medication period were computed with the registers of the visit preceding discontinuation (last observation carried forward), which were compared between the treatment groups by Fisher's exact test. Based on the assumption that every patient took the allocated drug, intention to treat analysis was made All randomized patients were analyzed (intent-to-treat)"
Selective reporting (reporting bias)	Low risk	Study protocol not available; results reported for all the outcomes declared in the method section

Reynaud 2017

Methods	<p>Study design: RCT</p> <p>Study grouping: parallel-group</p>
Participants	<p>Baseline Characteristics</p> <p>Baclofen:</p> <ul style="list-style-type: none"> • Age (years): mean 49 ± 10.7 • Gender: male 118 (76.1%) • Sample size: 158 • Race: NR • Marital status: NR • Educational level (years): NR • Current use (duration of AD (years): mean 12.8 • Comorbidity: anxiety: 23 (14.8%); depression: 51 (23.9%) • Current use (% HDDs/1 month): mean 17.9 ± 10.2 • Current use (g/d): mean 95.5 ± 75.6 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years): mean 49.8 ± 9.8 • Gender: male 107 (69%) • Sample size: 162 • Race: NR • Marital status: NR • Educational level (years): NR • Current use (duration of AD (years): mean 14.2 ± 9.4 • Comorbidity: anxiety 16 (10.3%); depression 55 (35.5%) • Current use (% HDDs/1 month): mean 17.6 ± 10 • Current use (g/d): mean 93.6 ± 65.5 <p>Inclusion criteria: adult men or non-pregnant, non-breastfeeding women, with a diagnosis of AD according to DSM-IV, who had experienced at least 1 previous abstinence attempt, and had been fully abstinent for 3–14 days before randomisation; this range of 3–14 days was established in order to allow patients needing in-patient detoxification to participate in the study. Comorbid psychiatric diseases were assessed according to the investigator’s judgment.</p> <p>Exclusion criteria: need for a prolonged residential treatment after detoxification; need for an intensive psychosocial intervention during follow-up; history of baclofen intake by prescription or by self-medication; epilepsy or history of epilepsy; concomitant treatment with 1 or several drugs for the maintenance of abstinence; concomitant treatment with psychotropic medications, except antidepressants at stable dose for ≥ 2 months, diazepam and oxazepam; severe renal, cardiac or pulmonary disorders; severe psychiatric conditions (schizophrenia and bipolar disorder); clinically significant cognitive disorders; hepatic encephalopathy; suicidal risk or history of suicide; other current dependence except nicotine</p>
Interventions	<p>Intervention characteristics</p> <p>Baclofen (participants = 158 + BRENDA sessions were provided during each visit to support participants in changing their behaviour and to enhance adherence to treatment.</p> <ul style="list-style-type: none"> • Dose: a 7-week titration period during which the daily dose was gradually increased from 1-9 tablets; the initial dose was provided twice a day (10 mg morning and evening) for 2 d, then 3 times/day and the dose increased by 10 mg every 4 d; a 17-week maintenance period at the dose reached at the end of the titration period and a 2-week tapering-off period • Duration of treatment: 26 weeks • Length of follow-up: 30 weeks

Reynaud 2017 (Continued)

Placebo (participants = 162) + BRENDA sessions were provided during each visit to support participants in changing their behaviour and to enhance adherence to treatment.

- Dose: identical table in the same frequency
- Duration of treatment: 26 weeks
- Length of follow-up: 30 weeks

Outcomes
Primary outcomes

- Rate of abstinent participants during 20 consecutive weeks from Day 29 (start of the 5th week of the titration period) to Day 168 (end of the maintenance period)

Secondary outcomes

- Alcohol consumption: change from baseline in TAC (g/d)
- HDD (d/month) to month 6, change from baseline
- Craving: OCDS change from baseline
- Clinical Global Impression-Severity (CGI-S), change from baseline
- Clinical Global Impression-Improvement (CGI-I) , change from baseline
- Anxiety and Depression: Hospital Anxiety and Depression (HAD) scale , change from baseline
- 9-item alcohol dependence quality of life (AIQoL9), change from baseline
- Adverse events (AEs)

Identification

Sponsorship source: study was supported by Ethypharm SAS

Country: France

Setting: outpatients

Author's name: Reynaud M

Institution: Actions Addictions-Saint Joseph Hospital, 185 Rue Raymond Losserand, 75014 Paris, France

