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[Intervention Review]

Baclofen for alcohol use disorder

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ABSTRACT

Background

Alcohol use disorder (AUD) is one of the most widespread psychiatric disorders leading to detrimental consequences to people with this disorder and others. Worldwide, the prevalence of heavy episodic drinking (30-day prevalence of at least one occasion of 60 g of pure alcohol intake among current drinkers) is estimated at 20% and the prevalence of AUD at 5% of the adult general population, with highest prevalence in Europe and North America. Therapeutic approaches, including pharmacotherapy, play an important role in treating people with AUD.

This is an update of a Cochrane Review first published in 2018.

Objectives

To evaluate the benefits and harms of baclofen on achieving and maintaining abstinence or reducing alcohol consumption in people with AUD compared to placebo, no treatment or any other pharmacological relapse prevention treatment.

Search methods

We used standard, extensive Cochrane search methods. The latest search was 22 November 2021.

Selection criteria

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

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were 1. relapse, 2. frequency of use, 3. amount of use, 4. adverse events, 5. dropouts from treatment and 6. dropouts from treatment due to adverse events. Our secondary outcomes were 7. craving, 8. anxiety, 9. depression and 10. frequency of most relevant adverse events.

Main results

We included 17 RCTs (1818 participants) with a diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition or International Classification of Diseases 10th edition criteria. Mean age was 46.5 years and 70% were men. Ten studies compared baclofen to placebo or another medication; seven compared two baclofen doses to placebo or another medication. Globally, 15 studies compared baclofen to placebo, two baclofen to acamprosate and two baclofen to naltrexone. In 16 studies, participants received psychosocial treatments.

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

Ten studies detoxified participants before treatment; in seven studies, participants were still drinking at the beginning of treatment. Treatment duration was 12 weeks for 15 RCTs and longer in two studies. Baclofen daily dose was 30 mg to 300 mg: 10 RCTs used low doses (30 mg or less); eight RCTs medium doses (above 30 and 100 mg or less) and four RCTs high doses (above 100 mg).

Compared to placebo, moderate-certainty evidence found that baclofen probably decreases the risk to relapse (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.77 to 0.99; 12 studies, 1057 participants). This result was confirmed among detoxified participants but not among other subgroups of participants.

High-certainty evidence found that baclofen increases the percentage of days abstinent (mean difference (MD) 9.07, 95% CI 3.30 to 14.85; 16 studies, 1273 participants). This result was confirmed among all subgroups of participants except non-detoxified or those who received medium doses.

There was no difference between baclofen and placebo in the other primary outcomes: heavy drinking days (standardised mean difference (SMD) −0.18, 95% CI −0.48 to 0.11; 13 studies, 840 participants; moderate-certainty evidence); number of drinks per drinking days (MD −0.45, 95% CI −1.20 to 0.30; 9 studies, 392 participants; moderate-certainty evidence); number of participants with at least one adverse event (RR 1.05, 95% CI 0.99 to 1.11; 10 studies, 738 participants; high-certainty evidence); dropouts (RR 0.88, 95% CI 0.74 to 1.03; 17 studies, 1563 participants; high-certainty evidence); dropouts due to adverse events (RR 1.39, 95% CI 0.89 to 2.18; 16 studies, 1499 participants; high-certainty evidence). These results were confirmed by subgroup analyses except than for the dropouts that resulted lower among participants who received high doses of baclofen and studies longer than 12 weeks.

Compared to placebo, there was no difference in craving (SMD −0.16, 95% CI −0.37 to 0.04; 17 studies, 1275 participants), anxiety (MD −0.01, 95% CI −0.14 to 0.11; 15 studies, 1123 participants) and depression (SMD 0.07, 95% CI −0.12 to 0.27; 11 studies, 1029 participants).

Concerning the specific adverse events, baclofen increases fatigue, dizziness, somnolence/sedation, dry mouth, paraesthesia and muscle spasms/rigidity. There was no difference in the other adverse events.

Compared to acamprosate, one study (60 participants) found no differences in any outcomes but the evidence was very uncertain: relapse (RR 1.25, 95% CI 0.71 to 2.20; very low-certainty evidence); number of participants with at least one adverse event (RR 0.63, 95% CI 0.23 to 1.69; very low-certainty evidence); dropouts (RR 0.56, 95% CI 0.21 to 1.46; very low-certainty evidence); dropouts due to adverse events (RR 0.33, 95% CI 0.01 to 7.87; very low-certainty evidence) and craving (MD 5.80, 95% CI −11.84 to 23.44); and all the adverse events evaluated.

Compared to naltrexone, baclofen may increase the risk of relapse (RR 2.50, 95% CI 1.12 to 5.56; 1 study, 60 participants; very low-certainty evidence) and decrease the number of participants with at least one adverse event (RR 0.35, 95% CI 0.15 to 0.80; 2 studies, 80 participants; very low-certainty evidence) but the evidence is very uncertain. One study (60 participants) found no difference between baclofen and naltrexone in the dropouts at the end of treatment (RR 1.00, 95% CI 0.32 to 3.10; very low-certainty evidence), craving (MD 2.08, 95% CI −3.71 to 7.87), and all the adverse events evaluated.

Authors' conclusions

Baclofen likely reduces the risk of relapse to any drinking and increases the percentage of abstinent days, mainly among detoxified participants. It does not increase the number of participants with at least one adverse event, those who dropout for any reason or due to adverse events. It probably does not reduce number of heavy drinking days and the number of drinks per drinking days. Current evidence suggests that baclofen may help people with AUD in maintaining abstinence. The results of comparisons of baclofen with acamprosate and naltrexone were mainly based on only one study.

PLAIN LANGUAGE SUMMARY

Baclofen for alcohol use disorder

Key messages of the review

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

Current evidence suggests that it may help people with AUD in maintaining abstinence, particularly in people who are already detoxified. The results of comparisons with other medications were mainly based on a single study and do not allow us to draw conclusions.

Review topics and aims

AUD is one of 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 (food pipe) cancer, liver disease, epilepsy (fits), motor vehicle accidents, murders and other intentional injuries.

For many years, the main treatments for AUD have been psychosocial strategies (helping people to recognise that they need help), but using only psychosocial treatments has limited success. A high proportion of people with AUD do not respond to treatment at all, and

those who do respond do not stay alcohol-free in the long-term. Medications such as baclofen could play an important role in treating people with AUD.

Review methods

We searched for randomised controlled trials (studies where people were allocated at random to one of two or more treatments or control groups) evaluating the effect of baclofen in reducing alcohol consumption or in achieving and maintaining abstinence (or both) when compared to placebo (inactive medication) or other medications. We pooled similar studies and evaluated the effects dividing the studies according to the doses of baclofen, duration of treatment, and alcohol consumption and the beginning of treatment (i.e. into detoxified or non-detoxified participants on the basis if they were abstinent or were still drinking at the beginning of treatment).

Summary of results

We found 17 studies with 1818 participants with AUD. The duration of the interventions ranged from three months to one year. Five studies were in the USA; two each in Australia, France, India and Italy; and one each in Germany, Israel and the Netherlands.

Doses of baclofen were 30 mg a day to 300 mg a day, and, in some cases, the doses were increased during the treatment. Seventeen studies compared baclofen to placebo (dummy medication), two compared baclofen to acamprosate (medication used to treat AUD), and two compared baclofen to naltrexone (medication used to treat AUD).

Compared with placebo, baclofen probably helps people with AUD at reducing the risk of relapse and increasing the rate of abstinent days. These effects may be more evident among detoxified than non-detoxified people with AUD. Baclofen probably makes no difference in the rate of heavy drinking days; drinks per drinking days; craving, anxiety and depression severity; number of participants who dropout from treatment for any reason; those who dropped out due to adverse events (side effects); or the number of participants with at least one adverse event. Baclofen may increase adverse events such as fatigue, vertigo (a feeling that everything is spinning), sleepiness, dry mouth, numbness and muscle spasm but we found no differences between baclofen and placebo for other adverse events.

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

Search date
The evidence is current to November 2021. This is an update of a Cochrane Review first published in 2018.

Summary of findings 1. Summary of findings table - Baclofen compared to placebo for alcohol use disorder

Baclofen compared to placebo for alcohol use disorder

Patient or population: alcohol use disorder
Setting: outpatients
Intervention: baclofen
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with baclofen				
Relapse: return to any drinking at end of treatment	816 per 1000	**710 per 1000** (628 to 808)	**RR 0.87** (0.77 to 0.99)	1057 (12 RCTs)	⊕⊕⊕⊖ Moderate[a]	Compared to placebo, baclofen probably decreases the risk to relapse to any drinking.
Frequency of use: % days abstinence at end of treatment	The mean frequency of use: % days abstinence at end of treatment was **53.58**	MD **9.07 higher** (3.3 higher to 14.85 higher)	-	1273 (16 RCTs)	⊕⊕⊕⊕ High	Compared to placebo, baclofen increases the % of days abstinent.
Frequency of use: heavy drinking days at end of treatment	-	SMD **0.18 lower** (0.48 lower to 0.11 higher)	-	840 (13 RCTs)	⊕⊕⊕⊖ Moderate[b]	Compared to placebo, baclofen may not reduce heavy drinking days.
Amount of use: drink per drinking days at end of treatment	The mean amount of use: drink per drinking days at end of treatment was **4.28**	MD **0.45 lower** (1.2 lower to 0.3 higher)	-	392 (9 RCTs)	⊕⊕⊕⊖ Moderate[c]	Compared to placebo, baclofen probably does not reduce the number of drinks per drinking days.
Adverse events: number of participants with ≥ 1 adverse event at end of treatment	636 per 1000	**668 per 1000** (629 to 706)	**RR 1.05** (0.99 to 1.11)	738 (10 RCTs)	⊕⊕⊕⊕ High	Compared to placebo, baclofen does not increase the number of participants with ≥ 1 adverse event at the end of treatment.

Dropouts at end of treatment	420 per 1000	**369 per 1000** (311 to 432)	**RR 0.88** (0.74 to 1.03)	1563 (17 RCTs)	⊕⊕⊕⊕ High	Compared to placebo, baclofen does not increase the number of participants who dropout at the end of treatment.
Dropouts due to adverse events	44 per 1000	**61 per 1000** (39 to 95)	**RR 1.39** (0.89 to 2.18)	1499 (16 RCTs)	⊕⊕⊕⊕ High	Compared to placebo, baclofen does not increase the number of dropouts due to adverse events.

*__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; **RR:** risk ratio; **SMD:** standardised mean difference

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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432179672169955326.

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

Summary of findings 2. Summary of findings table - Baclofen compared to acamprosate for alcohol use disorder

Baclofen compared to acamprosate for alcohol use disorder

Patient or population: alcohol use disorder
Setting:
Intervention: baclofen
Comparison: acamprosate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with acamprosate	Risk with baclofen				

Relapse: return to any drinking at end of treatment	400 per 1000	**500 per 1000** (284 to 880)	**RR 1.25** (0.71 to 2.20)	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	It is uncertain whether baclofen and acamprosate differ in the return to any drinking.
Adverse events: number of participants with at least one adverse event at end of treatment	267 per 1000	**168 per 1000** (61 to 451)	**RR 0.63** (0.23 to 1.69)	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	It is uncertain whether baclofen and acamprosate differ in the number of participants with ≥ 1 adverse event at the end of treatment.
Dropouts at end of treatment	300 per 1000	**168 per 1000** (63 to 438)	**RR 0.56** (0.21 to 1.46)	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	It is uncertain whether baclofen and acamprosate differ in dropouts at the end of treatment.
Dropouts due to adverse events	33 per 1000	**11 per 1000** (0 to 262)	**RR 0.33** (0.01 to 7.87)	60 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	It is uncertain whether baclofen and acamprosate differ in dropouts due to adverse events at the end of treatment.

*__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; **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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432318545502233572.

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

Summary of findings 3. Summary of findings table - Baclofen compared to naltrexone for alcohol use disorder

Baclofen compared to naltrexone for alcohol use disorder

Patient or population: alcohol use disorder
Setting:
Intervention: baclofen

Comparison: naltrexone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with naltrexone	Risk with baclofen				
Relapse: return to any drinking at end of treatment	200 per 1000	**500 per 1000** (224 to 1000)	**RR 2.50** (1.12 to 5.56)	60 (1 RCT)	⊕⊝⊝⊝ Very low[a,b]	It is uncertain whether baclofen and naltrexone differ in the risk to return to any drinking.
Adverse events: number of participants with ≥ 1 adverse event at end of treatment	450 per 1000	**158 per 1000** (68 to 360)	**RR 0.35** (0.15 to 0.80)	80 (2 RCTs)	⊕⊝⊝⊝ Very low[a,b]	It is uncertain whether baclofen and naltrexone differ in the number of participants with ≥ 1 adverse event at the end of treatment.
Dropouts at end of treatment	167 per 1000	**167 per 1000** (53 to 517)	**RR 1.00** (0.32 to 3.10)	60 (1 RCT)	⊕⊝⊝⊝ Very low[a,b]	It is uncertain whether baclofen and naltrexone differ in dropouts at the end of treatment.

*__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; **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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432318841614592889.

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

BACKGROUND

Description of the condition

Alcohol use disorder (AUD) is a severe mental disorder characterised by the inability to control alcohol consumption and frequent episodes of heavy drinking leading to detrimental consequences for both people with this disorder and others (Carvalho 2019; MacKillop 2022). AUD as a disease category has been introduced in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (APA 2013). While the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (APA 2000) and International Classification of Diseases 11th edition (ICD)-11 (WHO 2019) subdivided substance use disorders into dependence and a secondary category, called 'abuse' in DSM-IV and 'harmful use' in ICD-11 (MacKillop 2022), the DSM-5 integrates both categories into a single substance use disorder concept that ranges along a continuum from mild to severe (APA 2013).

AUD and alcohol-related impairments belong to the most widespread psychiatric disorders (Carvalho 2019; Grant 2015). Worldwide, according to the World Health Organization (WHO), one-year AUD prevalence was estimated at approximately 5% of the general population in 2016, equivalent to 1 in 20 adults (WHO 2018). Statistics vary between regions, with a higher prevalence of AUD in high-income countries compared to low- and middle-income countries (Glantz 2020), with the highest one-year prevalence of AUD in European countries and North America (WHO 2018). The latest WHO status report on alcohol and health selected the heavy episodic drinking (HED, defined as 60 g or more of pure alcohol on at least one single occasion at least once per month) as an indicator of the pattern of excessive alcohol consumption (WHO 2018). Worldwide, using survey data from 118 countries, the prevalence of HED was estimated at 20% of the adult general population (aged 15 years and older) (Manthey 2019), with the highest values in European countries (26% of the general population) and America (21% of the general population) (WHO 2018). There is evidence indicating an enormous increase in alcohol use, high-risk drinking and DSM-IV AUD in the US population between 2001/2002 and 2012/2013 (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 2018).

Irrespective of region, AUD is prevalent in more men than women (Glantz 2020), with lifetime prevalence estimated at 14.8% among men and 3.5% among women in the Europe and 11.5% among men and 5.1% among women in the Americas (WHO 2018). However, there is evidence on converging drinking patterns between genders (Slade 2016; White 2015).

The misuse of alcohol is one of the leading global health risk factors causing cancer, liver disease, heart disease, neurological disorders, fetal alcohol spectrum disorder, motor vehicle accidents, murder and other intentional injuries (GBD 2019 Cancer Risk Factors Collaborators 2022; GBD 2020 Alcohol Collaborators 2022). Worldwide, in 2016, alcohol use was the seventh leading risk factor for deaths accounting for 2.2% of female and 6.8% of male deaths (GBD 2018). It has been estimated that alcohol use will remain one of the leading risk factors for the burden of disease for the foreseeable future (Manthey 2019). The risk of all-cause mortality is dose related and the level of consumption that minimises health loss is zero (GBD 2018). Men with AUD have a three-fold higher mortality risk compared to men without AUD; in women, the risk is even higher (Roerecke 2013). In 2016, 5.3% of all global deaths and 5.0% of global disability-adjusted life-years were attributable to alcohol (Shield 2020). Studies also suggest that AUD increases the risk of COVID-19 infections and mortality (Fond 2021; Spagnolo 2020). The costs attributable to alcohol consumption are estimated to be on average 2.6% of gross domestic product, the majority of costs due to loss in productivity (Manthey 2021). 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 maintain abstinence in people with AUD (Haber 2021).

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 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 (Witkiewitz 2019). Four agents are approved for the pharmacological treatment of AUD: the opioid antagonists naltrexone and nalmefene; the glutamate antagonist acamprosate; and the aversive agent disulfiram (Mutschler 2016; Reus 2018). 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; Skinner 2014). 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). The best practice in the treatment of AUD should comprise both pharmacotherapy and psychotherapy (Haber 2021; Ray 2020). However, in the US, one recent national study that interviewed more than 42,000 adults estimated that only 1.6% of people with AUD received medications approved for this disorder (Han 2021). In Italy, among a sample of 345 people with severe AUD admitted to public services for outpatient treatment of this disorder, less than 30% received the combination of pharmacotherapy and psychotherapy even if they were still drinking during treatment (Agabio 2021a).

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 ($GABA_B$) receptor (Kent 2020). 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 2013; Agabio 2014; Agabio 2018a; Andrade 2020; Brennan 2013; Burnette 2022; de

Beaurepaire 2019; Morley 2021). 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 increasing by 5 mg every three days (Agabio 2018a; de Beaurepaire 2019). 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 2018a; 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; Colombo 2018). 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. Colombo 2018; 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; Colombo 2018). Thereby baclofen was more potent and effective in those rats seeking and taking larger amounts of alcohol (Colombo 2018; Maccioni 2012; Walker 2007).

A series of case reports found that the administration of baclofen markedly reduced alcohol intake in people with AUD (Agabio 2007; Ameisen 2005; Bucknam 2006; Flannery 2004; Krupitsky 1993; Pastor 2012). 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; de Beaurepaire 2019). He tested oral baclofen, starting with the 'conventional' dose of 30 mg a day and increased the daily dose 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 studies have been published indicating the effectiveness of baclofen in people with AUD, randomised controlled trials (RCTs) conducted to date have yielded conflicting results (for an overview see de Beaurepaire 2019). The diversity of findings has stimulated the discussion on potential moderators of effectiveness (Agabio 2018a; de Beaurepaire 2019; Leggio 2010; Morley 2021). Among others, severity of alcohol dependence (Agabio 2018a; de Beaurepaire 2019), baclofen dosing (Agabio 2018a; de Beaurepaire 2019; Thompson 2017), and comorbid anxiety (Agabio 2018b; Agabio 2021b; de Beaurepaire 2019) 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 (Agabio 2018a; 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 (Agabio 2018a; de Beaurepaire 2019). Sedation, somnolence, weakness, vertigo and psychological disturbances are the most common adverse events (Dario 2004). The administration of low doses of baclofen is considered safe in people affected by AUD, while an abrupt interruption and withdrawal from higher doses of baclofen may lead to serious adverse effects (Agabio 2018a; de Beaurepaire 2019). 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 studies (Brennan 2013). In October 2018, the French Medicines Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)) approved baclofen for the treatment of AUD at the maximum dose of 80 mg a day (Rolland 2020). In France, where this medication was frequently prescribed for the treatment of AUD at high doses, an alarming increase of self-poisonings with baclofen, including suicide attempts and unintentional overdose, has been reported (e.g. Holla 2015; Logge 2022; Pelissier 2017; Reynoard 2020) leading to the authorisation of a maximum daily dose of baclofen 80 mg for the treatment of AUD (Rolland 2020).

How the intervention might work

The mesolimbic dopamine pathway, including dopamine cells in the ventral tegmental area projecting into the nucleus accumbens, is 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 (de Beaurepaire 2018). Agonistic effects of baclofen at $GABA_B$ 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 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 not 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; Colombo 2018). In addition, substitutional effects of baclofen to replace alcohol have been discussed (Chick 2012; Rolland 2013).

In addition, $GABA_B$ receptors are highly expressed in limbic structures involved in the mediation of anxiety (Cryan 2005), while activation of $GABA_B$ receptors in these structures might reduce anxiety (Morley 2014-LD; Morley 2014-MD). Evidence from various clinical studies shows that baclofen may reduce anxiety in people with AUD (Addolorato 2002; Flannery 2004; Krupitsky 1993; Morley 2014-LD; Morley 2014-MD). Post-hoc analyses in one of the studies found that treatment with baclofen was most effective in people with comorbid anxiety (Morley 2014-LD; Morley 2018-MD). This result has been confirmed by one recent meta-analysis (Agabio 2021b). 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 related to the presence of anxiety symptoms (Agabio 2014; Agabio 2021b).

Why it is important to do this review

While several pharmacological treatments have been approved for the treatment of AUD (see Background), their clinical use is limited by a number of factors (Sinclair 2016). The aversive agent disulfiram supports abstinence (Jorgensen 2011), but due to its safety profile it is a therapeutic option for only selected patient groups with a high self-efficacy expectation to abstain from drinking after taking disulfiram (Mutschler 2016). Further substances such as 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 (Witkiewitz 2019). Baclofen as a treatment option for AUD has received much attention in recent years, initiated by pharmacological self-experimentation of Olivier Ameisen (Ameisen 2005), and suggested for people with AUD who do not respond to other medications for AUD (i.e. acamprosate, naltrexone and disulfiram) or have contraindications for the use of other medications (i.e. sever liver disease) (de Beaurepaire 2019). Even though numerous case reports and case series confirmed the effectiveness of baclofen in people with AUD, data from RCTs yielded conflicting results (de Beaurepaire 2019).

The planned review of baclofen to achieve abstinence or to reduce alcohol consumption in people with AUD will provide a systematic integration of the available evidence for health decision makers, 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. In addition, the planned review will evaluate the effects due to the different doses of baclofen considering that, in clinical practice, the daily dose used to help people with AUD to achieve abstinence or reduce alcohol consumption varies between patients over a 10-fold range (Agabio 2018a). In addition, the planned review will also evaluate two other factors that may influence the effects of baclofen in the treatment of AUD such as the duration of the treatment and the consumption of alcohol at the beginning of treatment (Agabio 2018a).

OBJECTIVES

To evaluate the benefits and harms of baclofen on achieving and maintaining abstinence or reducing alcohol consumption in people with AUD compared to placebo, no treatment or any other pharmacological relapse prevention treatment.

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 or reducing consumption in people with AUD. We planned to include studies employing a cross-over design, using data from the first active treatment stage only.