Email: michel.reynaud@actions-addictions.org

Address: Saint Joseph Hospital, 185 rue Raymond Losserand, 75014 Paris, France

Notes
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to baclofen or placebo in a 1:1 ratio, according to a computer generated randomization list (blocks size of 4)"
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was centralized via an Interactive Web Response System"
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	Quote: "The identical aspect of verum (20 mg coated scored baclofen tablet) and placebo tablets allowed a double-blind design. Sealed code envelopes were sent to the investigator centres with the corresponding study treatments. Access to the randomization codes and unblinding could only be performed in case of emergency"
Blinding of participants and personnel (performance bias) subjective outcomes	Low risk	Quote: "The identical aspect of verum (20 mg coated scored baclofen tablet) and placebo tablets allowed a double-blind design. Sealed code envelopes were sent to the investigator centres with the corresponding study treatments."

Baclofen for alcohol use disorder (Review)

Reynaud 2017 (Continued)

		Access to the randomization codes and unblinding could only be performed in case of emergency"
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	Quote: "The identical aspect of verum (20 mg coated scored baclofen tablet) and placebo tablets allowed a double-blind design. Sealed code envelopes were sent to the investigator centres with the corresponding study treatments. Access to the randomization codes and unblinding could only be performed in case of emergency"
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Quote: "The identical aspect of verum (20 mg coated scored baclofen tablet) and placebo tablets allowed a double-blind design. Sealed code envelopes were sent to the investigator centres with the corresponding study treatments. Access to the randomization codes and unblinding could only be performed in case of emergency"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The safety population, defined as patients having received at least one dose of study treatment, and considered for safety purpose; The full analysis set population, defined as randomized patients, having received at least one dose of study treatment and having reported at least one data regarding alcohol consumption in their diary, which is the main population for efficacy assessments" "Three methods of imputation were used for the management of missing data related to alcohol consumption: Multiple imputation with a placebo pattern mixture model (assuming that the alcohol consumption of dropped out patients was the same as those in the placebo group) was the main imputation method; it is one of the recommended method for handling missing data in alcohol clinical trials. Most plausible outcome (for abstinence endpoint only): for patients who did not report any alcohol consumption during the 20 consecutive weeks and had at least one missing data during the period, their profiles were reviewed by 2 blinded medical experts who filled in the missing data; Worst case: missing data were imputed to alcohol intake"
Selective reporting (reporting bias)	Low risk	Study protocol not available; results reported for all the outcomes declared in the method section

AD: alcohol dependence; **ADS:** alcohol dependence scale; **BBCET:** brief behavioral compliance enhancement treatment; **BDI:** Beck's Depression Inventory; **BSI:** Brief Symptom Inventory; **CBT:** cognitive behavioural therapy; **DSM-IV (TR):** *Diagnostic and Statistical Manual of Mental Disorders*, 4th revision (text revision); **HCV:** hepatitis C virus; **HD:** high-dose; **HDD:** heavy drinking day; **ICD:** International Classification of Diseases; **LD:** low-dose; **N/A:** not applicable; **NR:** not reported; **OCDS:** obsessive compulsive drinking scale; **RCT:** randomised controlled trial; **SD:** standard deviation; **SDU:** standard drink unit; **STAI:** State-Trait Anxiety Inventory; **SUD:** substance use disorder; **TAC:** total alcohol consumption; **ULN:** upper limit of normal

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Addolorato 2002	Duration of the study < 12 weeks
Flannery 2004	Study design not in the inclusion criteria: uncontrolled preliminary study on 14 participants
Leggio 2011	Study objective not in the inclusion criteria: human laboratory study to investigate putative behavioral mechanisms by which baclofen reduces drinking
Leggio 2013	Study objective not in the inclusion criteria: human laboratory study to investigate putative behavioral mechanisms by which baclofen reduces drinking

Characteristics of studies awaiting assessment [ordered by study ID]

Addolorato 2011

Methods	Study design: 12-week, 3-armed, parallel, double-blind, randomised clinical trial (post hoc analysis)
Participants	42 participants with a diagnosis of AD according to DSM IV-TR; median age of 44 years (range 23–60 years). 76% were men
Interventions	<ul style="list-style-type: none"> Experimental: with 2 doses of baclofen (10 mg 3 times/d or 20 mg 3 times/d) Control: placebo
Outcomes	<ul style="list-style-type: none"> Daily alcohol intake
Notes	The published study is a post hoc analysis. We wrote to the study authors to receive the results obtained from the primary analysis but we have not yet received the data.