Types of participants

Adults (aged 18 years and older), currently with AUD according to Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III; APA 1980), Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM- III-R; APA 1987), Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (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 included participants who were still drinking and those in the postdetoxification phase, if the detoxification was completed 28 days or less before starting treatment. We also included studies 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 at 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, no treatment or any other pharmacological relapse prevention treatment, including acamprosate, naltrexone or nalmefene. We did not consider disulfiram as a control intervention due to the psychological mediation of its effects.

Types of outcome measures

Primary outcomes

- Relapse: return to any drinking, measured by the number of people who had returned to any drinking at the end of the study.
- Frequency of use: measured as mean number or percentage of abstinent days (ratio of the total sum of days with abstinence, related to the entire duration of the study, multiplied by 100; and mean number or percentage of heavy drinking days (HDD)).
- 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 and objectively assessed.
- Dropouts from treatment: number of participants who did not complete the study protocol.
- Dropouts from treatment due to adverse events.

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

Secondary outcomes

- Craving, as measured by validated scales.
- Anxiety, as measured by validated scales.
- Depression, as measured by validated scales.
- Frequency of most relevant adverse events.

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 22 November 2021.

Electronic searches

We searched the following databases:

- Cochrane Drugs and Alcohol Group (CDAG) Specialised Register (22 November 2021; Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, issue 11) via onlinelibrary.wiley.com (Appendix 2);
- MEDLINE via Ovid (from January 2018 to 22 November 2021; Appendix 3);
- Embase via Ovid (from January 2018 to 30 January 2018; Appendix 4);
- PsycINFO (Ovid; from January 2018 to 22 November 2021; Appendix 5);
- Web of Science (Thomson Reuters; from January 2018 to 22 November 2021; Appendix 6);
- CINAHL (EBSCOhost; from January 2018 to 22 November 2021; 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 22 November 2021:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- 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 studies. We 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

After removing duplicates, two review authors (RA, SM) independently screened the abstracts of all publications obtained by the search strategy. Two review authors (RA, SM) independently assessed the full text of potentially relevant studies for inclusion. We excluded studies that did not meet eligibility criteria and recorded the reasons in the Characteristics of excluded studies table. We used Covidence software for study selection (Covidence). We resolved any disagreement by discussion, involving a third review author (RS) in case of persisting disagreements. We documented the search process in sufficient details to complete a PRISMA study flow diagram.

Data extraction and management

Two review authors (RA, SM) independently extracted data onto a data extraction form. 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 review authors (RA, SM) independently assessed the risk of bias of the included studies using 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. relapse measured by urine or breath analysis, duration of abstinence and dropout), and subjective outcomes (e.g. participant self-reported use of substance, adverse events, craving, psychiatric symptoms).

We considered incomplete outcome data (avoidance of attrition bias), for all outcomes except dropout from the treatment, which is very often the primary outcome measure in studies 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 95% confidence intervals (CI). We analysed continuous outcomes by calculating the mean difference (MD) with 95% CIs 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 doses of baclofen compared to the same control group), we divided the control group into two different groups, each group comprising half the participants of the original group 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. However, we did not include any cross-over studies.

Dealing with missing data

We contacted the original investigators to request information on incomplete or missing data from the studies. We included all randomised participants in the statistical analysis, without any imputation of missing data. If standard deviations (SD) were missing, we used the mean of the available SDs of the other included studies (Furukawa 2006).

Assessment of heterogeneity

We analysed heterogeneity using the I^2 statistic and the Chi^2 test (Higgins 2003). We regarded heterogeneity as substantial if the I^2 statistic was greater than 50% or P less than 0.10 for the Chi^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: 0% to 40% denoted no important, 30% to 60% moderate, 50% to 90% substantial and 75% to 100% considerable heterogeneity. If we found considerable 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 used 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 (Sterne 2017).

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis to investigate the sources of heterogeneity and assess any difference in treatment efficacy and safety in different subgroups. In detail, we planned to perform subgroup analyses for the following variables:

- daily doses of baclofen;
- participants with concomitant substance use disorders;
- comorbid psychiatric conditions;
- consumption of alcohol at the beginning of treatment;
- duration of treatment.

According to the daily doses of baclofen, we divided the studies into three subgroups: low doses (up to 30 mg), medium doses (above 30 and 100 mg or less) and high doses (above 100 mg).

According to the consumption of alcohol at the beginning of the treatment, we divided the studies into two subgroups: detoxified participants (when participants were abstinent for at least three days before treatment) and non-detoxified participants (when participants were still drinking at the beginning of the treatment).

According to the duration of treatment, we divided studies into two subgroups: 12-week studies and longer than 12-week studies.

We were able to perform subgroup analyses for different daily doses of baclofen, detoxified versus non-detoxified participants and duration of treatment.

Subgroup analyses did not explain heterogeneity, which remained very high in the subgroups were there was one outlying study with results that conflicted with the rest of the studies (Leggio 2015). Participants included in this study were both nicotine and alcohol dependent, the study had the aimed to obtain both smoking and drinking abstinence and the study was conducted in a laboratory setting. As these characteristics could explain the heterogeneity due to the different population of participants compared to those recruited by the other studies, we excluded the study from the meta-analyses.

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.

Summary of findings and assessment of the certainty of the evidence

We assessed the overall certainty of the evidence for the following primary outcomes using GRADE: relapse, frequency of use, amount of use, adverse events and dropout from treatment. The GRADE Working Group developed a system for grading the certainty of evidence that considers issues related to internal validity and external validity, such as directness of results. (GRADE 2004; Guyatt 2008; Guyatt 2011; Schünemann 2006).

We presented the main findings of the review in three summary of findings tables: baclofen versus placebo, baclofen versus acamprosate and baclofen versus naltrexone. This is a transparent and simple tabular format that provides key information concerning the certainty 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 GRADEpro GDT software to prepare the summary of findings tables (GRADEpro GDT).

RESULTS

Description of studies

Results of the search

Figure 1 shows the PRISMA flow diagram for screening, selection and assessment of studies.

Figure 1. PRISMA study flow diagram.

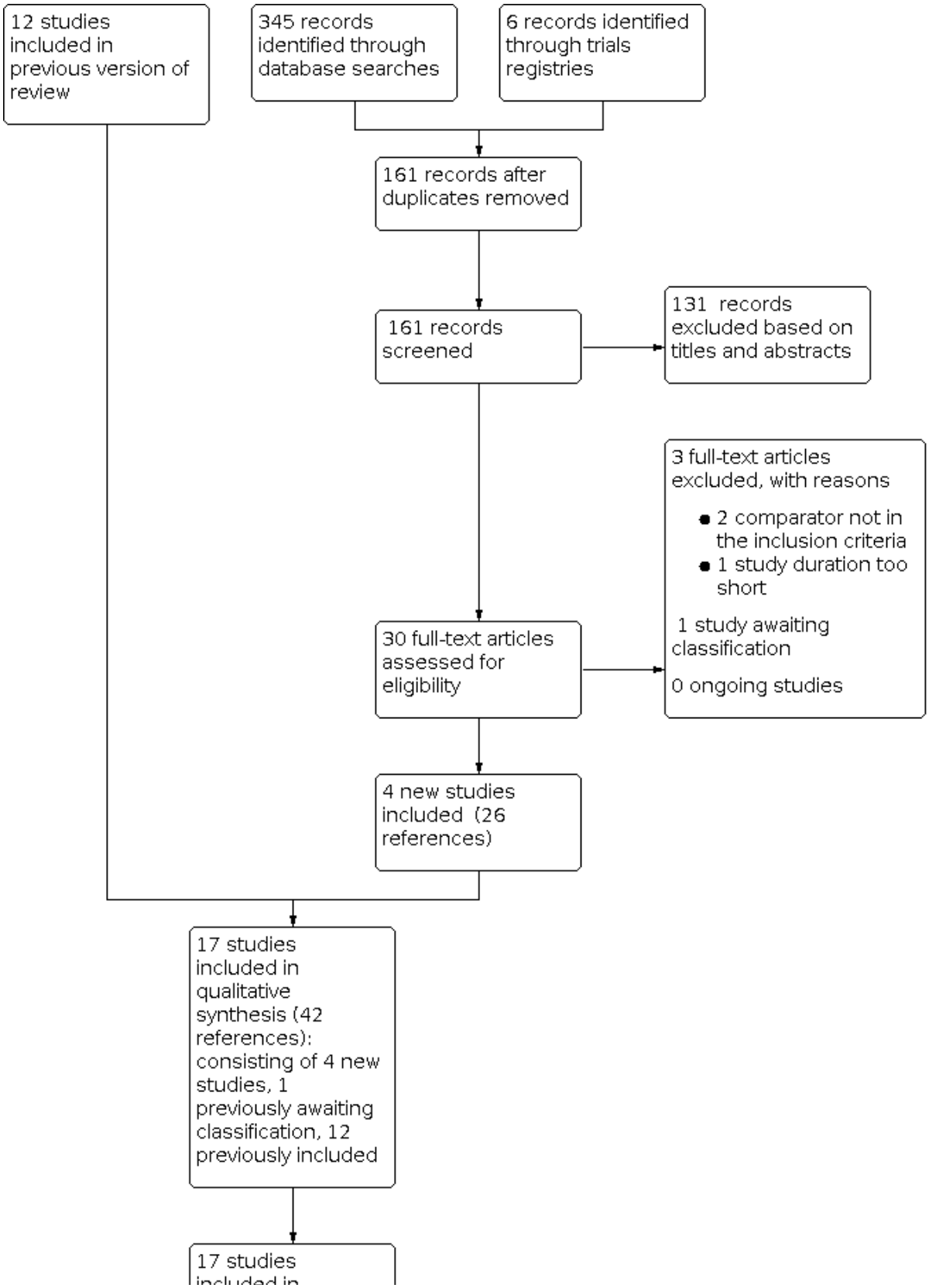
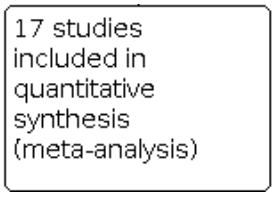


Figure 1. (Continued)



For this update, we identified 161 studies from all possible sources following the removal of duplicates. We excluded 131 studies based on title and abstract and assessed 30 full-text articles. We identified four studies meeting our inclusion criteria reported in 22 references. One study compared a single dose of baclofen to placebo (Rigal 2020), two studies compared two doses of baclofen to placebo (each included as two discrete data sets; Garbutt 2021-LD; Garbutt 2021-MD; Morley 2018-LD; Morley 2018-MD), and one study compared a single dose of baclofen to acamprosate and naltrexone (Kumar 2020a). In addition, the authors of a study previously awaiting classification that compared two doses of baclofen to placebo provided data allowing us to include the study (included as two discrete data sets; Addolorato 2011-LD; Addolorato 2011-MD). We excluded three studies (see Characteristics of excluded studies table) and one is awaiting classification (see Characteristics of studies awaiting classification table). Overall, we included five new RCTs.

We previously identified 12 studies, eight that compared a single dose of baclofen to placebo (Addolorato 2007; Garbutt 2010a; Hauser 2017; Krupitskii 2017; Leggio 2015; Muller 2015; Ponizovsky 2015; Reynaud 2017), two that compared two doses of baclofen to placebo (each included as two discrete data sets; Beraha 2016-HD; Beraha 2016-LD; Morley 2014-LD; Morley 2014-MD), one study that compared a single dose of baclofen to acamprosate (Mishra 2010), and one study that compared baclofen to placebo and naltrexone (included as two discrete data sets; Garbutt 2010b1; Garbutt 2010b2) in our original review (see Characteristics of included studies table).

Included studies

We included 17 RCTs involving 1818 participants (see Characteristics of included studies table). The mean study size was 107 participants, ranging from 30 in Leggio 2015 to 320 in Reynaud 2017. Six studies recruited more than 100 participants (Beraha 2016-LD; Beraha 2016-LD; Garbutt 2021-LD; Garbutt 2021-MD; Hauser 2017; Morley 2018-LD; Morley 2018-MD; Reynaud 2017; Rigal 2020). The mean age of participants was 46.5 years, and 69.6% were men. All studies except one recruited participants with a diagnosis of alcohol dependence according to the DSM-IV or ICD-10 criteria. Rigal 2020 did not require the diagnosis of alcohol dependence and recruited high-risk drinkers according to the WHO definition of at-risk drinking (alcohol consumption greater than 40 g/day or single occasion, greater than 280 g/week, or both for women; greater than 60 g/day or single occasion, greater than 420 g/week, or both for men; WHO 2000). To be included, these participants also had to voluntarily consult a physician for their alcohol problem and express the desire to achieve abstinence or reduce alcohol consumption. Accordingly, we assumed that these participants met at least three criteria for AUD (alcohol consumption in higher amounts than intended; desire to cut down or control alcohol use; craving; APA 2013), and we included the study.

Five studies took place in the USA (Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Garbutt 2021-LD; Garbutt 2021-MD; Hauser 2017; Leggio 2015); two studies in Australia (Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD), France (Reynaud 2017; Rigal 2020), Italy (Addolorato 2007; Addolorato 2011-LD; Addolorato 2011-MD), and India (Kumar 2020a; Mishra 2010); and one in Germany (Muller 2015), Israel (Ponizovsky 2015), Russia (Krupitskii 2017), and the Netherlands (Beraha 2016-HD; Beraha 2016-LD).

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

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

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

Interventions

The studies administered baclofen in daily doses ranging from 30 mg to 300 mg. Ten studies administered low daily doses (Addolorato 2007; Addolorato 2011-LD; Beraha 2016-LD; Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Garbutt 2021-LD; Hauser 2017; Mishra 2010; Morley 2014-LD; Morley 2018-LD), eight studies

medium daily doses (Addolorato 2011-MD; Garbutt 2021-MD; Krupitskii 2017; Kumar 2020a; Leggio 2015; Morley 2014-MD; Morley 2018-MD; Ponizovsky 2015), and four studies high daily doses of baclofen (Beraha 2016-HD; Muller 2015; Reynaud 2017; Rigal 2020).

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

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

Comparisons

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

Ten RCTs compared one dose of baclofen to placebo (Addolorato 2007; Garbutt 2010a; Hauser 2017; Krupitskii 2017; Leggio 2015; Mishra 2010; Muller 2015; Ponizovsky 2015; Reynaud 2017; Rigal 2020); five RCTs compared two doses of baclofen to placebo (Addolorato 2011-LD; Addolorato 2011-MD; Beraha 2016-HD; Beraha 2016-LD; Garbutt 2021-LD; Garbutt 2021-MD; Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD); one RCT compared baclofen to placebo and another medication (Garbutt 2010b1; Garbutt 2010b2); and one RCT compared baclofen to two other medications (Kumar 2020a). We found no studies comparing baclofen to no treatment.

Excluded studies

We excluded three studies: Gupta 2017 because the inactive medication used in the control group (benfothiamine) has an effect on both alcohol consumption and anxiety (Manzardo 2013; Manzardo 2015); Jose 2019 because its duration was less than 12 weeks and Kumar 2020b because both groups received baclofen. The previous version of this review excluded four studies (Addolorato 2002; Flannery 2004; Leggio 2011; Leggio 2013). In total, we excluded seven studies. For more details, see Characteristics of excluded studies table.

Studies awaiting classification

One new study is awaiting classification as it was a conference abstract providing insufficient information regarding the design and length of the study (Karthik 2018). We moved some references awaiting classification in the previous version of this review to the included studies as primary or secondary references (Addolorato 2011-LD; Addolorato 2011-MD; Farokhnia 2014; Jaury 2014; Morley 2013). In this review update, two studies are awaiting classification (Karthik 2018; Sharma 2012; see Characteristics of studies awaiting classification table).

Ongoing studies

We identified no new ongoing studies. Among the two studies considered ongoing in the previous version of this review, one (NCT01980706) was moved to the included studies section (Garbutt 2021-LD; Garbutt 2021-MD), and one remains in the ongoing studies section (CTRI/2011/11/002154). See Characteristics of ongoing studies table.

Risk of bias in included studies

See Figure 2 and Figure 3. For a detailed description of the reasons supporting our judgements, see the risk of bias table in the Characteristics of included studies table.

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

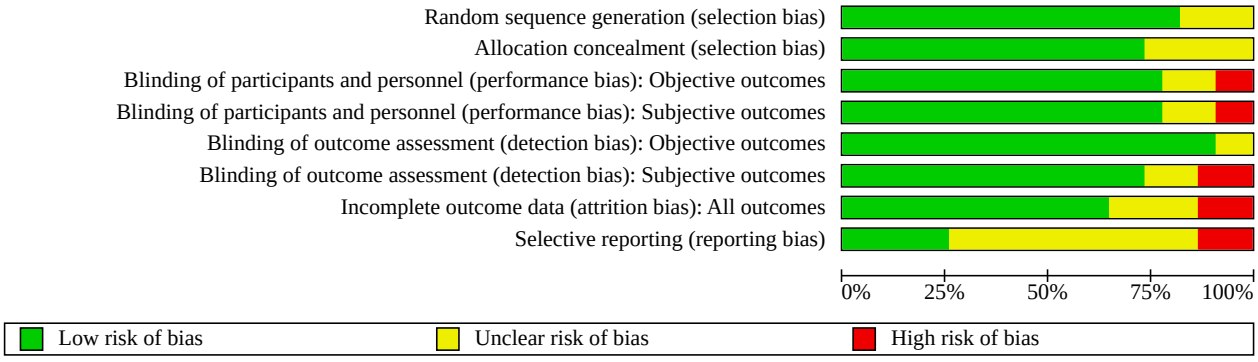


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

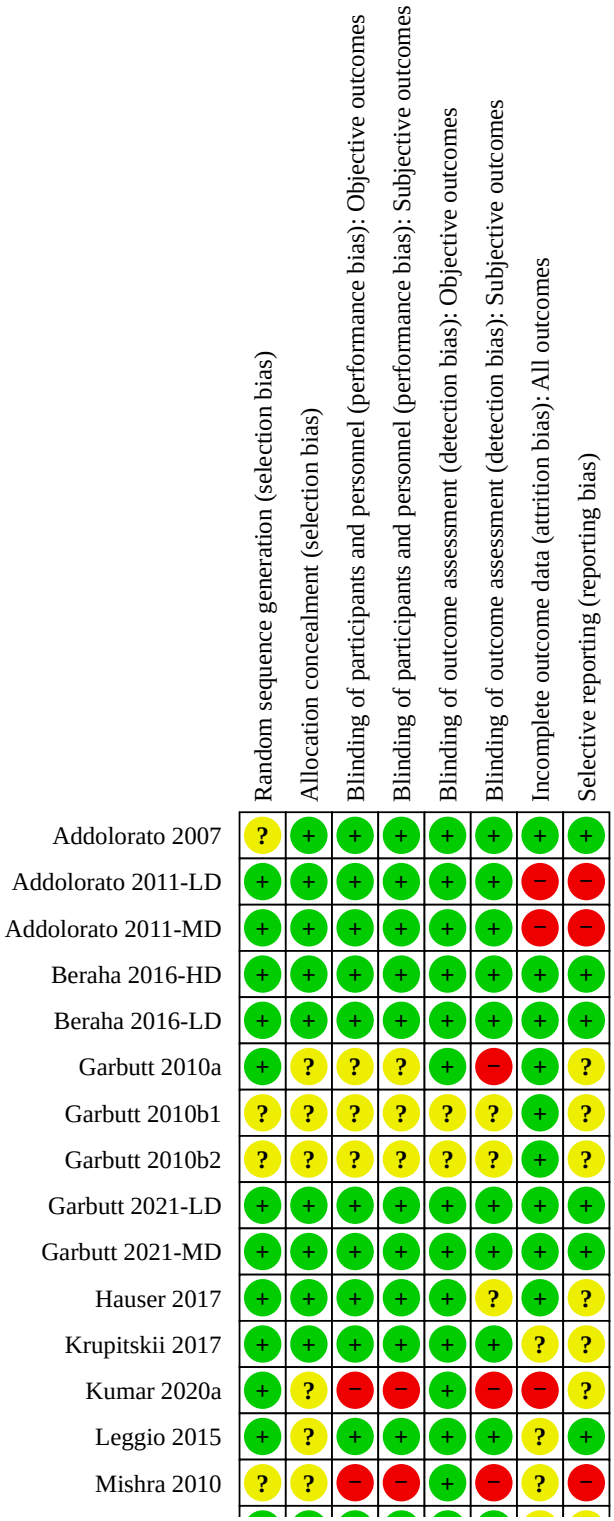
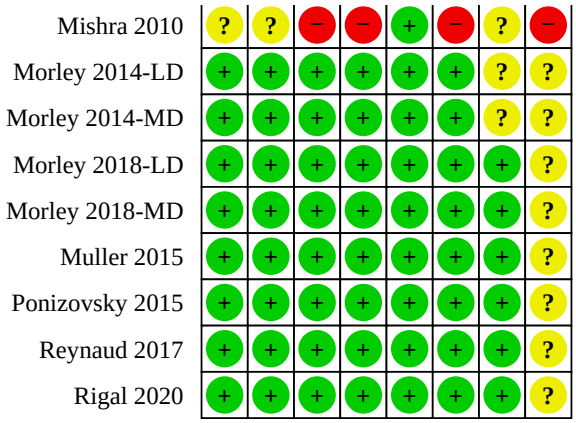


Figure 3. (Continued)



Allocation

Random sequence generation

We judged 14 studies 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 at unclear risk of bias (Addolorato 2007; Garbutt 2010b1; Garbutt 2010b2).

Allocation concealment

We judged 12 studies at low risk of bias. The other five studies did not report methods of allocation concealment, so we judged them at unclear risk of bias (Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Kumar 2020a; Leggio 2015; Mishra 2010).

Blinding

Performance bias

We judged 13 studies at low risk of bias for objective outcomes and two at high risk (Kumar 2020a; Mishra 2010). Two studies did not provide information about blinding, so we judged them at unclear risk of bias (Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2).

We judged 13 studies at low risk of bias for subjective outcomes and two at high risk (Kumar 2020a; Mishra 2010). Two studies did not report methods for blinding, so we judged them at unclear risk of bias (Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2).

Detection bias

For objective outcomes, we considered 16 studies at low risk of bias and one study at unclear risk (Garbutt 2010b1; Garbutt 2010b2).

For subjective outcomes, we considered 12 studies at low risk of bias and three studies at high risk of bias (Garbutt 2010a; Kumar 2020a; Mishra 2010). Two studies did not report sufficient information, so we judged them at unclear risk of bias (Garbutt 2010b1; Garbutt 2010b2; Hauser 2017).

Incomplete outcome data

We judged 11 studies at low risk of bias and two studies at high risk of bias (Addolorato 2011-LD; Addolorato 2011-MD; Kumar 2020a). Four studies did not report numbers and reasons of dropouts or missing data for each group, so we judged them at unclear risk of bias (Krupitskii 2017; Leggio 2015; Mishra 2010; Morley 2014-LD; Morley 2014-MD).

Selective reporting

We judged four studies at low risk of bias and two studies at high risk of bias (Addolorato 2011-LD; Addolorato 2011-MD; Mishra 2010). Eleven studies did not provide enough information, so we judged them at unclear risk of bias (Garbutt 2010a; Garbutt 2010b1; Garbutt 2010b2; Hauser 2017; Krupitskii 2017; Kumar 2020a; Morley 2014-LD; Morley 2014-MD; Morley 2018-LD; Morley 2018-MD; Muller 2015; Ponizovsky 2015; Reynaud 2017; Rigal 2020).

Other potential sources of bias

We identified no other sources of bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Baclofen compared to placebo for alcohol use disorder; **Summary of findings 2** Summary of findings table - Baclofen compared to acamprosate for alcohol use disorder; **Summary of findings 3** Summary of findings table - Baclofen compared to naltrexone for alcohol use disorder

For the comparison baclofen versus placebo, we first conducted the analyses including from all studies and found considerable heterogeneity in the rates of abstinent days (17 studies, 1303 participants; I^2 = 94%) and HDDs at the end of treatment (14 studies, 870 participants; I^2 = 98%). Conducting the subgroup analyses, we still found considerable heterogeneity in all subgroups where one outlying study was included (Leggio 2015). Accordingly, we excluded this study from all analyses and, for each primary outcome, provided its results separately.

We found sufficient data for conducting subgroup analyses according to the daily doses of baclofen, consumption of alcohol at the beginning of treatment and duration of treatment. We conducted subgroup analyses for the primary outcomes (relapse, frequency of use (rate of abstinent days), amount of use (rate of HDDs, drink per drinking days), adverse events (number of participants with at least one adverse event), dropouts from treatment, and dropouts from treatment due to adverse events).

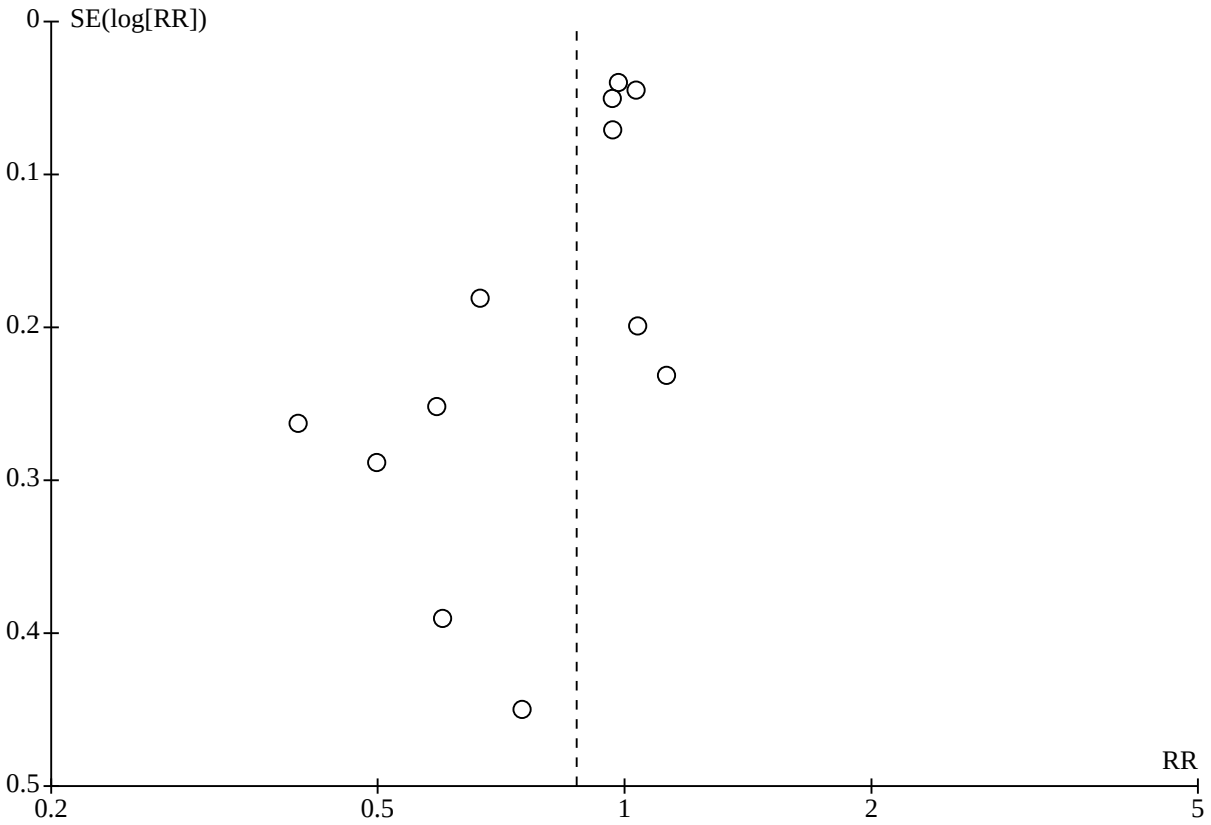
We did not conduct subgroup analyses according to the presence or not of comorbid substance use disorders or other mental disorders (or both) because all studies excluded people with substance use disorders of substances other than alcohol or nicotine and people with other comorbid severe mental disorders.

Comparison 1: baclofen versus placebo

1.1 Relapse: return to any drinking at end of treatment

Twelve studies involving 1057 participants reported relapse. Baclofen reduced the risk of relapse compared to placebo (RR 0.87, 95% CI 0.77 to 0.99; moderate-certainty evidence; Analysis 1.1; Figure 4; Summary of findings 1). There was substantial heterogeneity (Chi^2 = 40.60, degrees of freedom (df) = 11 (P < 0.001); I^2 = 73%). The study excluded from this meta-analysis found no difference in relapse between baclofen and placebo (RR −0.53, 95% CI −3.11 to 2.05; 30 participants; Leggio 2015).

Figure 4.



1.1.1 Subgroup analyses: daily doses of baclofen

We found no differences between baclofen and placebo among studies using low, medium or high doses (low: RR 0.82, 95% CI 0.64 to 1.04; considerable heterogeneity (Chi^2 = 32.98, df = 5 (P < 0.001); I^2 = 85%); 6 studies, 463 participants; medium: RR 0.73, 95% CI 0.37 to 1.45; considerable heterogeneity (Chi^2 = 11.20, df = 2 (P = 0.004); I^2 = 82%); 3 studies, 129 participants; high: RR 0.90, 95% CI 0.71 to 1.15; moderate heterogeneity (Chi^2 = 4.78, df = 2 (P = 0.09); I^2 = 58%); 3 studies, 465 participants; Analysis 2.1).

1.1.2 Subgroup analyses: duration of treatment

We found no differences between baclofen and placebo among 12-week studies and longer than 12-week studies (12 weeks: RR 0.63, 95% CI 0.40 to 1.00; considerable heterogeneity (Chi^2 = 54.47, df = 6 (P < 0.001); I^2 = 89%); 7 studies, 466 participants; longer than 12 weeks: RR 0.98, 95% CI 0.93 to 1.03; I^2 = 0%; 5 studies, 591 participants; Analysis 3.1).

1.1.3 Subgroup analyses: consumption of alcohol at beginning of treatment

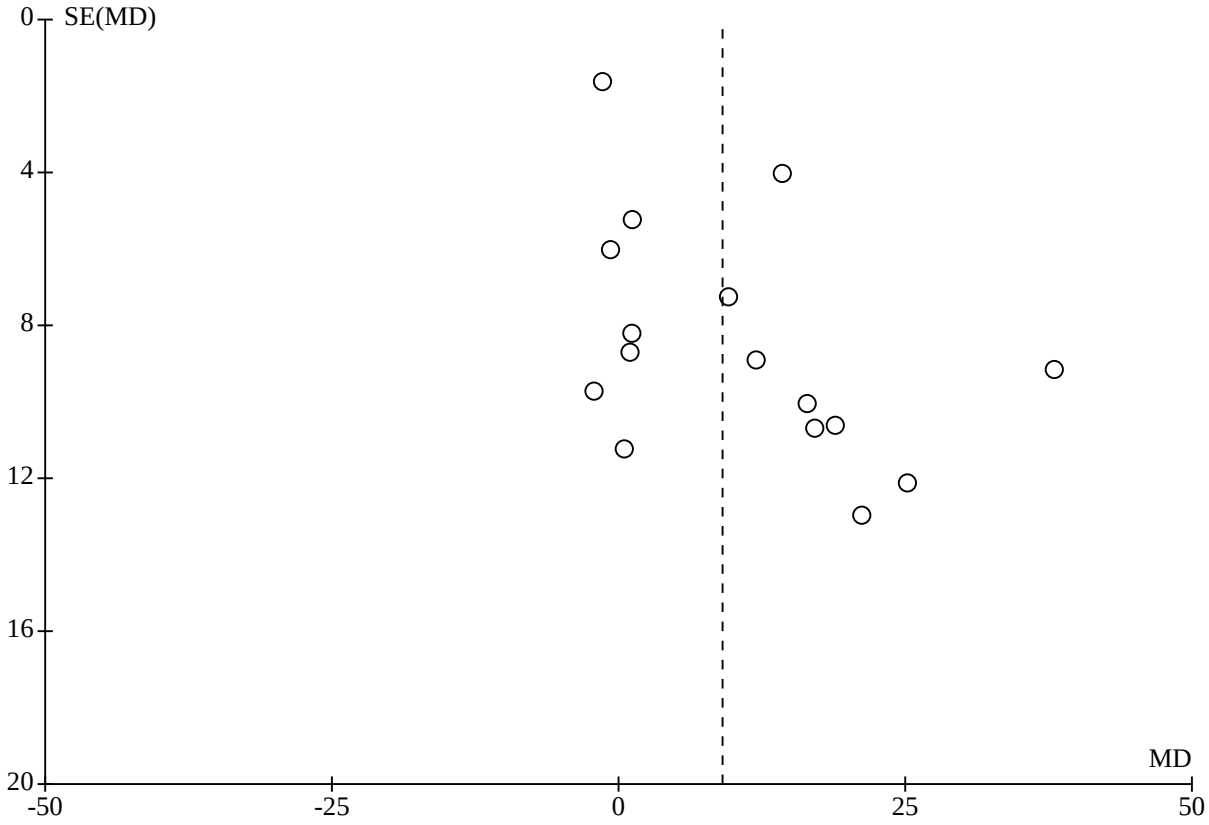
Baclofen reduced the risk of relapse compared to placebo among studies with detoxified participants (RR 0.73, 95% CI 0.55 to 0.95; considerable heterogeneity (Chi^2 = 33.42, df = 8 (P < 0.001); I^2 = 76%); 9 studies, 757 participants; Analysis 4.1). There were no differences between baclofen and placebo among studies with non-detoxified participants (RR 1.00, 95% CI 0.94 to 1.06; I^2 = 0%; 3 studies, 300 participants; Analysis 4.1).

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

We identified 16 studies involving 1273 participants reporting percentage of days abstinent at the end of treatment. Baclofen

increased the rate of abstinent days compared to placebo (MD 9.07%, 95% CI 3.30 to 14.85; high-certainty evidence; Analysis 1.2; Figure 5; Summary of findings 1). There was substantial heterogeneity (Chi^2 = 43.69, df = 15 (P = 0.001); I^2 = 66%). The study excluded from this meta-analysis found that placebo increased the rate of abstinent days compared to baclofen (MD −19.00 days, 95% CI −21.18 to −16.82; 30 participants; Leggio 2015).

Figure 5.



1.2.1 Subgroup analyses: daily doses of baclofen

Baclofen increased the rate of abstinent days compared to placebo among studies using low and high doses (low: MD 10.59%, 95% CI 0.77 to 20.41; substantial heterogeneity (Chi^2 = 19.68, df = 7 (P = 0.006); I^2 = 64%); 8 studies, 583 participants; high: MD 11.09%, 95% CI 4.39 to 17.80; I^2 = 6%; 3 studies, 465 participants; Analysis 2.2). We found no differences between baclofen and placebo among studies using medium doses (MD 7.14%, 95% CI −3.10 to 17.38; moderate heterogeneity (Chi^2 = 8.39, df = 4 (P = 0.08); I^2 = 52%); 5 studies, 225 participants; Analysis 2.2).

1.2.2 Subgroup analyses: duration of treatment

Baclofen increased the rate of abstinent days compared to placebo among 12-week studies and longer than 12-week studies (12 weeks: MD 10.90, 95% CI 3.17 to 18.62; substantial heterogeneity (Chi^2 = 33.61, df = 10 (P = 0.001); I^2 = 70%); 11 studies, 682 participants; longer than 12 weeks: MD 8.05, 95% CI 1.09 to 15.01; I^2 = 18%; 5 studies, 591 participants; Analysis 3.2).

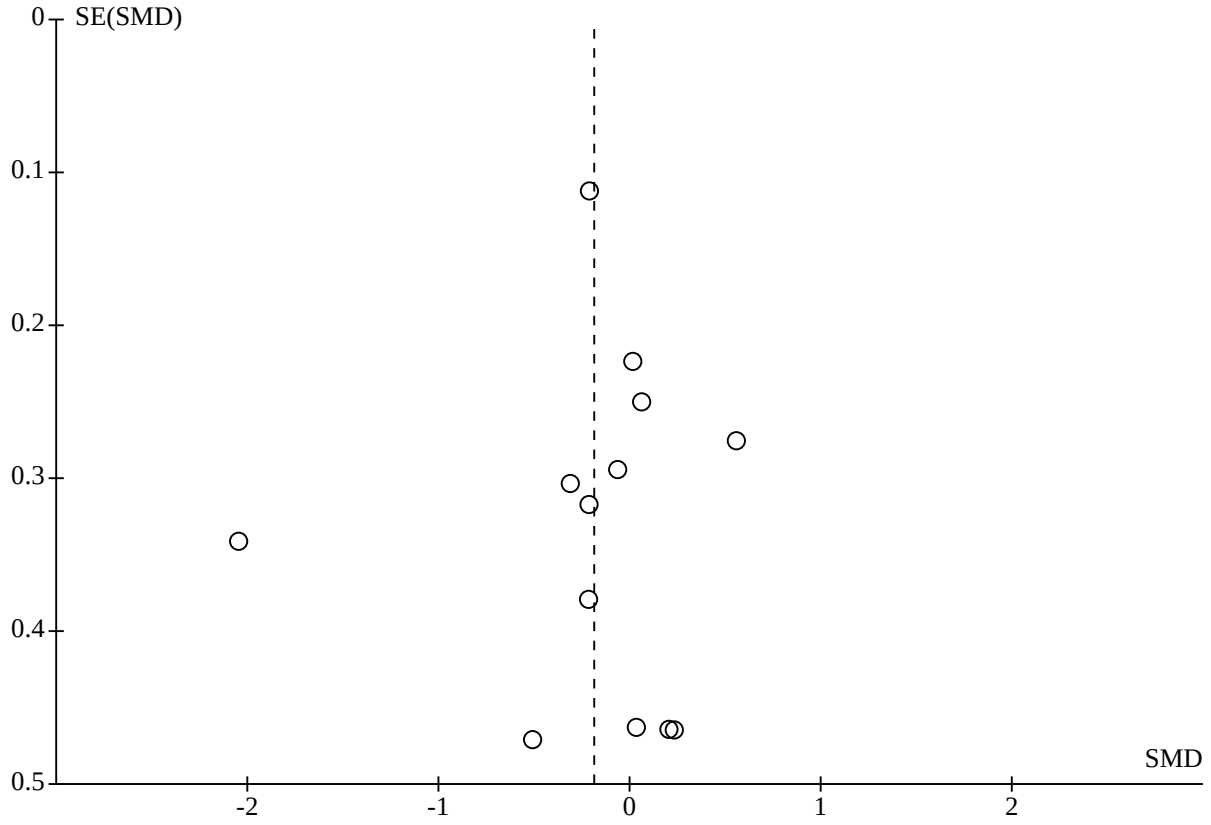
1.2.3 Subgroup analyses: consumption of alcohol at beginning of treatment

Baclofen increased the rate of abstinent days compared to placebo among studies with detoxified participants (MD 11.76, 95% CI 3.22 to 20.29; moderate heterogeneity (Chi^2 = 19.42, df = 9 (P = 0.02); I^2 = 54%); 10 studies, 549 participants; Analysis 4.2). There was no difference between baclofen and placebo among studies with non-detoxified participants (MD 6.03, 95% CI −1.59 to 13.64; substantial heterogeneity (Chi^2 = 16.88, df = 5 (P = 0.005); I^2 = 70%); 6 studies, 724 participants; Analysis 4.2).

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

We identified 13 studies involving 840 participants reporting HDDs at the end of treatment. There was no difference between baclofen and placebo (SMD −0.18, 95% CI −0.48 to 0.11; moderate-certainty evidence; Analysis 1.3; Figure 6; Summary of findings 1). There was substantial heterogeneity (Chi^2 = 41.40.55, df = 12 (P < 0.001); I^2 = 71%). The study excluded from this meta-analysis found no difference between baclofen and placebo (MD −2.00, 95% CI −13.22 to 9.22; 30 participants; Leggio 2015).

Figure 6.



1.3.1 Subgroup analyses: daily doses of baclofen

We found no difference between baclofen and placebo among the studies low, medium and high doses (low: SMD 0.10, 95% CI −0.15 to 0.34; I^2 = 0%; 6 studies, 278 participants; medium: SMD −0.47, 95% CI −1.15 to 0.20; considerable heterogeneity (Chi^2 = 28.68, df = 5 (P < 0.001); I^2 = 83%); 6 studies, 242 participants; high: SMD −0.21, 95% CI −0.43 to 0.01; 1 study, 320 participants; Analysis 2.3).

1.3.2 Subgroup analyses: duration of treatment

We found no difference between baclofen and placebo among 12-week and longer than 12-week studies (12 weeks: SMD −0.07, 95% CI −0.27 to 0.13; I^2 = 0%; 10 studies, 400 participants; longer than 12 weeks: SMD −0.54, 95% CI −1.68 to 0.60; considerable heterogeneity (Chi^2 = 36.40, df = 2 (P < 0.001); I^2 = 95%); 3 studies, 440 participants; Analysis 3.3).

1.3.3 Subgroup analyses: consumption of alcohol at beginning of treatment

We found no difference between baclofen and placebo among the studies with detoxified and non-detoxified participants (toxified: SMD −0.08, 95% CI −0.32 to 0.16; I^2 = 0%; 8 studies, 296 participants; non-detoxified: SMD −0.34, 95% CI −0.98 to 0.30; considerable heterogeneity (Chi^2 = 37.90, df = 4 (P < 0.001); I^2 = 89%); 5 studies, 544 participants; Analysis 4.3).

1.4 Amount of use: drinks per drinking days at end of treatment

We identified nine studies involving 392 participants reporting drinks per drinking days at the end of treatment. There were no differences between baclofen and placebo (MD −0.45, 95% CI −1.20 to 0.30; moderate-certainty evidence; Analysis 1.4; Summary of findings 1). There was no important heterogeneity (Chi^2 = 11.65, df = 8 (P = 0.17); I^2 = 31%). The study excluded from this meta-analysis found no difference between baclofen and placebo (MD −0.53, 95% CI −3.11 to 2.05; 30 participants; Leggio 2015).

1.4.1 Subgroup analyses: daily doses of baclofen

We found no differences between baclofen and placebo among studies using low and medium doses (low: MD −0.06, 95% CI −1.33 to 1.22; moderate heterogeneity (Chi^2 = 7.39, df = 4 (P = 0.12); I^2 = 46%); 5 studies, 242 participants; medium: MD −0.64, 95% CI −1.95 to 0.68; I^2 = 27%; 4 studies, 150 participants; Analysis 2.4). No study using high doses provided data on this outcome.

1.4.2 Subgroup analyses: duration of treatment

We found no difference between baclofen and placebo among 12-week and longer than 12-week studies (12 weeks: MD −0.36, 95% CI −1.29 to 0.57; moderate heterogeneity (Chi^2 = 11.07, df = 6 (P = 0.09); I^2 = 46%); 7 studies, 272 participants; longer than 12 weeks: MD −0.49, 95% CI −2.31 to 1.32; I^2 = 0%; 2 studies, 120 participants; Analysis 3.4).

1.4.3 Subgroup analyses: consumption of alcohol at beginning of treatment

We found no differences between baclofen and placebo among studies with detoxified and non-detoxified participants (detoxified: MD −0.36, 95% CI −1.29 to 0.57; moderate heterogeneity (Chi^2 =

11.07, df = 6 (P = 0.09); I^2 = 46%); 7 studies, 272 participants; non-detoxified: MD −0.49, 95% CI −2.31 to 1.32; I^2 = 0%; 2 studies, 120 participants; Analysis 4.4).

1.5 Adverse events: number of participants with at least one adverse event at end of treatment

We identified 10 studies involving 738 participants reporting the number of participants with at least one adverse event at the end of treatment. There was no difference between baclofen and placebo (RR 1.05, 95% CI 0.99 to 1.11; high-certainty evidence; Analysis 1.5; Summary of findings 1). There was no important heterogeneity (Chi^2 = 7.06, df = 9 (P = 0.63); I^2 = 0%). The study excluded from this meta-analysis found no difference between baclofen and placebo (RR 1.15, 95% CI 0.91 to 1.44; 30 participants; Leggio 2015).

1.5.1 Subgroup analyses: daily doses of baclofen

We identified no differences between baclofen and placebo among studies using low, medium and high doses (low: RR 1.23, 95% CI 0.92 to 1.64; I^2 = 0%; 5 studies, 260 participants; medium: RR 0.90, 95% CI 0.63 to 1.28; I^2 = 0%; 4 studies, 162 participants; high: RR 1.05, 95% CI 0.99 to 1.11; 1 study, 316 participants; Analysis 2.5).

1.5.2 Subgroup analyses: duration of treatment

We found no differences between baclofen and placebo among 12-week and longer than 12-week studies (12 weeks: RR 0.99, 95% CI 0.70 to 1.39; I^2 = 0%; 7 studies, 302 participants; longer than 12 weeks: RR 1.05, 95% CI 1.00 to 1.11; I^2 = 0%; 3 studies, 436 participants; Analysis 3.5).