CTRI/2016/01/006525

Methods	Prospective, randomised, open-label study
Participants	60 men aged 18-65 years, meeting diagnostic criteria for AD as per ICD-10 classification
Interventions	Baclofen (20-40 mg/d in 3 divided doses, orally for 12 weeks) vs topiramate (50-300 mg/day in 2 divided doses, orally for 12 weeks)
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Craving (OCDS) Motivation (Readiness to Change Questionnaire) Withdrawal symptoms by Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) Adverse events of drugs using checklist <p>Secondary outcomes</p> <ul style="list-style-type: none"> Craving and Visual Analogue scale (VAS) The World Health Organization Quality of Life (WHOQOL-BREF), Field Trial Version (Hindi version), Hemogram Adverse events checklist
Notes	

Farokhnia 2014

Methods	Double-blind, placebo-controlled RCT
Participants	30 treatment-seeking alcoholic smokers meeting the inclusion criteria of DSM-IV diagnoses of both alcohol and nicotine dependence in addition to heavy use of both alcohol (> 4 and > 5 standard drink units/d on average for women and men, respectively) and nicotine (> 10 cigarettes per day on average) during the last 90 d before screening
Interventions	Baclofen (80 mg/day) vs placebo for 12 weeks

Baclofen for alcohol use disorder (Review)

Farokhnia 2014 (Continued)

Outcomes	<ul style="list-style-type: none"> Percentage days of abstinence from alcohol-tobacco co-use Duration of abstinence Craving
Notes	Conference abstract without enough usable data

Jaury 2014

Methods	Multicentric, pragmatic, therapeutic, randomised, double-blind, phase 2 and phase 3 trial in primary care assessing the efficacy and safety of high-dose baclofen versus placebo during 1 year
Participants	<ul style="list-style-type: none"> People aged 18-65 years attending for a problem with alcohol (at high risk during the past 3 months (at least twice during each month) according to WHO standards, i.e. in women > 40 g/d or 280 g/week or > 40 g in one go; in men > 60 g/d or 420 g/week or > 60 g in one go, and expressing the desire to be abstinent or to reduce consumption to low risk). Volunteered to participate in the trial and gave written consent after receiving appropriate information Not treated for maintenance of abstinence (acamprosate, naltrexone) and the prevention of relapse (disulfiram) for at least 15 days before the beginning of the study Informed about the possibility of drowsiness in relation to the treatment and the associated risks of driving vehicles (motorised or not), the use of machines (including domestic use or recreation) and the execution of tasks requiring attention and precision Including woman of childbearing age (but taking effective contraception)
Interventions	<ul style="list-style-type: none"> Baclofen administered orally for a maximum of 52 consecutive weeks. For the first 3 days, participants will receive baclofen in a dose of 5 mg 3 times/d; then the dose of baclofen increased to a maximum of 300 mg/d. In case of intolerance, dosage can be decreased. Placebo: sugar pill administered orally for a maximum of 52 consecutive weeks. For the first 3 days, participants will receive sugar pill in a dose of 5 mg 3 times/d; then the dose of sugar pill increased to a maximum of 300 mg/d. In case of intolerance, dosage can be decreased
Outcomes	<p>Primary outcome</p> <p>Proportion of abstainer participants and participants with a low-risk consumption (time frame: 12 months after the initiation of treatment)</p> <p>Secondary outcome</p> <ul style="list-style-type: none"> TAC during the 12th month Average monthly alcohol consumption Numbers of abstinence and HDDs. Craving: Visual Analogue Scale and OCDS Scale 36-Item Short Form Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS). DSM-IV for AD Laboratory variables Alcohol consumption evaluated by the physician during the 12th month Characterisation of the population responding to baclofen Determination of the optimal dose of baclofen
Notes	<p>The pilot study is a protocol published on ClinicalTrials.gov, where it is reported that the study has been completed without results posted. Preliminary results were presented at the ISBRA/ESBRA Conference, Berlin 2016.</p> <p>We received information from the study authors that the study is under publication.</p>