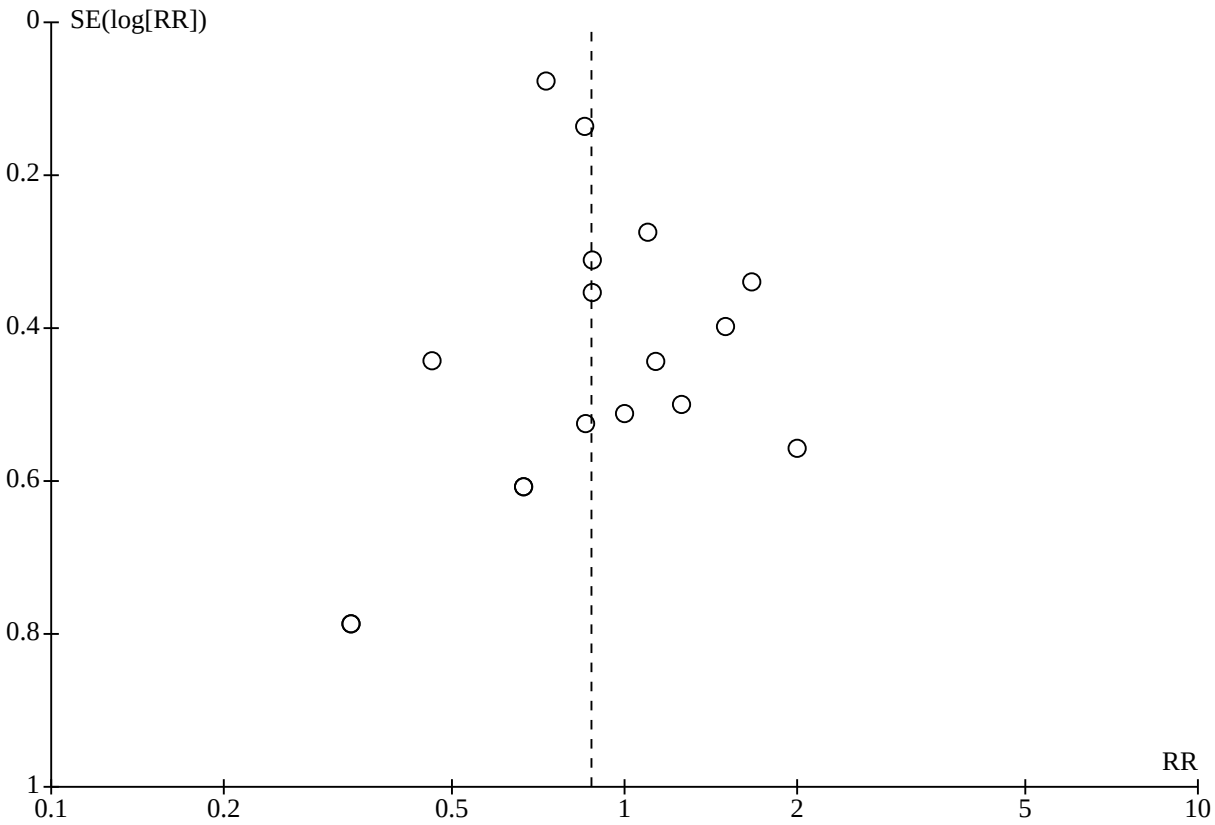
1.5.3 Subgroup analyses: consumption of alcohol at beginning of treatment

We found no differences between baclofen and placebo among studies with detoxified and non-detoxified participants (detoxified: RR 1.05, 95% CI 0.99 to 1.11; I^2 = 0%; 7 studies, 578 participants; non-detoxified: RR 1.11, 95% CI 0.84 to 1.45; I^2 = 0%; 3 studies, 160 participants; Analysis 4.5).

1.6 Dropouts at end of treatment

We identified 17 studies involving 1563 participants reporting dropouts at the end of treatment. There was no difference between baclofen and placebo (RR 0.88, 95% CI 0.74 to 1.03; high-certainty evidence; Analysis 1.6; Figure 7; Summary of findings 1). There was no important heterogeneity (Chi^2 = 19.55, df = 16 (P = 0.24); I^2 = 18%). The study excluded from this meta-analysis found no difference between baclofen and placebo (RR 0.50, 95% CI 0.11 to 2.33; 30 participants; Leggio 2015).

Figure 7.



1.6.1 Subgroup analyses: daily doses of baclofen

We found no differences between baclofen and placebo among studies using low and medium doses (low: RR 0.96, 95% CI 0.70 to 1.32; I^2 = 16%; 8 studies, 564 participants; medium: RR 1.03, 95% CI 0.65 to 1.61; I^2 = 19%; 5 studies, 214 participants). Baclofen decreased the number of dropouts at the end of treatment

compared with placebo among the studies using high doses (RR 0.76, 95% CI 0.67 to 0.87; I^2 = 0%; 4 studies, 785 participants; Analysis 2.6).

1.6.2 Subgroup analyses: duration of treatment

We found no differences between baclofen and placebo among 12-week studies (RR 0.98, 95% CI 0.73 to 1.31; I^2 = 13%; 11 studies, 652 participants; Analysis 3.6). Baclofen decreased the number of dropouts at the end of treatment compared with placebo in longer than 12-week studies (RR 0.78, 95% CI 0.69 to 0.88; I^2 = 0%; 6 studies, 911 participants; Analysis 3.6).

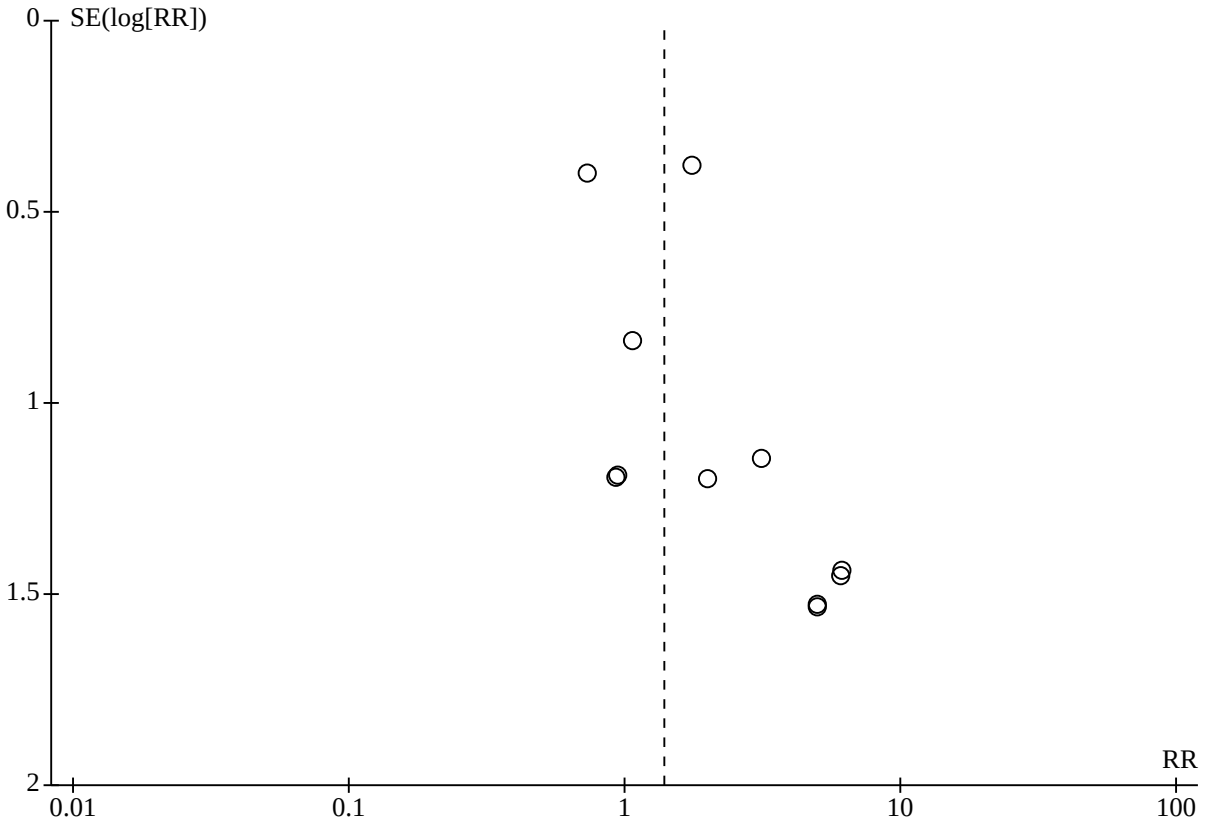
1.6.3 Subgroup analyses: consumption of alcohol at beginning of treatment

There were no differences between baclofen and placebo among studies with detoxified and non-detoxified participants (detoxified: RR 0.87, 95% CI 0.71 to 1.07; I^2 = 0%; 12 studies, 879 participants; non-detoxified: RR 0.93, 95% CI 0.69 to 1.28; moderate heterogeneity (Chi^2 = 8.28, df = 4 (P = 0.08); I^2 = 52%); 5 studies, 684 participants; Analysis 4.6).

1.7 Dropouts from treatment due to adverse events

We identified 16 studies involving 1499 participants reporting dropouts from treatment due to adverse events. There was no difference between baclofen and placebo (RR 1.39, 95% CI 0.89 to 2.18; high-certainty evidence; Analysis 1.7 and Figure 8; Summary of findings 1). There was no important heterogeneity (Chi^2 = 7.55, df = 10 (P = 0.67); I^2 = 0%). The study excluded from this meta-analysis found zero events in both groups (RR not estimable; Leggio 2015).

Figure 8.



1.7.1 Subgroup analyses: daily doses of baclofen

We found no differences between baclofen and placebo among studies using low, medium and high doses (low: RR 1.81, 95% CI 0.61 to 5.32; I^2 = 0%; 8 studies, 564 participants; medium: RR 6.11, 95% CI 0.82 to 42.25; I^2 = 0%; 4 studies, 150 participants; high: RR 1.21, 95% CI 0.68 to 2.13; I^2 = 13%; 4 studies, 785 participants; Analysis 2.7).

1.7.2 Subgroup analyses: duration of treatment

We found no differences between baclofen and placebo among 12-week and longer than 12-week studies (12 weeks: RR 3.00, 95% CI 0.93 to 9.66; I^2 = 0%; 10 studies, 588 participants; longer than 12-weeks: RR 1.22, 95% CI 0.76 to 1.98; I^2 = 0%; 6 studies, 911 participants; Analysis 3.7).

1.7.3 Subgroup analyses: consumption of alcohol at beginning of treatment

We found no differences between baclofen and placebo among studies with detoxified and non-detoxified participants (toxified: RR 1.08, 95% CI 0.59 to 1.98; I^2 = 0%; 12 studies, 879 participants; non-detoxified: RR 1.87, 95% CI 0.97 to 3.61; I^2 = 0%; 4 studies, 620 participants; Analysis 4.7).

1.8 Craving

We identified 17 studies with 1275 people reporting cravings. There was no difference between baclofen and placebo (SMD −0.16, 95% CI −0.37 to 0.04). Heterogeneity was substantial (Chi^2 = 39.36, df = 15 (P < 0.001); I^2 = 62%; Analysis 1.8).

1.9 Anxiety

We identified 15 studies with 1123 participants reporting anxiety. There was no difference between baclofen and placebo (SMD −0.01, 95% CI −0.14 to 0.11; Analysis 1.9).

1.10 Depression

We identified 11 studies with 1029 participants reporting depression. There was no difference between baclofen and placebo (SMD 0.07, 95% CI −0.12 to 0.27; Analysis 1.10).

1.11 Adverse events: fatigue, tiredness

We identified 13 studies involving 1311 participants. Baclofen increased the frequency of fatigue or tiredness (or both) compared with placebo (RR 1.31, 95% CI 1.09 to 1.59; Analysis 1.11).

1.12 Adverse events: insomnia

We identified 11 studies with 1100 participants reporting insomnia. There was no difference between baclofen and placebo (RR 0.92, 95% CI 0.62 to 1.35; Analysis 1.12).

1.13 Adverse events: pain (diverse)

We identified three studies with 98 participants reporting pain. There was no difference between baclofen and placebo (RR 0.51, 95% CI 0.19 to 1.33; Analysis 1.13).

1.14 Adverse events: vertigo, dizziness

We identified 15 studies with 1415 participants. Baclofen increased the frequency of vertigo compared with placebo (RR 1.70, 95% CI 1.35 to 2.13; Analysis 1.14).

1.15 Adverse events: constipation

We identified 11 studies with 1124 participants reporting constipation. There was no difference between baclofen and placebo (RR 0.95, 95% CI 0.61 to 1.47; Analysis 1.15).

1.16 Adverse events: somnolence, sleepiness, drowsiness or sedation

We identified 17 studies with 1543 participants. Baclofen increased the frequency of somnolence compared with placebo (RR 1.36, 95% CI 1.19 to 1.56; Analysis 1.16).

1.17 Adverse events: muscle pain

We identified five studies with 594 participants reporting muscle pain. There was no difference between baclofen and placebo (RR 0.93, 95% CI 0.38 to 2.25; Analysis 1.17).

1.18 Adverse events: dry mouth

We identified eight studies with 933 participants. Baclofen increased the frequency of dry mouth compared with placebo (RR 1.79, 95% CI 1.01 to 3.18; Analysis 1.18).

1.19 Adverse events: nausea

We identified 10 studies with 1060 participants reporting nausea. There was no difference between baclofen and placebo (RR 1.17, 95% CI 0.88 to 1.54; Analysis 1.19).

1.20 Adverse events: skin rash

We identified seven studies with 446 participants reporting skin rash. There was no difference between baclofen and placebo (RR 0.80, 95% CI 0.33 to 1.93; Analysis 1.20).

1.21 Adverse events: headaches

We identified 13 studies with 1304 participants. Baclofen increased the frequency of headaches compared with placebo (RR 1.31, 95% CI 1.04 to 1.64; Analysis 1.21).

1.22 Adverse events: paraesthesia/numbness

We identified six studies with 914 participants. Baclofen increased the frequency of paraesthesia (RR 2.87, 95% CI 1.17 to 7.06; Analysis 1.22).

1.23 Adverse events: diarrhoea

We identified three studies with 816 participants. There was no difference between baclofen and placebo (RR 0.64, 95% CI 0.40 to 1.02; Analysis 1.23).

1.24 Adverse events: tinnitus

We identified two studies with 496 participants reporting tinnitus. There was no difference between baclofen and placebo (RR 1.77, 95% CI 0.16 to 20.16). Heterogeneity was considerable (Chi^2 = 8.44, df = 1 (P = 0.004); I^2 = 88%; Analysis 1.24).

1.25 Adverse events: muscle spasm/rigidity

We identified three studies with 552 participants. Baclofen increased the frequency of muscle spasm (RR 1.94, 95% CI 1.07 to 3.52; Analysis 1.25).

1.26 Adverse events: hyperhidrosis

We identified three studies with 816 participants reporting hyperhidrosis. There was no difference between baclofen and placebo (RR 1.50, 95% CI 0.89 to 2.51; Analysis 1.26).

1.27 Adverse events: nasopharyngitis

We identified four studies with 872 participants reporting nasopharyngitis. There was no difference between baclofen and placebo (RR 0.89, 95% CI 0.40 to 1.95). Heterogeneity was considerable (Chi^2 = 7.53, df = 3 (P = 0.06); I^2 = 60%; Analysis 1.27).

1.28 Adverse events: decreased appetite/anorexia

We identified three studies with 816 participants reporting decreased appetite/anorexia. There was no difference baclofen and placebo (RR 0.74, 95% CI 0.31 to 1.75). Heterogeneity was substantial (Chi^2 = 5.16, df = 2 (P = 0.08); I^2 = 61%; Analysis 1.28).

1.29 Adverse events: dysgeusia/ageusia

We identified three studies with 816 participants reporting dysgeusia/ageusia. There was no difference between baclofen and placebo (RR 1.73, 95% CI 0.57 to 5.24). Heterogeneity was moderate (Chi^2 = 3.65, df = 2 (P = 0.16); I^2 = 45%; Analysis 1.29).

1.30 Adverse events: tremor

We identified three studies with 816 participants reporting tremor. There was no difference between baclofen and placebo (RR 0.69, 95% CI 0.42 to 1.15; Analysis 1.30).

1.31 Adverse events: weakness

We identified three studies with 552 participants reporting weakness. There was no difference between baclofen and placebo (RR 1.19, 95% CI 0.70 to 2.01; Analysis 1.31).

1.32 Adverse events: vomiting

We identified three studies with 816 participants reporting vomiting. There was no difference between baclofen and placebo (RR 1.07, 95% CI 0.66 to 1.71; Analysis 1.32).

1.33 Adverse events: urinary frequency

We identified four studies with 340 participants reporting urinary frequency. There was no difference between baclofen and placebo (RR 1.10, 95% CI 0.45 to 2.68; Analysis 1.33).

1.34 Adverse events: shortness of breath

We identified two studies with 104 participants reporting shortness of breath. There was no difference between baclofen and placebo (RR 0.89, 95% CI 0.04 to 22.31; Analysis 1.34).

Comparison 2: baclofen versus acamprosate

Two RCTs compared baclofen to acamprosate (Kumar 2020a; Mishra 2010).

2.1 Relapse: return to any drinking at end of treatment

We identified one study with 60 participants reporting return to any drinking at the end of treatment. There was no difference between baclofen and acamprosate (RR 1.25, 95% CI 0.71 to 2.20; very low-certainty evidence; Analysis 5.1; Summary of findings 2).

2.2 Adverse events: number of participants with at least one adverse event at end of treatment

We identified one study with 60 participants reporting number of participants with at least one adverse event at the end of treatment. There was no difference between baclofen and acamprosate (RR 0.63, 95% CI 0.23 to 1.69; very low-certainty evidence; Analysis 5.2; Summary of findings 2).

2.3 Dropouts at end of treatment

We identified one study with 60 participants reporting dropouts at the end of treatment. There was no difference between baclofen and acamprosate (RR 0.56, 95% CI 0.21 to 1.46; very low-certainty evidence; Analysis 5.3; Summary of findings 2).

2.4 Dropouts due to adverse events

We identified one study with 60 participants reporting dropouts due to adverse events. There was no difference between baclofen and acamprosate (RR 0.33, 95% CI 0.01 to 7.87; very low-certainty evidence; Analysis 5.4; Summary of findings 2).

2.5 Craving

We identified two studies with 109 participants. There was no difference between baclofen and acamprosate (MD 5.80, 95% CI −11.84 to 23.44). Heterogeneity was considerable (Chi^2 = 38.87, df = 1 (P < 0.001); I^2 = 97%; Analysis 5.5).

2.6 Adverse events: fatigue, tiredness

We identified one study with 60 participants reporting fatigue or tiredness (or both). There was no difference between baclofen and acamprosate (RR 3.00, 95% CI 0.13 to 70.83; Analysis 5.6).

2.7 Adverse events: vertigo, dizziness

We identified one study with 60 participants reporting vertigo or dizziness (or both). There was no difference between baclofen and acamprosate (RR 2.00, 95% CI 0.19 to 20.90; Analysis 5.7).

2.8 Adverse events: nausea

We identified one study with 60 participants reporting nausea. There was no difference between baclofen and acamprosate (RR 0.33, 95% CI 0.01 to 7.87; Analysis 5.8).

2.9 Adverse events: skin rash

We identified one study with 60 participants reporting skin rash. There was no difference between baclofen and acamprosate (RR 0.20, 95% CI 0.01 to 4.00; Analysis 5.9).

2.10 Adverse events: decreased appetite/anorexia

We identified one study with 60 participants reporting decreased appetite/anorexia. There was no difference between baclofen and acamprosate (RR 1.00, 95% CI 0.15 to 6.64; Analysis 5.10).

2.11 Adverse events: acidity

We identified one study with 60 participants reporting acidity. There was no difference between baclofen and acamprosate (RR 0.33, 95% CI 0.01 to 7.87; Analysis 5.11).

2.12 Adverse events: palpitations

We identified one study with 60 participants reporting palpitations. There was no difference between baclofen and acamprosate (RR 0.33, 95% CI 0.01 to 7.87; Analysis 5.12).

2.13 Adverse events: tremor

We identified one study with 60 participants reporting tremor (Kumar 2020a). There were no events in either group.

2.14 Adverse events: erectile dysfunction

We identified one study with 60 participants reporting erectile dysfunction (Kumar 2020a). There were no events in either group.

Comparison 3: baclofen versus naltrexone

Two RCTs compared baclofen to naltrexone (Garbutt 2010b2; Kumar 2020a).

3.1 Relapse: return to any drinking at end of treatment

We identified one study with 60 participants reporting return to any drinking at the end of treatment. Naltrexone reduced the risk of relapse compared to baclofen (RR 2.50, 95% CI 1.12 to 5.56; very low-certainty evidence; Analysis 6.1; Summary of findings 3).

3.2 Frequency of use: percentage of days abstinent at end of treatment

We identified one study with 20 participants (Garbutt 2010b1). The percentage of days abstinent at the of treatment was 55.4% with baclofen and 33.4% with placebo. Standard deviations were not reported.

3.3 Frequency of use: percentage of heavy drinking days at end of treatment

We identified one study with 20 participants (Garbutt 2010b1). The percentage of HDDs at the end of treatment was 17.9% with baclofen and 10.7% with placebo. Standard deviations were not reported.

3.4 Adverse events: number of participants with at least one adverse event at end of treatment

We identified two studies with 80 participants. Naltrexone may increase the risk of adverse events slightly compared to baclofen (RR 0.35, 95% CI 0.15 to 0.80; very low-certainty evidence; Summary of findings 3). There was no heterogeneity (Chi^2 = 0.73, df = 1 (P = 0.39); I^2 = 0%; Analysis 6.2).

3.5 Dropouts at end of treatment

We identified one study with 60 participants. There was no difference between baclofen and naltrexone (RR 1.00, 95% CI 0.32 to 3.10; very low-certainty evidence; see Summary of findings 3). There was no heterogeneity (Chi^2 = 0.73, df = 1 (P = 0.39); I^2 = 0%; Analysis 6.3).

3.6 Dropouts due to adverse events

We identified one study with 60 participants (Kumar 2020a). There were no dropouts in either group.

3.7 Craving

We identified one study with 60 participants reporting cravings. There was no difference between baclofen and naltrexone (MD 2.08, 95% CI −3.71 to 7.87; Analysis 6.4).

3.8 Adverse events: fatigue, tiredness

We identified one study with 60 participants reporting fatigue or tiredness (or both). There was no difference between baclofen and naltrexone (RR 3.00, 95% CI 0.13 to 70.83; Analysis 6.5).

3.9 Adverse events: insomnia

We identified one study with 20 participants reporting insomnia. There was no difference between baclofen and naltrexone (RR 0.14, 95% CI 0.01 to 2.45; Analysis 6.6).

3.10 Adverse events: vertigo, dizziness

We identified one study with 60 participants reporting vertigo or dizziness or both. There was no difference between baclofen and naltrexone (RR 0.40, 95% CI 0.08 to 1.90; Analysis 6.7).

3.11 Adverse events: somnolence, sleepiness, drowsiness or sedation

We identified one study with 20 participants reporting somnolence, sleepiness, drowsiness or sedation. There was no difference between baclofen and naltrexone (RR 0.33, 95% CI 0.04 to 2.69; Analysis 6.8).

3.12 Adverse events: nausea

We identified two studies with 80 participants reporting nausea. There was no difference between baclofen and naltrexone (RR 0.26, 95% CI 0.03 to 2.20; Analysis 6.9).

3.13 Adverse events: skin rash

We identified one study with 60 participants reporting skin rash (Kumar 2020a). There were no events in either group.

3.14 Adverse events: decreased appetite/anorexia

We identified one study with 60 participants. There was no difference between baclofen and naltrexone (RR 2.00, 95% CI 0.19 to 20.90; Analysis 6.10).

3.15 Adverse events: tremor

We identified one study with 60 participants reporting tremor. There was no difference between baclofen and naltrexone (RR 0.33, 95% CI 0.01 to 7.87; Analysis 6.11).

3.16 Adverse events: acidity

We identified one study with 60 participants reporting acidity. There was no difference between baclofen and naltrexone (RR 0.20, 95% CI 0.01 to 4.00; Analysis 6.12).

3.17 Adverse events: palpitations

We identified one study with 60 participants reporting palpitations (Kumar 2020a). There were no events in either group.

3.18 Adverse events: erectile dysfunction

We identified one study with 60 participants reporting erectile dysfunction. There was no difference between baclofen and naltrexone (RR 0.33, 95% CI 0.01 to 7.87; Analysis 6.13).

DISCUSSION

Summary of main results

We included 17 RCTs with 1818 participants. Ten RCTs had a single arm and the other 7 RCTs had two arms each. Fifteen RCTs compared baclofen with placebo, two RCTs compared baclofen with acamprosate, and two RCTs compared baclofen with naltrexone.

Comparison 1: baclofen versus placebo

In comparison to placebo, meta-analyses found moderate-certainty evidence suggesting that baclofen probably reduces the risk to return to any drinking and high-certainty evidence that it increases the rate of abstinent days at the end of treatment. Subgroup analyses found evidence that baclofen may reduce the risk to return to any drinking among detoxified participants but not among other subgroups of participants. We found evidence that baclofen may increase the rate of abstinent days in all the subgroups of participants except among those who received moderate doses of baclofen.

In addition, meta-analyses found moderate-certainty evidence suggesting that baclofen probably has no effect in the rate of HDDs

and in the number of drinks per drinking days, and high-certainty evidence that it does not increase the number of participants with at least one adverse event, the number of participants who dropped out for any reason, and those who dropped out due to adverse events at the end of treatment. These results were confirmed in all the subgroup analyses except for dropout that was lower among participants who received high doses of baclofen compared to placebo and among participants recruited to studies longer than 12 weeks.

Meta-analyses of all the studies found no differences between baclofen and placebo in craving, anxiety, and depression.

Finally, compared to placebo, baclofen increased the frequency of fatigue, dizziness, somnolence, dry mouth, paraesthesia and muscle spasms while, for all the other adverse events, there were no differences between baclofen and placebo.

Comparison 2: baclofen versus acamprosate

Compared to acamprosate, meta-analyses found no differences in any primary outcome evaluated: relapse, number of participants with at least one adverse event, dropouts, dropouts due to adverse events (very low-certainty evidence). We found no differences between baclofen and acamprosate in craving and nine different adverse events. However, most of these meta-analyses were based on a single study with 60 participants, so should be interpreted with caution.

Comparison 3: baclofen versus naltrexone

Compared to naltrexone, meta-analyses found very low-certainty evidence that baclofen may increase the risk of relapse and decrease slightly the number of participants with at least one adverse event. We found no differences between the treatments in dropouts at the end of treatment (very low-certainty evidence), craving, and 11 different adverse events. However, for most of these meta-analyses, results were based on a single study of 60 participants, so should be interpreted with caution.

Overall completeness and applicability of evidence

Overall completeness

In this review, the completeness rates of the analyses of primary outcomes range from 36% to 86%. In detail, considering that our database comprised 14 RCTs (after the exclusion of one study because of heterogeneity), the completeness rates of primary outcome analyses were the following: relapse (return to any drinking): 8 RCTs (57.1%); percentage of days abstinent: 11 RCTs (78.6%); HDDs: 9 RCTs (64.3%); number of drinks per drinking day: 5 RCTs (35.7%); number of people with at least one adverse event: 6 RCTs (42.9%); dropouts from treatment: 12 RCTs (85.7%); and dropouts due to adverse events: 11 RCTs (78.6%). The completeness rates of the analyses of secondary outcomes ranged from 7.1% (shortness of breath; 1 RCT) to 85.7% (sedation; 12 RCTs). The completeness rates of primary outcomes overlap those of other Cochrane Reviews on other medications for the treatment of AUD reflecting the large variety of outcomes used to evaluate the effectiveness of treatments in the field of AUD research (Rösner 2010a; Rösner 2010b). Despite this large variety, the present review achieves a good overall completeness. The larger range of completeness of secondary outcomes was mainly due to the inclusion of rare specific adverse event (e.g. shortness of breath) into the list of secondary outcomes.

Applicability of evidence

The RCTs included in this review largely vary in the daily dose of baclofen, titration schedules, duration of treatment, comorbidity, and baseline alcohol use. Despite these differences among RCTs and their participants, meta-analyses including all the selected RCTs found moderate-certainty evidence that baclofen reduces the risk of relapse and subgroup analyses confirmed this evidence among certain participants (i.e. detoxified participants) but not others (non-detoxified participants). Similarly, including all the RCTs, this review found high-certainty evidence that baclofen increases the rate of abstinent days and subgroup analyses confirmed this evidence among almost all the subgroup analyses. Finally, this review found moderate- to high-certainty evidence that baclofen probably has no effect in the other primary outcomes (HDDs, drinks per drinking days, participants with at least one adverse event, participants who dropout for any reason, participants who dropped out due to adverse events) and this evidence was confirmed by almost all the subgroup analyses. Globally, subgroup analyses sustained the generalisability of the evidence of the demonstrated results.

In addition, RCTs selected by this review took place in different countries including the USA (29.4%); Australia, France, Italy and India (11.8% each); and Germany, Israel, the Netherlands and Russia (5.9% each). This is an important issue in terms of generalisability of the evidence, because different social contexts can influence AUD severity and the availability to receive medical treatment for this disorder.

However, generalisability might be restricted from the exclusion of participants with severe psychiatric disorders by most of the selected RCTs. Furthermore, this review found that baclofen increased the risk of adverse events such as fatigue, dizziness and somnolence but did not increase the number of participants with at least one adverse event. Subgroup analyses indicated that no daily dose of baclofen increased the number of participants with at least one adverse event. However, the subgroup of high doses included only one large RCT (Reynaud 2017). These findings underline the paucity of literature for some important outcomes. Nevertheless, our findings do not allow conclusions on the safety of baclofen in combination with other sedative drugs (e.g. alcohol and benzodiazepines) or in specific patient subgroups, such as people with suicidal ideation (e.g. Agabio 2018a; de Beaurepaire 2019; Holla 2015; Pelissier 2017).

Finally, the results of two recent studies suggest that women may respond better to baclofen for the treatment of AUD than men (Garbutt 2021-LD; Garbutt 2021-MD; Morley 2022). In detail, one study observed that, compared to men, women required lower doses of baclofen to increase the rate of abstinent days (Garbutt 2021-LD; Garbutt 2021-MD). Another study found that baclofen delayed the time to the first drink for women with AUD but not men (Morley 2022). These results provide some support for the hypothesis that gender may be a potential moderator of baclofen response in the treatment of AUD. Although medications for the treatment of AUD have been studied almost exclusively in men (Agabio 2016), these findings are in line with other studies showing numerous gender differences in response to the other pharmacological treatments (Mauvais-Jarvis 2021). Unfortunately, the generalisability might be restricted as most RCTs did not provide separate data for men and women.

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 or unclear risk of selection, performance, detection (subjective outcome), attrition and reporting bias.

One potential threat of bias that concerns all RCTs applying inert placebo is the unmasking of blinding, which is a methodological limitation that is 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 studies is attributable to an overestimation of effects caused by an unmasking of treatment allocation.

Overall, we rated the certainty of evidence as high for the outcomes of percentage of days abstinent, participants with at least one adverse event, dropouts due to any reason and dropouts due to adverse events; moderate for relapse to any drinking, HDDs, number of drinks per drinking days and percent days abstinent. Reasons for downgrading were heterogeneity among study for the outcomes relapse and HDDs and inconsistency for the outcome drinks 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 had 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). Visual inspection of funnel plots for the analyses with more than 10 studies showed no asymmetry suggesting the risk of publication bias. Furthermore, we wrote to the authors of published studies and searched on ClincialTrials.gov and ICTRP to search for unpublished studies to minimise the risk of publication bias.

Agreements and disagreements with other studies or reviews

Compared to the previous Cochrane (Minozzi 2018) and non-Cochrane meta-analyses (Agabio 2021b; Bschor 2018; Lesouef 2014; Pierce 2018; Rose 2018), the present review included four recent RCTs (Garbutt 2021-LD; Garbutt 2021-MD; Kumar 2020a; Morley 2018-LD; Morley 2018-MD; Rigal 2020), and one previously unavailable RCT (Addolorato 2011-LD; Addolorato 2011-MD).

The results of the present review suggest that baclofen may reduce the risk to return to any drinking. Other non-Cochrane systematic reviews found that baclofen significantly increases the number of abstinent participants (Lesouef 2014; Pierce 2018; Rose 2018). As return to any drinking and abstinent participants are complementary outcomes, these results of the present review are in line with those of other systematic reviews. In addition, the present review provides the results of subgroup analyses conducted dividing participants according to the daily dose of baclofen, the duration of the studies and the consumption of alcohol at the beginning of the treatment. These subgroup analyses showed that baclofen probably reduces the risk to return to any drinking (or increases the number of abstinent participants) only among participants already detoxified at the beginning of treatment but not among other subgroups of participants (e.g. participants who were still drinking at the beginning of treatment).

The present review found that baclofen increases the rate of abstinent days at the end of treatment while the previous version of this Cochrane Review (Minozzi 2018), and many of the non-Cochrane Reviews (Bschor 2018; Lesouef 2014; Pierce 2018; Rose 2018), found no differences between baclofen and placebo in this outcome. However, another systematic review found that baclofen may increase the rate of abstinent days (Agabio 2021b). As this review was aimed at investigating the potential role of anxiety in influencing the effects of baclofen, it included only RCTs that provided anxiety levels of participants both at baseline and at the end of treatment. This review found that baclofen increases the rate of abstinent days only among participants with high anxiety levels and not among participants with low anxiety levels at baseline (Agabio 2021b). These findings suggest that baclofen may be useful only for certain people with AUD and that treatment should be personalised.

The present review found moderate-certainty evidence of no difference between baclofen and placebo in the number of drinks per drinking days. In the previous version of this review, we found that baclofen increased the number of drinks per drinking days compared to placebo (Minozzi 2018). However, this finding was mainly based on one study that we excluded in the present update from the meta-analyses because of the elevated heterogeneity due to its inclusion and the substantial difference of the participants and setting of this study when compared to the other included studies (Leggio 2015).

Finally, the present review found no difference between baclofen and placebo in anxiety, depression and anxiety. These findings are in line with those of previous meta-analyses (Agabio 2021b; Lesouef 2014; Minozzi 2018; Rose 2018).

AUTHORS' CONCLUSIONS

Implications for practice

Based on evidence from 17 randomised controlled trials with 1818 participants with alcohol use disorder (AUD), the review demonstrates the effectiveness of baclofen for treatment of AUD in reducing the risk of relapse and increasing the percentage of abstinent days. Compared to placebo, baclofen reduces the risk to return to any drinking at the end of treatment by approximately 13%. That is, 13 additional participants out of 100 avoid any drinking, for the entire duration of treatment when they receive baclofen compared to participants who receive placebo. This finding is particularly relevant considering that the duration of treatment of studies selected by this review ranged from three months to one year. Among detoxified participants, this effect was higher with an additional 27 participants out of 100 maintaining abstinence when treated with baclofen compared to placebo.

Regarding the percentage of abstinent days, baclofen increases this percentage by 9% compared to placebo. This finding means that participants treated with baclofen spend almost three additional abstinent days, per month, compared to participants who receive

placebo. This effect is equal to almost four additional abstinent days, per month, among the subgroup of detoxified participants, compared to participants who receive placebo.

This review also demonstrates that baclofen does not increase the number of participants with at least one adverse event at the end of treatment, compared to placebo. That means that participants who receive baclofen do not experience a higher number of adverse events compared to those who receive placebo. In addition, participants who receive baclofen do not differ from those who receive placebo in the numbers who prematurely interrupt the trial because of any reason or adverse events. Similarly, baclofen does seem to reduce HDDs, the number of drinks per drinking days, or the severity of craving, anxiety, and depression. These findings mean that baclofen does not have an effect in other important measures of alcohol consumption compared to placebo.

Finally, this review demonstrates that, compared to placebo, baclofen increases specific adverse events such as fatigue, dizziness and somnolence/sedation but not others.

Conversely, this review provides no evidence on possible differences between baclofen and acamprosate or naltrexone because of the limited number of the available studies for these comparisons.

Regarding its safety, our findings do not allow conclusions on the possible risk related to the combination of baclofen with sedative drugs (e.g. alcohol or benzodiazepines, or both) or in specific patient subgroups, such as people with suicidal ideation.

Globally, current evidence suggests that baclofen may help people with AUD aimed at maintaining abstinence.

Implications for research

Further studies should investigate baclofen's profile of efficacy and safety among certain categories of people with AUD such as people with other mental disorders (bipolar disorder, anxiety disorders) or physical disorders (e.g. severe liver disease) and data should always be reported separately for men and women to investigate possible gender differences.

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).

The exploration of baclofen's profile of efficacy and safety and the identification of moderators and mediators of baclofen's effects remains a challenge mainly due to the risk of specific adverse events such as sedation. Preclinical data suggest that γ-aminobutyric acid type B ($GABA_B$)-positive allosteric modulators may constitute the possible solution to overcome these risks (Maccioni 2019). $GABA_B$-positive allosteric modulators indeed reproduce baclofen-induced effects on alcohol-related behaviours displaying a more favourable safety profile. At present, the first clinical trial to evaluate the efficacy and safety of a $GABA_B$-positive allosteric modulator for the treatment of AUD is ongoing (NCT05096117).

As most people with AUD still receive no treatment (Han 2021), the development of new, effective, safe and manageable medications is expected to considerably increase the number of people who seek and receive medical treatment.

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* Indicates the major publication for the study

References to other published versions of this review

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CHARACTERISTICS OF STUDIES

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

Addolorato 2007

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **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)
Participants	**Baseline characteristics** Baclofen • Age (years): median 49.0 (IQR 43.0–61.0) • Gender: 32 (76%) male • Sample size: 42 • Race: NR • Marital status: 27 (64%) married • Educational level (number with education for > 13 years): 12 (29%) • Current use: OCDS scores, OCDS total: median 28.0 (IQR 23.0–32.0) • Comorbidity: Child-Pugh score median 90 (IQR 80–110); hepatitis B virus-positive 10 (24%); HCV-positive 12 (29%) Placebo • Age (years): median 49.0 (IQR 4.0–60.0) • Gender: 29 (69%) male • Sample size: 42 • Race: NR • Marital status: 24 (57%) married • Educational level (number with education for > 13 years): 9 (21%) • 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%); HCV-positive 12 (29%) **Inclusion criteria:** aged 18–75 years; diagnosis of alcohol dependence according to DSM-IV criteria; diagnosis of liver cirrhosis; an alcohol intake of ≥ 2 HDD/week on average (men ≥ 5 drinks/day; women ≥ 4 drinks/day) and an average overall consumption of ≥ 21 drinks/week for men and ≥ 14 drinks/week for

Addolorato 2007 *(Continued)*

	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. **Detoxification:** participants had an alcohol intake of ≥ 2 HDD/week on average (men ≥ 5 drinks/day; women ≥ 4 drinks/day) and an average overall consumption of 21 drinks/week or more for men and 14 drinks/week or more for women during the 4 weeks before enrolment (1 standard drink = 12 g absolute alcohol).
Interventions	Baclofen + counselling (42 participants) • Dose: for first 3 days, baclofen 5 mg, 3 times/day; subsequently, dose increased to 10 mg 3 times/day • Duration of treatment: 12 consecutive weeks • Length of follow-up: 16 weeks Placebo + counselling (42 participants) • Dose: N/A • Duration of treatment: 12 consecutive weeks • Length of follow-up: 16 weeks
Outcomes	**Primary outcomes** • Proportion of participants achieving and maintaining alcohol abstinence • Total abstinence duration • Cumulative abstinence duration (as total number of days abstinent from alcohol) • Alcohol relapse (as daily alcohol intake of > 4 drinks or an overall consumption of ≥ 14 drinks/week during ≥ 4 weeks) • Alcohol lapse (as any episode of alcohol consumption not classified as relapse) • Adverse events attributable to drug withdrawal **Secondary outcomes** • Difference in craving measures between groups (craving level was ascertained using Italian version of the OCDS) • Measurement of liver enzymes and biological markers of alcohol abuse (i.e. amounts of AST, ALT, GGT and total bilirubin; international normalised ratio and mean cellular volume), concentrations in blood of creatinine and ammonia
Identification	**Sponsorship source:** Italian Ministry for University, Scientific and Technological Research (MURST), and by the European Research Advisory Board (ERAB) **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	During the updating, the authors allowed us to use the original database to collect the lacking data.

Risk of bias

Bias	Authors' judgement	Support for judgement

Addolorato 2007 *(Continued)*

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) 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."
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."
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 primary and secondary outcomes described in protocol.

Addolorato 2011-LD

Study characteristics

Addolorato 2011-LD *(Continued)*

Methods	**Study design:** 12-week, 3-arm parallel, double-blind, RCT **Country:** Italy
Participants	**Baseline characteristics** Baclofen: low dose (14 participants) • Age (years): median 45.6 (IQR 32.0–60.0) • Gender: 12 (86%) male • Sample size: 14 • Race: 14 (100%) white • Marital status: 8 (57%) married • Educational level (number with education for ≤ 13 years): 4 (28%) • Current use: median 13.91 (IQR 10.37–17.46) drinks per drinking days (1 drink = 12 g alcohol) • Comorbidity: NR • Duration of alcohol abuse: NR • Number of previous detoxifications: NR Placebo (7 participants) • Age (years): median 43.1 (IQR 23.0–59.0) • Gender: 78% male • Sample size: 7 • Race: white 7 (100%) • Marital status: 36.0% married • Educational level (number with education for ≤ 13 years): 10 (71.0%) • Current use: median 11.98 (IQR 9.05–14.91) drinks per drinking days (1 drink = 12 g alcohol) • Comorbidity: NR • Duration of alcohol abuse (years): NR • Number of previous detoxifications: NR **Inclusion criteria:** aged 18–60 years (inclusive); diagnosis of alcohol dependence according to DSM IV-TR; alcohol intake ≥ 2 HDD (≥ 5 drinks/day for men and ≥ 4 drinks/day for women) per week on average and a mean overall consumption ≥ 21 drinks/week for men and ≥ 14 drinks/week for women in the 4 weeks before enrolment. **Exclusion criteria:** clinically significant medical and psychiatric disease that might interfere with the evaluation of the study medication or that might represent a safety concern; concurrent use of psychotropic medication, including antidepressant, mood stabilisers, antipsychotics, anxiolytics or hypnotics; concurrent use of anticonvulsants, insulin or oral hypoglycaemics. **Detoxification:** participants had to refrain from drinking for ≥ 3 days prior to randomisation day; participants abstinent from alcohol for > 10 days prior to randomisation were excluded.
Interventions	Baclofen: low dose + medical management • Dose: 30 mg/day • Duration of treatment: 16 weeks (2 weeks' uptitration, 12 weeks of low-dose baclofen, 2 weeks' downtitration) • Length of follow-up: 4 weeks Placebo (7 participants) + medical management • Dose: N/A • Duration of treatment: 16 weeks (2 weeks' placebo uptitration, 12 weeks of placebo, 2 weeks' placebo downtitration) • Length of follow-up: 4 weeks

Addolorato 2011-LD *(Continued)*

Outcomes	**Primary outcomes** • HDDs • Abstinent days • Craving score **Secondary outcomes** • Time to first lapse • Time to first relapse
Identification	EudraCT Number: 2006-000713-37
Notes	In this review update, we divided the study into the 2 following arms: • Addolorato 2011-LD: baclofen 30 mg/day (14 participants) vs placebo (7 participants) • Addolorato 2011-MD: baclofen 60 mg/day (14 participants) vs placebo (7 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list produced by the pharmacist who prepared the drug and the placebo.
Allocation concealment (selection bias)	Low risk	Quote: "To maintain masking, an independent colleague, who did not have any further role in the study, concealed the randomization codes in a safe box."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. Placebo and baclofen were prepared by a local compounding pharmacy. Placebo, baclofen 10 mg and baclofen 20 mg tablets were identical in size, colour, shape and taste."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. Placebo and baclofen were prepared by a local compounding pharmacy. Placebo, baclofen 10 mg and baclofen 20 mg tablets were identical in size, colour, shape and taste."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information. However, objective outcomes are unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Participants were blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	24% lost at follow-up. Unbalanced between groups.
Selective reporting (reporting bias)	High risk	Study protocol unavailable. The authors declared that (quote) "they reported the results of a secondary analysis, which was also conducted only on the Italian sub sample of the original multicentre study. The planned outcome was based on the reduction of heavy drinking, this post hoc analysis used the number of drinks per day."