Morley 2013

Methods	<p>This is a double-blind, randomised, placebo-controlled, phase 3 study investigating the efficacy of baclofen for the treatment of alcohol dependence in people with alcoholic liver disease. Medications will be given for 12 weeks, with a further 6 months' follow-up. Both male and female participants will be recruited to this study.</p> <p>Trial participants will be randomised to one of three treatment groups:</p> <ul style="list-style-type: none"> • baclofen 30 mg/d (10 mg 3 times/d) • baclofen 75 mg/d (25 mg 3 times/d) • placebo (3 matched tabs/d) <p>This study will also include a second, parallel group of participants with AD (non alcoholic-liver disease patients), who will undergo the trial protocol as described above.</p> <p>These participants will be randomised according to a separate list into one of three treatment groups:</p> <ul style="list-style-type: none"> • baclofen 30 mg/day (10 mg 3 times/d) • baclofen 75mg/day (25 mg 3 times/d) • placebo (3 matched tabs/d) <p>Masking: 1uadruple (participant, care provider, investigator, outcomes assessor)</p> <p>Primary purpose: treatment</p>
Participants	<ul style="list-style-type: none"> • People with Alcoholic Liver Disease and Alcohol Dependence
Interventions	<ul style="list-style-type: none"> • Drug: baclofen 30 mg/d • Drug: baclofen 75 mg/d • Drug: placebo
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Alcohol consumption (time frame: 12 weeks) as measured by the number of days abstinent, • Number of HDDs • Time to relapse • Time to lapse • Number of drinks per drinking day <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Clinical markers of liver injury (time frame: 12 weeks) • Incidence of hepatic adverse events (time frame: 12 weeks) • Craving for alcohol (time frame: 12 weeks) • Early termination due to adverse events (time frame: 12 weeks)
Notes	<p>The pilot study is a protocol published on ClinicalTrials.gov, where it is reported that the study has been completed without results being posted.</p> <p>We received information form the study authors that the study is under publication.</p>

Sharma 2012

Methods	Randomised, double-blind, controlled trial
---------	--

Sharma 2012 (Continued)

Participants	54 participants
Interventions	Baclofen 10 mg/d vs 12 mg for 12 weeks (n: 18) vs placebo (n:18)
Outcomes	Daily number of drinks
Notes	Conference abstract without enough usable data

AD: alcohol dependence; **DSM-IV (TR):** *Diagnostic and Statistical Manual of Mental Disorders*, 4th revision (text revision); **HDD:** heavy drinking days; **ICD:** International Classification of Diseases; **OCDS:** obsessive compulsive drinking scale; **RCT:** randomised controlled trial; **WHO:** World Health Organization

Characteristics of ongoing studies [ordered by study ID]

CTRI/2011/11/002154

Trial name or title	CTRI/2011/11/002154
Methods	Randomised, phase III, parallel-group, placebo-controlled trial
Participants	180 male or female participants aged 21-75 years, meeting DSM-IV-TR criteria for current AD
Interventions	Baclofen vs placebo
Outcomes	<ul style="list-style-type: none"> • Time to relapse • Time to first lapse • Number of abstinent days • Number of drinks per drinking day • Number HDDs • Liver biomarkers • AD severity • Extent of craving for alcohol • Compliance to treatment • Compliance to study • Investigator's global impression of change and subject's global impression of change <p>Safety variables</p> <ul style="list-style-type: none"> • Physical examination • Vital signs • Treatment emergent adverse events • Clinically significant changes in laboratory parameters
Starting date	24 December 2011
Contact information	shravanti.bhowmik@sparcmail.com
Notes	

NCT01980706

Trial name or title	NCT01980706
---------------------	-------------

Baclofen for alcohol use disorder (Review)

NCT01980706 (Continued)

Methods	Phase II, randomised, placebo-controlled trial
Participants	Men and women aged 18-65 meeting DSM-IV criteria for current AD
Interventions	Baclofen vs placebo Baclofen will be titrated to 10 mg 3 times/d over 3 days and to 30 mg 3 times/d over 12 days and maintained at that level for 12 weeks and then down-titrated for a total study time of 16 weeks
Outcomes	Primary outcome <ul style="list-style-type: none"> Mean % HDDs Secondary outcomes <ul style="list-style-type: none"> Mean % abstinent drinking days (time frame: every 1-2 weeks up to 107 days of active trial) Anxiety level based on Spielberger Scale for State Anxiety
Starting date	28 October 2013
Contact information	Principal investigator: James C Garbutt, MD
Notes	