Addolorato 2011-MD

Study characteristics	
Methods	**Study design:** 12-week, 3-arm parallel, double-blind, RCT **Country:** Italy
Participants	**Baseline characteristics** Baclofen: medium dose (14 participants) • Age (years): median 43.1 (IQR 30.0–57.0) • Gender: 9 (64%) male • Sample size: 14 • Race: 14 (100%) white • Marital status: 43.0% married • Educational level (number with education for ≤ 13 years): 9 (64.0%) • Current use: median 9.65 (IQR 7.30–12.01) drinks per drinking days (1 drink = 12 g alcohol) • Comorbidity: NR • Duration of alcohol abuse (years): NR • Number of previous detoxifications: NR Placebo (7 participants) • Age (years): median 43.1 (IQR 23.0–59.0) • Gender: 78% male • Sample size: 7 • Race: white 7 (100%) • Marital status: 36.0% married • Educational level (number with education for ≤ 13 years): 71.0% • Current use: median 11.98 (IQR 9.05–14.91) drinks per drinking days (1 drink = 12 g alcohol) • Comorbidity: NR • Duration of alcohol abuse (years): NR • Number of previous detoxifications: NR **Inclusion criteria:** aged 18–60 years (inclusive); diagnosis of alcohol dependence according to DSM IV-TR; alcohol intake ≥ 2 HDD (≥ 5 drinks/day for men and ≥ 4 drinks/day for women) per week on average and a mean overall consumption ≥ 21 drinks/week for men and ≥ 14 drinks/week for women in the 4 weeks before enrolment. **Exclusion criteria:** clinically significant medical and psychiatric disease that might interfere with the evaluation of the study medication or that might represent a safety concern; concurrent use of psychotropic medication, including antidepressant, mood stabilisers, antipsychotics, anxiolytics or hypnotics; concurrent use of anticonvulsants, insulin or oral hypoglycaemics. **Detoxification:** participants had to refrain from drinking for ≥ 3 days prior to randomisation day; participants abstinent from alcohol for > 10 days prior to randomisation were excluded.
Interventions	Baclofen medium dose (14 participants) + medical management • Dose: 90 mg/day • Duration of treatment: 16 weeks (2 weeks' uptitration, 12 weeks of medium-dose baclofen, 2 weeks' downtitration) • Length of follow-up: 4 weeks Placebo (14 participants) + medical management • Dose: N/A

Addolorato 2011-MD *(Continued)*

- Duration of treatment: 16 weeks (2 weeks' placebo uptitration, 12 weeks of placebo, 2 weeks' placebo downtitration)
- Length of follow-up: 4 weeks

Outcomes	**Primary outcomes** • HDDs • Abstinent days • Craving score **Secondary outcomes** • Time to first lapse • Time to first relapse
Identification	EudraCT Number: 2006-000713-37
Notes	In this review update, we divided the study into the 2 following arms: • Addolorato 2011-LD: baclofen 30 mg/day (14 participants) vs placebo (7 participants) • Addolorato 2011-MD: baclofen 60 mg/day (14 participants) vs placebo (7 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list produced by the pharmacist who prepared the drug and the placebo.
Allocation concealment (selection bias)	Low risk	Quote: "To maintain masking, an independent colleague, who did not have any further role in the study, concealed the randomization codes in a safe box."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. Placebo and baclofen were prepared by a local compounding pharmacy. Placebo, baclofen 10 mg and baclofen 20 mg tablets were identical in size, colour, shape and taste."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Participants and investigators were unaware of treatment assignment. Placebo and baclofen were prepared by a local compounding pharmacy. Placebo, baclofen 10 mg and baclofen 20 mg tablets were identical in size, colour, shape and taste."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information. However, objective outcomes are unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Participants were blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	24% lost at follow-up. Unbalanced between groups.
Selective reporting (reporting bias)	High risk	Study protocol unavailable. The authors declared that (quote) "they reported the results of a secondary analysis, which was also conducted only on the Italian sub sample of the original multicentre study. The planned outcome was

Addolorato 2011-MD *(Continued)*

based on the reduction of heavy drinking, this post hoc analysis used the number of drinks per day."

Beraha 2016-HD

Study characteristics

Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** the Netherlands **Setting:** SolutionS Center, Voorthuizen, the Netherlands; U-Center, Epen, The Netherlands; The Home Clinic, Weesp, the Netherlands; Roder Sana Addiction Treatment, Oirschot, the Netherlands
Participants	**Baseline characteristics** Baclofen: high dose (58 participants) • Age (years): mean 45.8 (SD 9.2) • Gender: 41 (70.7%) male • Sample size: 58 • Race: NR • Marital status: 62.1% married • Educational level: NR • Current use: mean 147.0 (SD 84.9) g/day alcohol • Comorbidity: mean 19.6 (SD 10.0) BDI; mean 49.7 (SD 12.4) Spielberger State-Trait Inventory • Duration of alcohol abuse (years): mean 18.8 (SD 10.7) • Number of previous detoxifications: mean 1.1 (SD 1.6) Placebo (31 participants) • Age (years): mean 44.0 (SD 9.2) • Gender: 69% male • Sample size: 31 • Race: NR • Marital status: 47% married • Educational level: NR • Current use: mean 141.7 (SD 85.5) g/day alcohol • Comorbidity: mean 18.2 (SD 7.8) BDI; mean 48.6 (SD 10.6) Spielberger State-Trait Inventory • Duration of alcohol abuse (years): mean 19.0 (SD 11.5) • Number of previous detoxifications: mean 2.0 (SD 3.6) **Inclusion criteria:** aged 18–70 years; DSM-IV AD-diagnosis; breath alcohol concentration < 0.5% at the screening visit (informed consent); mean alcohol consumption ≥ 14 units for women and ≥ 21 units for men/week over consecutive 30 days in the 90-day period before start of study and ≥ 2 HDDs (women ≥ 5 units; men ≥ 6 units) in past 90 days; minimum of 96 hours and maximum of 21 days of abstinence prior to start of 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 study), pharmacological treatment for alcohol dependence

Beraha 2016-HD *(Continued)*

	(i.e. acamprosate, naltrexone, disulfiram, ortopiramate); pregnancy or breastfeeding; > 7 days inpatient treatment for SUD in the 30 days before the start of the study; and use of baclofen in the past 30 days. **Detoxification:** participants followed 4–6 weeks' inpatient detoxification.
Interventions	Baclofen: high dose (58 participants) + CBT • Dose: baclofen up to 150 mg/day (mean dose 93.6 mg/day) • Duration of treatment: 16 weeks (6 weeks' titration and 10 weeks' high-dose baclofen) • Length of follow-up: trial consisted of a 6-week titration phase and a 10-week high-dose phase, where the dose was stabilised Placebo (31 participants) + CBT • Dose: N/A • Duration of treatment: 16 weeks; trial consisted of a 6-week titration phase and a 10-week placebo phase • Length of follow-up: 16-weeks
Outcomes	**Primary outcomes** • Time to first relapse in high-dose phase (10 weeks) and complete medication period (16 weeks): relapse defined as first HDD, i.e. alcohol intake > 5 (women) or > 6 (men) standard drinks per occasion, following a lapse (any alcohol intake) **Secondary outcomes** • TAC: assessed for participants who terminated the study • Number of HDDs during treatment • Proportion of participants relapsed, proportion of participants continuously abstinent throughout study period and cumulative abstinence duration (abstinence was defined as breath alcohol concentration of 0%, negative self-report at every visit and % CDT within a normal range at end of study) • Dropout rate: defined as participants who terminated treatment before end of study due to reasons other than relapse • Safety and tolerability of study medication • Changes in craving, anxiety, depression and % CDT at end of first phase
Identification	**Sponsorship source:** funding by private donation through the University of Amsterdam Fund (AUF7344) **Author's name:** Dr Esther M Beraha **Institution:** Addiction Development and Psychopathology (ADAPT) Laboratory, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands **Email:** R.W.H.J.Wiers@uva.nl (RW Wiers) **Address:** Addiction Development and Psychopathology Lab, Department of Psychology, University of Amsterdam, Nieuwe Achtergracht 129 B, 1018 WS Amsterdam, the Netherlands
Notes	In this review update, we divided the study into the 2 following arms: • Beraha 2016-LD: baclofen 30 mg/day (31 participants) vs placebo (31 participants) • Beraha 2016-HD: baclofen up to 150 mg/day (58 participants) vs placebo (31 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement

Beraha 2016-HD *(Continued)*

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) Objective 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) Subjective 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 groups (3%) (Beraha 2016-HD: 1 participant lost; Beraha 2016-LD: 2 participants lost).
Selective reporting (reporting bias)	Low risk	Study protocol available; results reported for all primary and secondary outcomes reported in protocol.

Beraha 2016-LD

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** the Netherlands **Setting:** SolutionS Center, Voorthuizen, the Netherlands; U-Center, Epen, The Netherlands; The Home Clinic, Weesp, the Netherlands; Roder Sana Addiction Treatment, Oirschot, the Netherlands
Participants	**Baseline characteristics** Baclofen: low dose (31 participants) • Age (years): mean 44.7 (SD 11.3) • Gender: 20 (64.5%) male • Sample size: 31 • Race: NR • Marital status: 54.9% married

Beraha 2016-LD *(Continued)*

- Educational level: NR
- Current use: mean 132.5 (SD 85.2) g/day alcohol
- Comorbidity: mean 22.0 (SD 11.3) BDI; mean 52.1 (SD 9.5) Spielberger State-Trait Inventory
- Duration of alcohol abuse (years): mean 21.5 (SD 13.1)
- Number of previous detoxifications: mean 1.8 (SD 2.9)

Placebo (31 participants)

- Age (years): 44.0 (SD 9.2)
- Gender: 69% male
- Sample size: 31
- Race: NR
- Marital status: 47% married
- Educational level: NR
- Current use: mean 141.7 (SD 85.5) g/day alcohol
- Comorbidity: mean 18.2 (SD 7.8) BDI; mean 48.6 (SD 10.6) Spielberger State-Trait Inventory
- Duration of alcohol abuse (years): mean 19.0 (SD 11.5)
- Number of previous detoxifications: mean 2.0 (SD 3.6)

Inclusion criteria: aged 18–70 years; DSM-IV AD-diagnosis; breath alcohol concentration < 0.5% at screening visit (informed consent); mean alcohol consumption ≥ 14 units for women and ≥ 21 units for men/week over consecutive 30 days in 90-day period before start of study and ≥ 2 HDDs (women ≥ 5 units; men ≥ 6 units) in past 90 days; minimum of 96 hours and maximum of 21 days of abstinence prior to start of 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 alcohol dependence (i.e. acamprosate, naltrexone, disulfiram, ortopiramate); pregnancy or breastfeeding; > 7 days inpatient treatment for SUD in 30 days before start of study; and use of baclofen in past 30 days.

Detoxification: participants followed 4–6 weeks' inpatient detoxification.

Interventions	Baclofen: low dose (31 participants) + CBT • Dose: 30 mg/day • Duration of treatment: 16 weeks (6 weeks' titration and 10 weeks' low-dose baclofen) • Length of follow-up: trial consisted of a 6-week titration phase and a 10-week low-dose phase Placebo (31 participants) + CBT • Dose: N/A • Duration of treatment: 16 weeks; trial consisted of a 6-week titration phase and a 10-week placebo phase • Length of follow-up: 16 weeks
Outcomes	**Primary outcomes** • Time to first relapse in the low-dose 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) **Secondary outcomes** • TAC: assessed for participants who terminated the study

Beraha 2016-LD *(Continued)*

- 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%, negative self-report at every visit, and % CDT 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 treatment phase

Identification	**Sponsorship source:** funding provided by a private donation through the University of Amsterdam Fund (AUF7344) **Author's name:** Dr Esther M Beraha **Institution:** Addiction Development and Psychopathology (ADAPT) Laboratory, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands **Email:** R.W.H.J.Wiers@uva.nl (RW Wiers) **Address:** Addiction Development and Psychopathology Lab, Department of Psychology, University of Amsterdam, Nieuwe Achtergracht 129 B, 1018 WS Amsterdam, the Netherlands
Notes	In this review update, we divided the study into the 2 following arms: • Beraha 2016-LD: baclofen 30 mg/day (31 participants) vs placebo (31 participants) • Beraha 2016-HD: baclofen up to 150 mg/day (58 participants) vs placebo (31 participants)

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) Objective 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) Subjective outcomes	Low risk	Quote: "The investigators and responsible physicians remained blind with regard to the study medication during the whole study period."

Beraha 2016-LD *(Continued)*

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 groups (3%) (Beraha 2016-HD: 1 participant lost; Beraha 2016-LD: 2 participants lost).
Selective reporting (reporting bias)	Low risk	Study protocol available; results reported for all primary and secondary outcomes reported in the protocol.

Garbutt 2010a

Study characteristics

Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** USA **Setting:** Department of Psychiatry and the Bowles Center for Alcohol Studies (JCG, ABKP, LKJ, BAF), University of North Carolina (outpatients)
Participants	**Baseline characteristics** Baclofen • Age (years): mean 47.5 (SD 7.6) • Gender: 22 (55%) male • Sample size: 40 • Race: 95% white • Marital status: NR • Educational level (% with college degree): 32% • Current use (drinks/drinking day): mean 7.3 (SD 3.2) • Comorbidity: Zung Self-Rating Depression (maximum = 80): 35.4 (SD 8.1); Spielberger State Anxiety (maximum = 80): mean 34.1 (SD 10.8); Spielberger Trait Anxiety (maximum = 80): mean 38.3 (SD 8.7) Placebo • Age (years): mean 50.3 (SD 7.2) • Gender: 22 (55%) male • Sample size: 40 • Race: 7% white • Marital status: NR • Educational level (% with college degree): 37% • Current use (drinks/drinking day): mean 6.9 (SD 3.2) • Comorbidity: Zung Self-Rating Depression (maximum = 80): mean 37.0 (SD 10.5); Spielberger State Anxiety (maximum = 80): mean 38.5 (SD 12.7); Spielberger Trait Anxiety (maximum = 80): mean 42.1 (SD 11.4) **Inclusion criteria:** meeting DSM-IV criteria for current alcohol dependence; ≥ 2 HDDs/week (men ≥ 5 standard drinks/day, women ≥ 4 standard drinks/day) 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 psy-

Garbutt 2010a *(Continued)*

	chotic 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 receiving antidepressants); concurrent use of anticonvulsants, insulin or oral hypoglycaemics; AST, ALT, or GGT level > 3 times the ULN, bilirubin > ULN, or serum creatinine > ULN; positive urine toxicology screen except 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 contraception (oral or depot contraceptive, or barrier methods such as diaphragm or condom with spermicidal); people requiring inpatient treatment or more intense outpatient treatment for their alcohol dependency. **Detoxification:** participants consumed ≥ 2 HDDs/week (men ≥ 5 standard drinks/day, women ≥ 4 standard drinks/day) on average during the 4 weeks prior to screening.
Interventions	Baclofen (40 participants) • Dose: 30 mg/day • Duration of treatment: 12 weeks of treatment and utilising 8 sessions of BRENDA, a low-intensity psychosocial intervention • Length of follow-up: 12 weeks Placebo (40 participants) • 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** • Percent of HDDs **Secondary outcomes** • Percent abstinent days • Craving • Anxiety • Depression • Safety, tolerability and tablet 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 NIH **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, North Carolina, 27599-7160, USA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Garbutt 2010a *(Continued)*

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	Unclear risk	Only stated that study was double-blind. No further description provided.
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) 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)." Comment: not stated whether the outcome assessor was blinded, but objective outcomes unlikely to be biased by lack or incomplete blinding.
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 adverse events of baclofen easy recognisable.
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% of participants from placebo group and 27.5% from baclofen group lost at follow-up. But reasons balanced between groups and most unlikely to be related to the intervention or the outcome.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable.

Garbutt 2010b1

Study characteristics	
Methods	**Study design:** randomised phase 1 study **Study grouping:** parallel group **Blinding:** quadruple (participant, care provider, investigator, outcomes assessor) **Country:** USA
Participants	**Baseline characteristics** 40 men and women aged 25–60 years meeting DSM-IV criteria for current alcohol dependence **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; mean

Garbutt 2010b1 *(Continued)*

	≥ 2 HDDs per/week (≥ 5 drinks/day for men, ≥ 4 drinks/day for women); mean overall consumption ≥ 21 drinks/week (men) and ≥ 14 drinks/week (women) during 4 weeks prior to admission or screening; ≤ 3 months of abstinence in 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, North Carolina, USA. **Detoxification:** individuals were not required to be abstinent from alcohol prior to randomisation.
Interventions	**Intervention characteristics** Baclofen + placebo naltrexone + behaviour therapy (10 participants) • Dose: baclofen 10 mg 3 times/day; placebo naltrexone 50 mg/day; behaviour therapy 9 sessions • Duration of treatment: baclofen/naltrexone 12 weeks • Length of follow-up: 12 weeks Baclofen + naltrexone + behaviour therapy (10 participants) • Dose: baclofen 10 mg 3 times/day; naltrexone 50 mg/day; behaviour therapy, 9 sessions • Duration of treatment: baclofen/naltrexone 12 weeks • Length of follow-up: 12 weeks **Placebo characteristics** Placebo baclofen + naltrexone + behaviour therapy (10 participants) • Dose: placebo baclofen 10 mg 3 times/day; naltrexone 50 mg/day; behaviour therapy 9 sessions • Duration of treatment: placebo baclofen/naltrexone 12 weeks • Length of follow-up: 12 weeks Placebo baclofen + placebo naltrexone + behaviour therapy (10 participants) • Dose: placebo baclofen 10 mg 3 times/day; placebo naltrexone 50 mg/day; behaviour therapy 9 sessions • Duration of treatment: placebo baclofen/placebo naltrexone 12 weeks • Length of follow-up: 12 weeks
Outcomes	This is an exploratory study to gain experience with the combination of baclofen and naltrexone **Primary outcomes** • Pilot data on cytokine levels • Recruitment and retention of study participants **Secondary outcomes** • 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. In this review update, we divided the study into the 2 following arms: • Garbutt 2010b1: baclofen 30 mg/day (baclofen + placebo naltrexone (10 participants) + baclofen + naltrexone (10 participants) equal to 20 participants) vs placebo (placebo baclofen + naltrexone (10

Garbutt 2010b1 *(Continued)*

participants) + placebo baclofen + placebo naltrexone (participants) equal to 20 participants) included in the analysis baclofen vs placebo

- Garbutt 2010b2: baclofen 30 mg/day (baclofen + placebo naltrexone (10 participants)) vs naltrexone 50 mg/day (placebo baclofen + naltrexone (10 participants)) included in the analysis baclofen vs naltrexone

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) Objective 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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals from the study.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable; data available only from conference proceedings.

Garbutt 2010b2

Study characteristics

Methods	**Study design:** randomised phase 1 study **Study grouping:** parallel group **Blinding:** quadruple (participant, care provider, investigator, outcomes assessors) **Country:** USA
Participants	**Baseline characteristics** 20 men and women aged 25–60 years meeting DSM-IV criteria for current alcohol dependence

Garbutt 2010b2 *(Continued)*

	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; mean ≥ 2 HDDs per/week (≥ 5 drinks/day for men, ≥ 4 drinks/day for women); mean overall consumption ≥ 21 drinks/week (men) and ≥ 14 drinks/week (women) during 4 weeks prior to admission or screening; ≤ 3 months of abstinence in 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, North Carolina, USA. **Detoxification:** individuals were not required to be abstinent from alcohol prior to randomisation.
Interventions	**Intervention characteristics** Baclofen + placebo naltrexone + behaviour therapy (10 participants) • Dose: baclofen 10 mg 3 times/day; placebo naltrexone 50 mg/day; behaviour therapy 9 sessions • Duration of treatment: baclofen/placebo naltrexone 12 weeks • Length of follow-up: 12 weeks **Placebo characteristics** Placebo baclofen + naltrexone + behaviour therapy (10 participants) • Dose: placebo baclofen 10 mg 3 times/day; naltrexone 50 mg/day; behaviour therapy 9 sessions • Duration of treatment: placebo baclofen/naltrexone 12 weeks • Length of follow-up: 12 weeks
Outcomes	This is an exploratory study to gain experience with the combination of baclofen + naltrexone **Primary outcomes** • Pilot data on cytokine levels • Recruitment and retention of study participants **Secondary outcomes** • 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. In this review update, we divided the study into the 2 following arms: • Garbutt 2010b1: baclofen 30 mg/day (baclofen + placebo naltrexone (10 participants) + baclofen + naltrexone (10 participants) equal to 20 participants) vs placebo (placebo baclofen + naltrexone (10 participants) + placebo baclofen + placebo naltrexone (10 participants) equal to 20 participants) included in the analysis baclofen vs placebo • Garbutt 2010b2: baclofen 30 mg/day (baclofen + placebo naltrexone (10 participants)) vs naltrexone 50 mg/day (placebo baclofen + naltrexone (10 participants)) included in the analysis baclofen vs naltrexone

Risk of bias

Bias	Authors' judgement	Support for judgement

Garbutt 2010b2 *(Continued)*

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) Objective 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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals from the study.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable, data available only from conference proceedings.

Garbutt 2021-LD

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** USA **Setting:** Department of Psychiatry and the Bowles Center for Alcohol Studies (JCG, ABKP, CP, MS, RJ, LW), University of North Carolina (outpatients)
Participants	**Baseline characteristics** Baclofen: low dose (43 participants) • Age (years): mean 46.1 (SD 10.4) • Gender: 22 (51.2%) male • Sample size: 43 • Race: Hispanic 1 (2.3%); white 37 (86.1%) • Marital status: 46.5% married • Educational level (years): mean 15.9 (SD 2.4) • Current use (g/day alcohol): mean 149.1 (SD 107.52); calculated by mean drinks/drinking day with 1 standard drink = 14 g

Garbutt 2021-LD *(Continued)*

	• Comorbidity: 5 (11.6%) receiving antidepressants; Spielberger State-Trait Inventory: mean 36.28 (SD 12.41) • Duration of alcohol abuse (years): NR • Number of previous detoxifications: NR Placebo (20 participants) • Age (years): mean 47.1 (SD 9.6) • Gender: 50.0% male • Sample size: 20 • Race: Hispanic 0%; white 90.0% • Marital status: 40.0% married • Educational level (years): mean 14.8 (SD 2.4) • Current use (g/day alcohol): mean 130.34 (SD 54.6); calculated by mean drinks per drinking days with 1 standard drink = 14 g • Comorbidity: 40.0% receiving antidepressants; Spielberger State-Trait Inventory: mean 35.03 (SD 10.46) • Duration of alcohol abuse: NR • Number of previous detoxifications: NR **Inclusion criteria:** aged 21–65 years, diagnosis of DSM-IV alcohol dependence, to have a reported drinking pattern > 14 standard drinks (women) or 21 drinks (men)/week including ≥ 2 HDDs/week on average (men ≥ 5 standard drinks/day; women ≥ 4 standard drinks/day) during a consecutive 30-day period within the 90 days prior to screening based on Time-Line Follow Back interview and to express an interest in significantly reducing or stopping alcohol use. **Exclusion criteria:** significant medical illness, e.g. diabetes mellitus; significant psychiatric illness, e.g. bipolar disorder or were receiving psychotropic medication except for stable doses of antidepressants for ≥ 1 month; evidence of another SUD except for nicotine dependence or cannabis abuse. **Detoxification:** sobriety was not a requirement for randomisation.
Interventions	Baclofen low dose (43 participants) + medical management • Dose: 30 mg/day • Duration of treatment: 16 weeks (2 weeks' uptitration, 12 weeks' low-dose baclofen, 2 weeks' down-titration) • Length of follow-up: 4 weeks Placebo (20 participants) + medical management • Dose: N/A • Duration of treatment: 16 weeks (2 weeks' uptitration, 12 weeks' placebo, 2 weeks' downtitration) • Length of follow-up: 4 weeks
Outcomes	**Primary outcomes** • % HDDs over the active treatment period • % abstinent days over the active treatment period **Secondary outcomes** • Craving for alcohol evaluated using the Penn Alcohol Craving Scale • % of responders (participants without heavy drinking in final 8 weeks of trial) • % CDT • GGT • Anxiety evaluated using the Spielberger State-Trait Inventory (STAI)
Identification	**Sponsorship source:** National Institute of Alcohol Abuse and Alcoholism Grant R21 AA020824

Garbutt 2021-LD *(Continued)*

Author's name: James C Garbutt

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Notes

In the previous version of this review (Minozzi 2018), this was included among the ongoing studies (NCT01980706).