AD: alcohol dependence; **DSM-IV (TR):** *Diagnostic and Statistical Manual of Mental Disorders*, 4th revision (text revision); **HDD:** heavy drinking days

DATA AND ANALYSES

Comparison 1. Baclofen vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse: return to any drinking at end of treatment	5	781	Risk Ratio (IV, Random, 95% CI)	0.88 [0.74, 1.04]
2 Frequency of use: % days abstinence at end of treatment	6	465	Mean Difference (IV, Random, 95% CI)	0.39 [-11.51, 12.29]
3 Frequency of use: % of heavy drinking days at end of treatment	3	186	Mean Difference (IV, Random, 95% CI)	0.25 [-1.25, 1.76]
4 Amount of use: drink per drinking days at end of treatment	2	72	Mean Difference (IV, Random, 95% CI)	1.55 [1.32, 1.77]
5 Adverse events: number of participants with at least one adverse event at end of treatment	4	430	Risk Ratio (IV, Random, 95% CI)	1.04 [0.99, 1.10]
6 Dropout at end of treatment	8	977	Risk Ratio (IV, Random, 95% CI)	0.98 [0.77, 1.26]
7 Dropout due to adverse events	7	913	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.59, 2.07]

Baclofen for alcohol use disorder (Review)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Craving	5	469	Mean Difference (IV, Random, 95% CI)	1.38 [-1.28, 4.03]
9 Anxiety	5	509	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.14, 0.28]
10 Depression	3	387	Std. Mean Difference (IV, Random, 95% CI)	0.27 [0.05, 0.48]
11 Adverse events: fatigue, tiredness	6	828	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.98, 1.56]
12 Adverse events: insomnia	4	577	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.51]
13 Adverse events: pain (diverse)	2	86	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.28, 3.27]
14 Adverse events: vertigo, dizziness	7	858	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.24, 3.74]
15 Adverse events: constipation	4	567	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.54, 1.58]
16 Adverse events: somnolence, sleepiness, drowsiness or sedation	9	986	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.11, 1.96]
17 Adverse events: muscle pain	4	593	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.39, 2.26]
18 Adverse events: dry mouth	3	509	Risk Ratio (M-H, Random, 95% CI)	2.68 [0.77, 9.32]
19 Adverse events: nausea	4	577	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.61, 2.30]
20 Adverse events: skin rash	3	251	Risk Ratio (M-H, Random, 95% CI)	2.59 [0.78, 8.55]
21 Adverse events: headaches	7	821	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.84, 1.81]
22 Adverse events: paresthesia/numbness	4	593	Risk Ratio (M-H, Random, 95% CI)	4.28 [2.11, 8.67]
23 Adverse events: diarrhoea	2	495	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.31, 1.31]
24 Adverse events: tinnitus	2	495	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.16, 20.05]
25 Adverse events: muscle spasm/rigidity	3	551	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.08, 3.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26 Adverse events: hyperhidrosis	2	495	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.86, 4.63]
27 Adverse events: nasopharyngitis	3	551	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.23, 2.23]
28 Adverse events: decrease appetite/anorexia	2	495	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.49, 2.12]
29 Adverse events: dysgeusia/ageusia	2	495	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.44, 11.94]
30 Adverse events: tremor	2	495	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.46, 1.65]
31 Adverse events: weakness	2	495	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.60, 1.92]
32 Adverse events: vomiting	2	495	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.50, 1.88]
33 Adverse events: urinary frequency	3	265	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.35, 7.63]

Analysis 1.1. Comparison 1 Baclofen vs placebo, Outcome 1 Relapse: return to any drinking at end of treatment.

Analysis 1.2. Comparison 1 Baclofen vs placebo, Outcome 2 Frequency of use: % days abstinence at end of treatment.

Analysis 1.3. Comparison 1 Baclofen vs placebo, Outcome 3 Frequency of use: % of heavy drinking days at end of treatment.