In this review update, we divided the study into the 2 following arms:

- Garbutt 2021-LD: baclofen 30 mg/day (43 participants) vs placebo (20 participants)
- Garbutt 2021-MD: baclofen 90 mg/day (37 participants) vs placebo (20 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants who met criteria were randomized to either placebo, 30 mg/day baclofen or 90 mg/day baclofen using randomization blocks provided by Dr. Gallop [SAS Institute Inc.] (2015). "A minimization random assignment procedure were used to match subjects."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization blocks were prepared by the statistician and provided to the Investigational Drug Services. Randomization was linked to sequential study number which subjects received as they were enrolled in the study (see Protocol, page 10)."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Blinded baclofen/placebo was provided in blister packs to the research assistant. Investigators had no access to this information. If a medical or other emergency necessitated breaking the blind, IDS personnel had to provide the identity of the medication to the medical study team member" (see protocol, page 10; NCT01980706).
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Blinded baclofen/placebo was provided in blister packs to the research assistant. Investigators had no access to this information. If a medical or other emergency necessitated breaking the blind, IDS personnel had to provide the identity of the medication to the medical study team member" (see protocol, page 10; NCT01980706).
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Information not reported; however, objective outcomes are unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	39% dropout. However, proportions and reasons were balanced across groups.
Selective reporting (reporting bias)	Low risk	Study protocol was available and all study's prespecified outcomes were provided.

Garbutt 2021-MD

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** USA **Setting:** Department of Psychiatry and the Bowles Center for Alcohol Studies (JCG, ABKP, CP, MS, RJ, LW), University of North Carolina (outpatients)
Participants	**Baseline characteristics** Baclofen: medium dose (37 participants) • Age (years): mean 45.0 (SD 10.4) • Gender: 20 (54.1%) male • Sample size: 37 • Race: Hispanic 1 (2.7%); white 30 (81.1%) • Marital status: 46.0% married • Educational level (years): 16.0 (SD 2.4) • Current use (g/day alcohol): mean 139.7 (SD 58.8) calculated by mean drinks/drinking day with 1 standard drink = 14 g • Comorbidity: 8 (21.6%) receiving antidepressants; Spielberger State-Trait Inventory: mean 35.65 (SD 9.67) • Duration of alcohol abuse: NR • Number of previous detoxifications: NR Placebo (20 participants) • Age (years): 47.1 (SD 9.6) • Gender: 50.0% male • Sample size: 20 • Race: Hispanic 0%; white 90.0% • Marital status: 40.0% married • Educational level (years): 14.8 (SD 2.4) • Current use (g/day alcohol): mean 130.34 (SD 54.6); calculated by mean drinks/drinking day with 1 standard drink = 14 g • Comorbidity: 40.0% receiving antidepressants; Spielberger State-Trait Inventory: mean 35.03 (SD 10.46) • Duration of alcohol abuse: NR • Number of previous detoxifications: NR **Inclusion criteria:** aged 21–65 years, diagnosis of DSM-IV alcohol dependence, to have a reported drinking pattern > 14 standard drinks (women) or 21 drinks (men)/week including ≥ 2 HDDs/week on average (men ≥ 5 standard drinks/day; women ≥ 4 standard drinks/day) during a consecutive 30-day period within the 90 days prior to screening based on Time-Line Follow Back interview and to express an interest in significantly reducing or stopping alcohol use. **Exclusion criteria:** significant medical illness, e.g. diabetes mellitus; significant psychiatric illness, e.g. bipolar disorder or were receiving psychotropic medication except for stable doses of antidepressants for ≥ 1 month, or had evidence of another SUD except for nicotine dependence or cannabis abuse. **Detoxification:** sobriety was not a requirement for randomisation.
Interventions	Baclofen medium dose (37 participants) + medical management • Dose: 90 mg/day

Garbutt 2021-MD *(Continued)*

- Duration of treatment: 16 weeks (2 weeks' uptitration, 12 weeks' medium-dose baclofen, 2 weeks' downtitration)
- Length of follow-up: 4 weeks

Placebo (40 participants) + medical management

- Dose: N/A
- Duration of treatment: 16 weeks (2 weeks' uptitration, 12 weeks' placebo, 2 weeks' downtitration)
- Length of follow-up: 4 weeks

Outcomes

Primary outcomes

- % HDD over the active treatment period
- % abstinent days over the active treatment period

Secondary outcomes

- Craving for alcohol evaluated using the Penn Alcohol Craving Scale
- % of responders (participants without heavy drinking in final 8 weeks of trial)
- % of CDT
- GGT
- Anxiety evaluated using the Spielberger State-Trait Inventory (STAI)

Identification

Sponsorship source: National Institute of Alcohol Abuse and Alcoholism Grant R21 AA020824

Author's name: James C Garbutt

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

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Notes

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In this review update, we divided the study into the 2 following arms:

- Garbutt 2021-LD: baclofen 30 mg/day (43 participants) vs placebo (20 participants)
- Garbutt 2021-MD: baclofen 90 mg/day (37 participants) vs placebo (20 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants who met criteria were randomized to either placebo, 30 mg/day baclofen or 90 mg/day baclofen using randomization blocks provided by Dr. Gallop [SAS Institute Inc.] (2015). "A minimization random assignment procedure were used to match subjects."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization blocks were prepared by the statistician and provided to the Investigational Drug Services. Randomization was linked to sequential study number which subjects received as they were enrolled in the study (see protocol, page 10; NCT01980706)."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Blinded baclofen/placebo was provided in blister packs to the research assistant. Investigators had no access to this information. If a medical or other emergency necessitated breaking the blind, IDS personnel had to provide the identity of the medication to the medical study team member" (see protocol, page 10; NCT01980706).

Garbutt 2021-MD *(Continued)*

Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Blinded baclofen/placebo was provided in blister packs to the research assistant. Investigators had no access to this information. If a medical or other emergency necessitated breaking the blind, IDS personnel had to provide the identity of the medication to the medical study team member" (see protocol, page 10; NCT01980706).
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Information not reported; however, objective outcomes are unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	39% dropout. However, proportions and reasons were balanced across groups.
Selective reporting (reporting bias)	Low risk	Study protocol available and all study's prespecified outcomes were provided.

Hauser 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** USA **Setting:** outpatients setting in 4 VA medical centres with established hepatology clinics (VA Long Beach, VA Minneapolis, VA Portland and VA San Diego)
Participants	**Baseline characteristics** Baclofen • Age (years): mean 55.7 (SD 7.1) • Gender: 85 (96.5%) male • 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: Abuse: 13 (14.8%); Dependence: 75 (85.2%); AUDIT-C: mean 8.50 (SD 2.41); number of days abstinent (prior 2 weeks): mean 5.4 (SD 4.6); number of drinks/week: mean 30.0 (SD 23.4); drinking days/week: mean 4.3 (SD 2.3); drinks/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); PTSD Checklist: mean 38.83 (SD 15.75); OCDS total: mean 20.55 (SD 9.54) Placebo • Age (years): mean 57.5 (SD 6.9)

Hauser 2017 *(Continued)*

- Gender: 92 (100%) male
- 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: Structured Clinical Interview for DSM-IV: Abuse 12 (13.0%); Dependence 80 (87.0%); AUDIT-C: mean 8.22 (SD 2.47); number of days abstinent (prior 2 weeks): mean 5.0 (SD 4.4); number of drinks/week: mean 33.6 (SD 24.5); drinking days/week: mean 4.5 (SD 2.2); drinks/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); PTSD Checklist: mean 35.80 (SD 16.35); OCDS total: mean 19.50 (SD 9.65).

Inclusion criteria: men or women, veterans aged ≥ 18 years; chronic HCV diagnosis with confirmed viraemia by polymerase chain reaction; an AUD (abuse or dependence) according to the DSM-IV or DSM-IV-TR, using the Structured Clinical Interview for the DSM-IV-TR; and ongoing alcohol use defined by > 7 standard drinks/week for each preceding 2 weeks or 1 HDD/week for each preceding 2 weeks (HDD: > 4 drinks in 1 day for men and > 3 drinks in 1 day for women). No requirements for any period of abstinence before entry
into study.

Exclusion criteria: presence of DSM-IV-TR (Structured Clinical Interview for DSM-IV) 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).

Detoxification: participants were required an ongoing alcohol use as defined by > 7 standard drinks/week for each preceding 2 weeks or 1 HDD/week for each preceding 2 weeks (HDD: > 4 drinks in 1 day for men and > 3 drinks in 1 day for women). No requirements for any period of abstinence before entry into study.

Interventions	**Intervention characteristics** Baclofen (88 participants) + BBCET • Dose: 30 mg (10 mg 3 times/day) • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks Placebo (92 participants) + 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 behaviour.
Outcomes	**Primary outcomes** • Abstinence from alcohol (% of days abstinent) **Secondary outcomes** • Complete abstinence between weeks 4 and 12 of study

Hauser 2017 *(Continued)*

- % of veterans who achieved no heavy drinking between weeks 4 and 12 of study
- Craving, symptoms of anxiety and depression and post-traumatic stress disorder
- Measurements of biomarkers of alcohol use (including ethyl glucuronide, ethyl sulphate and % CDT)

Identification	**Sponsorship source:** US Department of Veteran Affairs Clinical Sciences Research and Development Service – VA Merit **Author's name:** Peter Hauser **Institution:** Division of Mental Health, Long Beach VA Medical Center, Long Beach, California, USA **Email:** peter.hauser2@va.gov **Address:** Long Beach VA Medical Center, 300 Oceangate, Suite 700, Long Beach, California 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) Objective outcomes	Low risk	Stated as double-blind; quote: "Study medication and placebo were placed in identical capsules."
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) Objective outcomes	Low risk	Information not reported but objective outcomes unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Information not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	24% dropout from baclofen group and 21% dropout from placebo group. Reason reported and balanced between groups.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable.

Krupitskii 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** Russia **Setting:** Department of Narcology, Bekhterev St Petersburg Science Research Psychoneurological Institute
Participants	**Baseline characteristics** Baclofen • Age (years): 46.00 (SD 2.43) • Gender: 12 (75%) male • Sample size: 16 • Race: NR • Marital status: NR • Educational level (number of participants): 5 (31.3%) intermediate level; 11 (68.8%) higher level • Current use (number of participants): type of alcohol consumption: bingeing 10 (62.5%); constant 4 (25.0%); intermittent 2 (12.5%) • Comorbidity: NR Placebo • Age (years): 44.00 (SD 2.12) • Gender: 14 (87.5%) male • Sample size: 16 • Race: NR • Marital status: NR • Educational level (number of participants): 7 (43.75%) intermediate level; 10 (62.5%) higher level • Current use (number of participants): type of alcohol consumption: bingeing 11 (68.8%); constant 2 (12.5%); intermittent 3 (18.75%) • Comorbidity: NR **Inclusion criteria:** men and women aged 18–65 years with negative tests for alcohol in exhaled air, ICD-10 diagnoses of alcohol dependence, and abstention from alcohol consumption for ≥ 7 days (recovered alcohol withdrawal syndrome); pregnancy; women agreeing to use adequate contraception during study; provided 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; use of any other medication or psychotherapy for alcohol dependence (including so-called placebo therapy ('chemical protection'), 'coding', etc). **Detoxification:** individuals were required to be abstinent from alcohol prior to randomisation for ≥ 7 days (recovered alcohol withdrawal syndrome).
Interventions	**Intervention characteristics** Baclofen (16 participants) + CBT • Dose: 50 mg/day (25 mg in the morning and evening) • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks

Krupitskii 2017 *(Continued)*

	Placebo (16 participants) + CBT • Dose: N/A • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks
Outcomes	**Primary outcomes** • Remission (alcohol consumption): assessed using the CGI scale **Secondary outcomes** • 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) • GGT activity and compliance with medication (urine riboflavin)
Identification	**Sponsorship source:** Pharmaceutical Company Akrikhin **Author's name:** EM 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."
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) 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."

Krupitskii 2017 *(Continued)*

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."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear data reported about dropout from study.
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable.

Kumar 2020a

Study characteristics	
Methods	**Study design:** comparative open RCT **Country:** India
Participants	**Baseline characteristics** Baclofen • Age (years): mean 42.73 (SD 10.62) • Gender: 100% male • Sample size: 30 • Race: NR • Marital status: 27 (90%) married • Educational level (number of participants with > 10 years of education): 15 (50.%) • Current use: participants were detoxified before treatment • Comorbidity: excluded individuals with comorbid medical or psychiatric illness • Family history (number of participants with): 21 (70%) • Duration of alcohol dependence (years): 18.6 (SD 10.62) • Past de-addiction attempts (number of participants): 24 (80%) Acamprosate • Age (years): mean 39.67 (SD 9.88) • Gender: 29 (96.7%) male • Sample size: 30 • Race: NR • Marital status: 27 (90%) married • Educational level (number of participants with > 10 years of education): 24 (80%) • Current use: participants were detoxified before treatment • Comorbidity: excluded individuals with comorbid medical or psychiatric illness • Family history (number of participants with): 27 (90%) • Duration of alcohol dependence (years): 15.4 (SD 8.7) • Past de-addiction attempts (number of participants): 18 (60%) Naltrexone • Age (years): mean 38.47 (SD 10.86) • Gender: 100% male • Sample size: 30

Kumar 2020a *(Continued)*

- Race: NR
- Marital status (married): 26 (86.7%)
- Educational level (number of participants with > 10 years of education): 17 (56.7%)
- Current use: participants were detoxified before treatment
- Comorbidity: excluded individuals with comorbid medical or psychiatric illness
- Family history (number of participants with): 26 (86.7%)
- Duration of alcohol dependence (years): 15.7 (SD 10)
- Past de-addiction attempts (number of participants): 21 (70%)

Inclusion criteria: diagnosis of current alcohol dependence according to ICD-10 criteria.

Exclusion criteria: individuals with comorbid medical or psychiatric illness; participants were detoxified before treatment; use of other psychoactive substances.

Detoxification: participants started study after detoxification. Duration of detoxification not reported.

Interventions	Baclofen (30 participants) • Dose: 20 mg/day for first day and 40 mg/day subsequently for total duration of 6 consecutive months • Duration of treatment: 24 weeks • Participants had to purchase the baclofen • Length of follow-up: not provided Acamprosate (30 participants) • Dose: 333 mg 3 times/day for first day and then 1021.20 mg/day (mean bodyweight = 58.67 kg) subsequently for total duration of 6 consecutive months • Duration of treatment: 24 weeks • Participants had to purchase the acamprosate • Length of follow-up: not provided Naltrexone (30 participants) • Dose: 25 mg/day for first day and 50 mg/day subsequently for a total duration of 6 consecutive months • Duration of treatment: 24 weeks • Naltrexone was available free of cost • Length of follow-up: not provided
Outcomes	• Craving • Relapse risk • Medication adherence
Identification	
Notes	Participants had to purchase the baclofen and acamprosate treatment. Naltrexone was free of cost.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation of the participants was done using a computerised random table.
Allocation concealment (selection bias)	Unclear risk	No information provided.

Kumar 2020a *(Continued)*

Blinding of participants and personnel (performance bias) Objective outcomes	High risk	Open label study.
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Open label study.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment; however, the objective outcomes were unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	No blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	15% dropout from baclofen and acamprosate groups; 30% dropout from naltrexone group; unbalanced.
Selective reporting (reporting bias)	Unclear risk	Study protocol was unavailable.

Leggio 2015

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** USA **Setting:** Brown University Center for Alcohol and Addiction Studies (CAAS) and Roger Williams Medical Center (RWMC), Providence, Rhode Island, USA
Participants	**Baseline characteristics** Baclofen • Age (years): 47.9 (SD 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 (SD 27.3); ADS score: mean 15.8 (SD 8.4) • Comorbidity: NR Placebo • Age (years): 44.7 (SD 7.0) • Gender: 73% male • Sample size: (%): American Indian 0; Asian 7; white 67; African American 27; multiracial or others 0

Leggio 2015 *(Continued)*

	• Race: NR • Marital status: NR • Educational level: NR • Current use: HDDs: mean 70.5 (SD 26.7); ADS score: mean 13.5 (SD 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/day, women ≥ 4 SDUs/day on average) and cigarettes (≥ 10 cigarettes/day on average) during the last 90 days before screening; interested in receiving treatment for both drinking and smoking (either reducing or stopping both substances; or reducing 1 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 score > 10; history of hospitalisation for alcohol intoxication delirium, alcohol withdrawal delirium or seizure; participation in any research study for alcoholism or smoking treatment (or both) 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 childbearing potential and not using effective contraception. **Detoxification:** participants were heavy drinkers (men ≥ 5 SDUs/day, women ≥ 4 SDUs/day on average) and smokers (≥ 10 cigarettes/day on average) during the last 90 days before screening. They were interested in receiving treatment for both drinking and smoking (either reducing or stopping both substances; or reducing 1 substance and stopping the other).
Interventions	Baclofen (15 participants) + 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) • Dose: 80 mg/day • Duration of treatment: 12 weeks • Length of follow-up: 16 weeks Placebo (15 participants) + 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) • Dose: N/A • Duration of treatment: 12 weeks • Length of follow-up: 16 weeks
Outcomes	**Primary outcomes/secondary outcomes (no distinction)** • Drinking and smoking co-use as abstinence from alcohol-tobacco co-use • Duration of abstinence from alcohol or tobacco
Identification	**Sponsorship source:** grant from the ABMRF/The Foundation for Alcohol Research (Principal investigator: 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; Principal Investigator: 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

Leggio 2015 *(Continued)*

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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 [baclofen] or PLA [placebo] 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 [baclofen] at 80 mg/day (20 mg, q.i.d. [4 times/day]), or PLA [placebo] was placed into blister packs as opaque capsules containing drug and 25 mg riboflavine."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "BACL [baclofen] at 80 mg/day (20 mg, q.i.d. [4 times/day]), or PLA [placebo] was placed into blister packs as opaque capsules containing drug and 25 mg riboflavine."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Study described as double-blind. Outcome unlikely to be biased by lack or inadequate blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants blinded to treatments assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "while 30 individuals were eligible and randomized; 24 completed the study (Supplemental Fig. 1) [of the publication]." Comment: 20% dropout. Number of participants who dropped out from each group not reported. Figure 1 (of the publication) reporting participants lost to follow-up and those who completed the study is unreadable in the supplementary file so that it is impossible to give a judgement 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

Study characteristics

Methods

Study design: RCT

Study grouping: parallel group

Mishra 2010 *(Continued)*

	Country: India **Setting:** outpatients
Participants	**Baseline characteristics** Baclofen • Age (years): mean 41.28 (SD 6.83) • Gender: NR • Sample size: 25 • Race: NR • Marital status: 16 (64%) married • Educational level (number of participants with > 10 years of education): 13 (52%) • Current use: NR • Comorbidity: NR Acamprosate • Age (years): mean 42.08 (SD 7.07) • Gender: NR • Sample size: 24 • Race: NR • Marital status: 16 (68%) married • Educational level (number of participants with > 10 years of education): 15 (63%) • Current use: NR • Comorbidity: NR **Inclusion criteria:** aged 18–70 years; diagnosis of current alcohol dependence according to ICD-10 criteria; last alcohol intake reported to have taken place in the 24 hours 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. **Detoxification:** last alcohol intake reported to have taken place in the 24 hours preceding observation was an inclusion criterion.
Interventions	Baclofen (25 participants) • Dose: 15 mg/day for the first 3 days and 30 mg/day subsequently for a total duration of 3 consecutive months • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks Acamprosate (24 participants) • Dose: 666.66 mg 3 times/day for 3 consecutive months • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks
Outcomes	**Primary outcome/secondary outcome (no distinction)** • % of participants in abstinence • Craving score • Obsessive and compulsive drinking score • Safety and tolerability

Mishra 2010 *(Continued)*

Identification	**Sponsorship source:** NR **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	Quote: "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	Quote: "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	Low risk	No information provided. However, the objective outcomes are unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "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 unavailable. Primary and secondary outcomes not reported in the method section. Some results on specific outcomes were partially reported (e.g. for abstinence: quote: "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-LD

Study characteristics

Methods	**Study design:** RCT

Morley 2014-LD *(Continued)*

Study grouping: parallel group

Country: Australia

Setting: outpatients

Participants	**Baseline characteristics** Baclofen • Age (years): mean 47 • Gender: 35.5% male • Sample size: 14 • Race: NR • Marital status: NR • Educational level: NR • Current use (drinks/drinking days): 15.20 • Comorbidity: NR • Current use (HDDs/week): 4.35 Placebo • Age (years): mean 46 • Gender: 64% male • Sample size: 7 • Race: NR • Marital status: NR • Educational level: NR • Current use (drinks/drinking days): 14.30 • Comorbidity: NR • Current use (HDDs/week): 4.31 **Inclusion criteria:** men and women aged 18–60 years; DSM-IV criteria for current alcohol dependence; ability to understand and provide written informed consent; abstinence from alcohol for ≥ 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. **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 for 2 months were still considered eligible); concurrent use of anticonvulsants, insulin or oral hypoglycaemic; pregnant or breastfeeding; participation in any clinical trial within last 60 days; use of alcohol pharmacotherapy within last 60 days; court-mandated participation in alcohol treatment or pending incarceration. **Detoxification:** participants had to be abstinent from alcohol for ≥ 3 days prior to randomisation and resolution of any withdrawal symptoms.
Interventions	Baclofen (14 participants) + up to 9 sessions of BRENDA, a low-intensity psychosocial intervention • Dose: 30 mg/day (14 participants) • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks Placebo (7 participants) + up to 9 sessions of BRENDA, a low-intensity psychosocial intervention • Dose: N/A

Morley 2014-LD *(Continued)*

- Duration of treatment: 12 weeks
- Length of follow-up: 12 weeks

Outcomes	**Primary outcomes** • 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 mean number of drinks/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:** New South Wales Health Drug and Alcohol grant (PH, AB, KM). Conflict of interest statement. None declared **Author's name:** KC Morley **Institution:** NHMRC Centre of Research Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, University of Sydney, Sydney, New South Wales, Australia **Email:** kirsten.morley@sydney.edu.au **Address:** University of Sydney, Sydney, New South Wales 2006, Australia
Notes	In this review update, we divided the study into the 2 following arms: • Morley 2014-LD: baclofen 30 mg/day (14 participants) vs placebo (7 participants) • Morley 2014-MD: baclofen 60 mg/day (14 participants) vs placebo (7 participants)

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 place-

Morley 2014-LD *(Continued)*

		bo pills, which were identical in appearance, were also titrated upward and downward to maintain the double blind."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Information not reported; however, objective outcomes unlikely to be biased by lack or incomplete blinding of outcome assessor.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear 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 (χ [Chi]^2 = 1.5, P = 0.47) or medication compliance rates (χ^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 (χ^2 = 1.21, P = 0.55)." Comment: reason for discontinuation not reported for each group
Selective reporting (reporting bias)	Unclear 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 difference for either of these outcomes. Comment: selective reporting bias judged unlikely.