Analysis 1.4. Comparison 1 Baclofen vs placebo, Outcome 4 Amount of use: drink per drinking days at end of treatment.

Analysis 1.5. Comparison 1 Baclofen vs placebo, Outcome 5 Adverse events: number of participants with at least one adverse event at end of treatment.

Analysis 1.6. Comparison 1 Baclofen vs placebo, Outcome 6 Dropout at end of treatment.

Analysis 1.7. Comparison 1 Baclofen vs placebo, Outcome 7 Dropout due to adverse events.

Analysis 1.8. Comparison 1 Baclofen vs placebo, Outcome 8 Craving.

Analysis 1.9. Comparison 1 Baclofen vs placebo, Outcome 9 Anxiety.

Analysis 1.10. Comparison 1 Baclofen vs placebo, Outcome 10 Depression.

Analysis 1.11. Comparison 1 Baclofen vs placebo, Outcome 11 Adverse events: fatigue, tiredness.

Analysis 1.12. Comparison 1 Baclofen vs placebo, Outcome 12 Adverse events: insomnia.

Analysis 1.13. Comparison 1 Baclofen vs placebo, Outcome 13 Adverse events: pain (diverse).

Analysis 1.14. Comparison 1 Baclofen vs placebo, Outcome 14 Adverse events: vertigo, dizziness.

Analysis 1.15. Comparison 1 Baclofen vs placebo, Outcome 15 Adverse events: constipation.

Analysis 1.16. Comparison 1 Baclofen vs placebo, Outcome 16 Adverse events: somnolence, sleepiness, drowsiness or sedation.

Analysis 1.17. Comparison 1 Baclofen vs placebo, Outcome 17 Adverse events: muscle pain.

Analysis 1.18. Comparison 1 Baclofen vs placebo, Outcome 18 Adverse events: dry mouth.

Analysis 1.19. Comparison 1 Baclofen vs placebo, Outcome 19 Adverse events: nausea.

Analysis 1.20. Comparison 1 Baclofen vs placebo, Outcome 20 Adverse events: skin rash.

Analysis 1.21. Comparison 1 Baclofen vs placebo, Outcome 21 Adverse events: headaches.

Analysis 1.22. Comparison 1 Baclofen vs placebo, Outcome 22 Adverse events: paresthesia/numbness.

Analysis 1.23. Comparison 1 Baclofen vs placebo, Outcome 23 Adverse events: diarrhoea.

Analysis 1.24. Comparison 1 Baclofen vs placebo, Outcome 24 Adverse events: tinnitus.

Analysis 1.25. Comparison 1 Baclofen vs placebo, Outcome 25 Adverse events: muscle spasm/rigidity.

Analysis 1.26. Comparison 1 Baclofen vs placebo, Outcome 26 Adverse events: hyperhidrosis.

Analysis 1.27. Comparison 1 Baclofen vs placebo, Outcome 27 Adverse events: nasopharyngitis.

Analysis 1.28. Comparison 1 Baclofen vs placebo, Outcome 28 Adverse events: decrease appetite/anorexia.

Analysis 1.29. Comparison 1 Baclofen vs placebo, Outcome 29 Adverse events: dysgeusia/ageusia.

Analysis 1.30. Comparison 1 Baclofen vs placebo, Outcome 30 Adverse events: tremor.

Analysis 1.31. Comparison 1 Baclofen vs placebo, Outcome 31 Adverse events: weakness.

Analysis 1.32. Comparison 1 Baclofen vs placebo, Outcome 32 Adverse events: vomiting.

Analysis 1.33. Comparison 1 Baclofen vs placebo, Outcome 33 Adverse events: urinary frequency.

Comparison 2. Baclofen vs acamprosate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Craving	1	49	Mean Difference (IV, Random, 95% CI)	14.62 [12.72, 16.52]

Analysis 2.1. Comparison 2 Baclofen vs acamprosate, Outcome 1 Craving.

APPENDICES

Appendix 1. Cochrane Drug and Alcohol Group Specialised Register search strategy

CDAG Specialised Register (via CRSLive)

30 January 2018 (53 hits)

baclofen (all fields)

Appendix 2. CENTRAL search**Cochrane Central Register of Controlled Trials (CENTRAL) (via onlinelibrary.wiley.com)****2017, issue 12 (59 hits)**

#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 in Trials

Appendix 3. MEDLINE via PubMed search**30 January 2018 (125 hits)**

1. alcohol-related disorders[MeSH]

2. ((alcohol[tiab]) AND (abuse*[tiab] OR addict*[tiab] OR dependen*[tiab] OR disorder*[tiab] OR drink*[tiab] OR consumption[tiab]))

3. Drinking behaviour[MeSH]

4. #1 OR #2 OR #3

5. Baclofen [MeSH]

6. Chlorophenyl GABA [tiab]

7. beta-(p-Chlorophenyl)-gamma-aminobutyric Acid [tiab]

8. "gamma-amino butyric acid-B receptor agonists

9. "Lioresal [tiab]

10.#5 OR #6 OR #7 OR #8 OR #9

11.randomized controlled trial [pt]

12.controlled clinical trial [pt]

13.random* [tiab]

14.placebo [tiab]

15.drug therapy [MeSH]

16.trial [tiab]

17.groups [tiab]

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

19.animals [mh] NOT human [mh]

20.#18 NOT #19

21.#4 AND #10 AND #20

Appendix 4. Embase search strategy**Embase (OVID)****30 January 2018 (329 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

Appendix 5. PsycINFO

PsycINFO (OVID)

30 January 2018 (137 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. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. 1 or 2
4. exp BACLOFEN/
5. baclofen.mp.
6. 4 or 5
7. 3 and 6
8. (control* or random*).tw. or exp Treatment/
9. 7 and 8

Appendix 6. Web of Science search strategy

30 January 2018 (126 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

Appendix 7. CINAHL search strategy

CINAHL (EBSCOhost)

30 January 2018 (29 hits)

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 8. Criteria for 'Risk of bias' assessment

Item	Judgment	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement

(Continued)

3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers ensured and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
6. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.

(Continued)

7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	<p>No missing outcome data.</p> <p>Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).</p> <p>Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically-relevant impact on the intervention effect estimate.</p> <p>For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically-relevant impact on observed effect size.</p> <p>Missing data have been imputed using appropriate methods.</p> <p>All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat).</p>
	High risk	<p>Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically-relevant bias in intervention effect estimate.</p> <p>For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically-relevant bias in observed effect size.</p> <p>'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.</p>
	Unclear risk	<p>Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group).</p>
8. Selective reporting (reporting bias)	Low risk	<p>The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.</p> <p>The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).</p>
	High risk	<p>Not all of the study's prespecified primary outcomes have been reported.</p> <p>One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.</p> <p>One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).</p> <p>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.</p>

(Continued)

The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear risk

Insufficient information to permit judgement of low or high risk.

Appendix 9. Trials registers

ClinicalTrials.gov

30 January 2018

22 studies found for: baclofen | Interventional Studies | alcohol (www.clinicaltrials.gov)

World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

30 January 2018

34 records for 33 trials found for: baclofen AND alcohol (apps.who.int/trialsearch/)

CONTRIBUTIONS OF AUTHORS

SM conceived and co-ordinated the protocol. SR wrote the background section, the discussion and the conclusion section. SM and RS wrote the Methods section.

SM and RS conducted screenings, extracted data and completed the 'Risk of bias' assessment. SM and RS undertook data analysis. SR contributed to screening in case of doubt or disagreement and wrote the discussion. All review authors contributed to writing and revising the final report.

DECLARATIONS OF INTEREST

Silvia Minozzi: no conflict of interest known

Rosella Saulle: no conflict of interest known

Susanne Rösner: no conflict of interest known

SOURCES OF SUPPORT

Internal sources

- Department of Epidemiology, Lazio Regional Health Service, Rome, Italy.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the primary outcome, 'dropout due to adverse events' and the secondary outcome, 'frequency of most relevant adverse events' because of their relevance.

INDEX TERMS

Medical Subject Headings (MeSH)

Acamprosate [therapeutic use]; Alcohol Deterrents [adverse effects] [*therapeutic use]; Alcohol Drinking [*prevention & control]; Alcoholism [*drug therapy]; Baclofen [adverse effects] [*therapeutic use]; Craving [drug effects]; Depression [chemically induced]; GABA-B Receptor Agonists [adverse effects] [*therapeutic use]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Female; Humans; Male; Middle Aged