Morley 2014-MD

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** Australia **Setting:** outpatients
Participants	**Baseline characteristics** Baclofen • Age (years): mean 47 • Gender: 35.5% male • Sample size: 14 • Race: NR • Marital status: NR • Educational level: NR • Current use (drinks/drinking days): 15.20 • Comorbidity: NR • Current use (HDDs/week): 4.35 Placebo • Age (years): mean 46

Morley 2014-MD *(Continued)*

- Gender: 64% male
- Sample size: 7
- Race: NR
- Marital status: NR
- Educational level: NR
- Current use (drinks/drinking days): 14.30
- Comorbidity: NR
- Current use (HDDs/week): 4.31

Inclusion criteria: men and women aged 18–60 years; DSM-IV criteria for current alcohol dependence; ability to understand and provide written informed consent; abstinence from alcohol for ≥ 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.

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; pregnant or breastfeeding; participation in any clinical trial within last 60 days; use of alcohol pharmacotherapy within the last 60 days; court-mandated participation in alcohol treatment or pending incarceration.

Detoxification: participants had to be abstinent from alcohol for ≥ 3 days prior to randomisation and resolution of any withdrawal symptoms.

Interventions	Baclofen (14 participants) + up to 9 sessions of BRENDA, a low-intensity psychosocial intervention • Dose: 60 mg/day (14 participants) • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks Placebo (7 participants) + up to 9 sessions of BRENDA, a low-intensity psychosocial intervention • Dose: N/A • Duration of treatment: 12 weeks • Length of follow-up: 12 weeks
Outcomes	**Primary outcomes** • 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 mean number of drinks/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:** New South Wales Health Drug and Alcohol grant (PH, AB, KM). Conflict of interest statement. None declared **Author's name:** KC Morley **Institution:** NHMRC Centre of Research Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, University of Sydney, Sydney, New South Wales, Australia

Morley 2014-MD *(Continued)*

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Notes

In this review update, we divided the study into the 2 following arms:

- Morley 2014-LD: baclofen 30 mg/day (14 participants) vs placebo (7 participants)
- Morley 2014-MD: baclofen 60 mg/day (14 participants) vs placebo (7 participants)

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) Objective outcomes	Low risk	Information not reported; however, objective outcomes unlikely to be biased by lack or incomplete blinding of outcome assessor.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear 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 (χ [Chi]^2 = 1.5, P = 0.47) or medication compliance rates (χ^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 (χ^2 = 1.21, P = 0.55)." Comment: reason for discontinuation not reported for each group.

Morley 2014-MD *(Continued)*

Selective reporting (reporting bias)	Unclear 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 difference for either of these outcomes. Comment: selective reporting bias judged unlikely.

Morley 2018-LD

Study characteristics

Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** Australia **Setting:** outpatients
Participants	**Baseline characteristics** Baclofen: low dose (36 participants) • Age (years): mean 46.25 (SD 8.81) • Gender: 26 (77.78%) male • Sample size: 36 • Race: NR • Marital status: NR • Educational level (years of): 13.25 (SD 3.09) • Current use (drinks/drinking day (1 drink = 10 g)): mean 17.03 (SD 12.09) • Comorbidity: 21/36 (58%) receiving antidepressants • Comorbidity: 20/36 (56%) had alcoholic liver diseases • Duration of alcohol abuse (years): mean 16.86 (SD 10.44) • Number of previous detoxifications: NR Placebo (17 participants) • Age (years): 48.18 (SD 9.91) • Gender: 69.70% male • Race: NR • Marital status: NR • Educational level (years of): 14.23 (SD 2.87) • Current use (drinks/drinking day (1 drink = 10 g)): 14.10 (SD 7.04) • Comorbidity: 52% receiving antidepressants • Comorbidity: 55% had alcoholic liver diseases • Duration of alcohol abuse (years): 16.26 (SD 11.55) • Number of previous detoxifications: NR **Inclusion criteria:** alcohol dependence according to ICD-10 criteria; aged 18–75 years; adequate cognition and English language skills to give valid consent and complete research interviews; willingness to give written informed consent; abstinence from alcohol for 3–21 days before enrolment; resolution of any clinically evident alcohol withdrawal (on the Clinical Institute Withdrawal Assessment for alcohol); < 48 hours after ceasing any diazepam required for withdrawal management. **Exclusion criteria:** active major mental disorder associated with psychosis or significant suicide risk; pregnant or breastfeeding; concurrent use of any psychotropic medication other than antidepressants (provided these are taken at stable doses for ≥ 2 months); unstable substance use; clinical evidence of

Morley 2018-LD *(Continued)*

	persisting hepatic encephalopathy (drowsiness, sleep inversion or asterixis); pending incarceration; lack of stable housing; peptic ulcer; unstable diabetes mellitus. **Detoxification:** participants had to be abstinent from alcohol for 3–21 days before enrolment.
Interventions	Baclofen low dose (36 participants) + medical care + brief adherence therapy • Dose: 30 mg/day • Duration of treatment: 12 weeks • Length of follow-up: NR Placebo (17 participants) + medical care + brief adherence therapy • Dose: N/A • Duration of treatment: 12 weeks • Length of follow-up: NR
Outcomes	**Primary outcomes** • Time to first lapse (1 standard drink = 10 g of absolute alcohol) • Time to relapse (≥ 4 drinks for women, ≥ 5 drinks for men) • Mean drinks per drinking day • Number of HDDs • % days abstinent • % participants abstinent **Secondary outcomes** • Alcohol dependence severity • Craving • Depression, Anxiety and Stress Scale scores for depression, anxiety and stress • Sleep disturbance • Liver function tests • Frequency of adverse events • Treatment adherence
Identification	**Sponsorship source:** grant from the National Health and Medical Research Council of Australia (PSH, AB, KCM). Conflict of interest statement: none declared **Author's name:** KC Morley **Institution:** NHMRC Centre of Research Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, University of Sydney, Sydney, New South Wales, Australia **Email:** kirsten.morley@sydney.edu.au **Address:** University of Sydney, Sydney, New South Wales 2006, Australia **Trial registration:** ClinicalTrials.gov: NCT01711125
Notes	In this review update, we divided the study into the 2 following arms: • Morley 2018-LD: baclofen 30 mg/day (36 participants) vs placebo (17 participants) • Morley 2018-MD: baclofen 75 mg/day (35 participants) vs placebo (16 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement

Morley 2018-LD *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Participants randomly were allocated 1:1:1. Allocation was made by a computer-generated block randomisation sequence that was developed by an independent team at a neighbouring institution (National Drug and Alcohol Research Centre, University of New South Wales), and then sent to the hospital clinical trials pharmacists."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was made by a computer-generated block randomisation sequence that was developed by an independent team at a neighbouring institution (National Drug and Alcohol Research Centre, University of New South Wales), and then sent to the hospital clinical trials pharmacists."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Participants, clinicians and research team members were masked. The integrity of the double-blind procedure was assessed by obtaining a prediction from each client as to their allocated treatment and, in addition, a prediction from the therapist and researcher (active or placebo)."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Participants, clinicians and research team members were masked. The integrity of the double-blind procedure was assessed by obtaining a prediction from each client as to their allocated treatment and, in addition, a prediction from the therapist and researcher (active or placebo)."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Research team members were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	27% dropped out of baclofen group and 31% from placebo group, reasons for withdrawal provided. Quote: "in the case of primary outcomes (survival and multivariate), we employed sensitivity analyses to compare the results from raw data with those from multiple imputation (with ten iterations). Raw data are presented given that analyses revealed no change between the results for raw data v. using multiple imputation. Mixed models were also used where possible."
Selective reporting (reporting bias)	Unclear risk	Study protocol was unavailable.

Morley 2018-MD

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** Australia **Setting:** outpatients
Participants	**Baseline characteristics** Baclofen: medium dose (35 participants) • Age (years): mean 50.71 (SD 10.59)

Morley 2018-MD *(Continued)*

- Gender: 25 (71.43%) male
- Sample size: 35
- Race: NR
- Marital status: NR
- Educational level (years of): 12.7 (SD 3.75)
- Current use (drinks/drinking day (1 drink = 10 g)): mean 13.78 (SD 9.47)
- Comorbidity: 19/35 (54%) receiving antidepressants
- Comorbidity: 20/35 (57%) had alcoholic liver diseases
- Duration of alcohol abuse (years): mean 18.74 (SD 12.33)
- Number of previous detoxifications: NR

Placebo (16 participants)

- Age (years): 48.18 (SD 9.91)
- Gender: 69.70% male
- Race: NR
- Marital status: NR
- Educational level (years of): 14.23 (SD 2.87)
- Current use (drinks/drinking day (1 drink = 10 g)): 14.10 (SD 7.04)
- Comorbidity: 52% receiving antidepressants
- Comorbidity: 55% had alcoholic liver diseases
- Duration of alcohol abuse (years): 16.26 (SD 11.55)
- Number of previous detoxifications: NR

Inclusion criteria: alcohol dependence according to ICD-10 criteria; aged 18–75 years; adequate cognition and English language skills to give valid consent and complete research interviews; willingness to give written informed consent; abstinence from alcohol for 3–21 days before enrolment; resolution of any clinically evident alcohol withdrawal (on the Clinical Institute Withdrawal Assessment for alcohol; < 48 hours after ceasing any diazepam required for withdrawal management.

Exclusion criteria: active major mental disorder associated with psychosis or significant suicide risk; pregnant or breastfeeding; concurrent use of any psychotropic medication other than antidepressants (provided these are taken at stable doses for ≥ 2 months); unstable substance use; clinical evidence of persisting hepatic encephalopathy (drowsiness, sleep inversion or asterixis); pending incarceration; lack of stable housing; peptic ulcer; unstable diabetes mellitus.

Detoxification: participants had to be abstinent from alcohol for 3–21 days before enrolment.

Interventions	Baclofen medium dose (35 participants) + medical care + brief adherence therapy • Dose: 75 mg/day • Duration of treatment: 12 weeks • Length of follow-up: NR Placebo (16 participants) + medical care + brief adherence therapy • Dose: N/A • Duration of treatment: 12 weeks • Length of follow-up: NR
Outcomes	**Primary outcomes** • Time to first lapse (1 standard drink = 10 g of absolute alcohol) • Time to relapse (≥ 4 drinks for women, ≥ 5 drinks for men) • Mean drinks per drinking day • Number of HDDs • % days abstinent

Morley 2018-MD *(Continued)*

- % patients abstinent

Secondary outcomes

- Alcohol dependence severity
- Craving
- Depression, Anxiety and Stress Scale scores for depression, anxiety and stress
- Sleep disturbance
- Liver function tests
- Frequency of adverse events
- Treatment adherence

Identification	**Sponsorship source:** the study was supported by a grant from the National Health and Medical Research Council of Australia (P.S.H., A.B., K.C.M.). Conflict of interest statement. None declared **Author's name:** KC Morley **Institution:** NHMRC Centre of Research Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, University of Sydney, Sydney, New South Wales, Australia **Email:** kirsten.morley@sydney.edu.au **Address:** University of Sydney, Sydney, New South Wales 2006, Australia **Trial registration:** ClinicalTrials.gov: NCT01711125
Notes	In this review update, we divided the study into the 2 following arms: • Morley 2018-LD: baclofen 30 mg/day (36 participants) vs placebo (17 participants) • Morley 2018-MD: baclofen 75 mg/day (35 participants) vs placebo (16 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants randomly were allocated 1:1:1. Allocation was made by a computer-generated block randomisation sequence that was developed by an independent team at a neighbouring institution (National Drug and Alcohol Research Centre, University of New South Wales), and then sent to the hospital clinical trials pharmacists."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was made by a computer-generated block randomisation sequence that was developed by an independent team at a neighbouring institution (National Drug and Alcohol Research Centre, University of New South Wales), and then sent to the hospital clinical trials pharmacists."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Participants, clinicians and research team members were masked. The integrity of the double-blind procedure was assessed by obtaining a prediction from each client as to their allocated treatment and, in addition, a prediction from the therapist and researcher (active or placebo)."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Participants, clinicians and research team members were masked. The integrity of the double-blind procedure was assessed by obtaining a prediction from each client as to their allocated treatment and, in addition, a prediction from the therapist and researcher (active or placebo)."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Research team members were blinded to treatment assignment.

Morley 2018-MD *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	31% and 27% dropped out from placebo and baclofen group respectively, reason for withdrawal provided. Quote: "in the case of primary outcomes (survival and multivariate), we employed sensitivity analyses to compare the results from raw data with those from multiple imputation (with ten iterations). Raw data are presented given that analyses revealed no change between the results for raw data v. using multiple imputation. Mixed models were also used where possible."
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable.

Muller 2015

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** Germany **Setting:** outpatients
Participants	**Baseline characteristics** Baclofen • Age (years): mean 47.4 (SD 7) • Gender: 20 (71.4%) male • Sample size: 28 • Race: NR • Marital status: 5 (17.9%) married • Educational level (number with university degree): 4 (14.3%) • Current use (alcohol consumption/day (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 • Age (years): mean 45.6 (SD 7) • Gender: 19 (67.9%) male • Sample size: 28 • Race: NR • Marital status: 11 (39.3) married • Educational level (number with university degree): 10 (35.7%) • Current use (alcohol consumption/day (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 to < 65 years; diagnosis of alcohol dependence according to ICD-10 and DSM-IV-TR; alcohol consumption of ≥ 2 HDDs/week on average (men ≥ 5 drinks/day; women < 4 drinks/

Muller 2015 *(Continued)*

	day; 1 standard drink = 12 g absolute alcohol) and a mean overall alcohol intake of ≥ 21 drinks/week (men) and ≥ 14 drinks/week (women) during the 4 weeks before detoxification; completed inpatient or outpatient detoxification before randomisation; last alcohol consumption within 7–21 days 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 or currently breastfeeding (or both); intolerance to baclofen; terminal renal failure; ALT or AST values 5 times the ULN, bilirubin 41.9 mg/dL, international normalised ratio 41.6; gastrointestinal ulcers; treatment mandated by a legal authority. **Detoxification:** a complete inpatient or outpatient detoxification before randomisation was an inclusion criterion. However, participants had their last alcohol consumption within 7–21 days before randomisation.
Interventions	Baclofen (28 participants) + up to 9 medical management sessions that focused on psychoeducation and enhancement of motivation and adherence • Dose: 30–270 mg/day; mean dose during high-dose phase: 180 mg • Duration of treatment: 12 weeks' high-dose phase • Length of follow-up: 12 weeks Placebo (28 participants) + up to 9 Medical Management sessions that focus on psychoeducation and enhancement of motivation and adherence • Dose: N/A • Duration of treatment: 12 weeks' placebo phase • Length of follow-up: 12 weeks
Outcomes	**Primary outcomes** • Total abstinence and cumulative abstinence duration during the high-dose baclofen/placebo phase. Abstinence defined as negative subjective report plus negative breathalyzer test and level of CDT within the normal range, or, if increased, lower compared to baseline level **Secondary outcomes** • 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	**Trial Registration Identifier:** BACLAD study at ClinicalTrials.gov: NCT01266655. **Sponsorship source:** supported by the German Research Foundation (DFG; Cluster of Excellence EXC 257) **Author's name:** Christian A Müllera **Institution:** Department of Psychiatry, Campus Charité Mitte, Charité, Universitätsmedizin Berlin, Germany **Email:** ch.mueller@charite.de **Address:** Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
Notes	
Risk of bias	

Muller 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
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. Quote: "Participants received baclofen or placebo in identical capsules in a dose of 5 mg 3 times/d. 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) Subjective outcomes	Low risk	Stated as double-blind. Quote: "Participants received baclofen or placebo in identical capsules in a dose of 5 mg 3 times/d. 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 outcome assessment (detection bias) Objective outcomes	Low risk	Quote: "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 outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment. Quote: "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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% lost at follow-up; balanced between groups
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable.

Ponizovsky 2015

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** Israel **Setting:** outpatients

Ponizovsky 2015 *(Continued)*

Participants	**Baseline characteristics** Baclofen • Age (years): mean 42.6 (SD 9.6) • Gender: 24 (75%) male • Sample size: 32 • Race (immigrants): 66% • Marital status: 48% • Educational level (years of): mean 11.5 (SD 1.2) • Current use (duration of harmful alcohol consumption in years): mean 15.1 • Comorbidity: NR • Current use (% HDDs during the 6 weeks before the enrolment): 66% • Current use (drinks/drinking days): mean 7.4 (SD 1.5) Placebo • Age (years): mean 44.7 (SD 8.7) • Gender: 24 (75%) male • Sample size: 32 • Race (immigrants): 59% • Marital status: 59% • Educational level (years of): mean 11.7 (SD 3.7) • Current use (duration of harmful alcohol consumption in years): mean 14.1 • Comorbidity: NR • Current use (% HDDs during the 6 weeks before the enrolment): 69% • Current use (drinks/drinking days): mean 8.2 (SD 1.6) **Inclusion criteria:** aged 18–60 years; ICD-10 diagnosis of AD; sought treatment to stop alcohol consumption; alcohol intake ≥ 2 HDDs/week (men ≥ 5 drinks/day; women ≥ 4 drinks/day) and mean 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 per month on average; reliable family member able to help with drug administration and monitoring. Study population defined as mild AUD according to DSM-5 criteria. **Exclusion criteria:** 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. **Detoxification:** a detoxification treatment for acute alcohol withdrawal syndrome (requiring hospitalisation) during the month before randomisation was an exclusion criterion.
Interventions	Baclofen (32 participants) + 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 treatment protocol, the dose of baclofen was decreased to 15 mg/day in 3 divided doses. • Duration of treatment: 12 weeks • Length of follow-up: 52 weeks Placebo (32 participants) + 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

Ponizovsky 2015 *(Continued)*

Outcomes	**Primary outcomes** • Proportion of HDDs (% HDD) • Proportion of total abstinent days (%) • Assessed at week 6 (T1), week 12 (T2) of the medication period and week 26 (T3) and week 52 (T4) of the follow-up period (these proportions were calculated on the basis of a participant's self-report of alcohol intake as the mean number of standard drinks/day for each period by the Time Line Follow Back) **Secondary outcomes** • Craving (OCDS), depression (abridged BDI), emotional distress (12 item General Health Questionnaire) • Self-efficacy (General Self-Efficacy Scale) • Perceived social support (Multidimensional Scale of Perceived Social Support) • Quality of life at T1, T2, T3 and T4 (Quality of Life Enjoyment and Satisfaction Questionnaire)
Identification	**Sponsorship source:** Israeli Anti-Drug Authority Grant #535-28. AM Ponizovsky was supported in part by the Ministry of Immigrant Absorption **Author's name:** AM Ponizovsky **Institution:** Research Unit, Mental Health Services, Ministry of Health, Jerusalem, Israel **Email:** alexpon8@gmail.com **Address:** Ministry of Health 39 Yirmiyahu St, PO Box 1176, Jerusalem 9446724, Israel
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)	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."
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) Objective outcomes	Low risk	Not reported whether the outcome assessor was blinded. However, objective outcomes are unlikely to be biased by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment assignment.

Ponizovsky 2015 *(Continued)*

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)	Unclear risk	Study protocol unavailable.

Reynaud 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Country:** France **Setting:** outpatients
Participants	**Baseline characteristics** Baclofen • Age (years): mean 49 (SD 10.7) • Gender: 118 (76.1%) male • Sample size: 158 • Race: NR • Marital status: NR • Educational level: NR • Current use (duration of alcohol dependence in years): mean 12.8 • Current use (% HDDs/1 month): mean 17.9 (SD 10.2) • Current use (g/day): mean 95.5 (SD 75.6) • Comorbidity (number of participants with): anxiety: 23 (14.8%); depression: 51 (23.9%) Placebo • Age (years): mean 49.8 (SD 9.8) • Gender: 107 (69%) male • Sample size: 162 • Race: NR • Marital status: NR • Educational level: NR • Current use (duration of alcohol dependence in years): mean 14.2 (SD 9.4) • Current use (% HDDs/1 month): mean 17.6 (SD 10) • Current use (g/day): mean 93.6 (SD 65.5) • Comorbidity (number of participants with): anxiety 16 (10.3%); depression 55 (35.5%) **Inclusion criteria:** adult men or non-pregnant, non-breastfeeding women, with a diagnosis of alcohol dependence according to DSM-IV, who had experienced ≥ 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 participants needing inpatient detoxification to participate in the study. Comorbid psychiatric diseases were assessed according to the investigator's judgement.

Reynaud 2017 *(Continued)*

	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 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. **Detoxification:** participants had been fully abstinent for 3–14 days before randomisation; this range of 3–14 days was established to allow participants needing inpatient detoxification to participate in the study.
Interventions	Baclofen (158 participants) + BRENDA (a low-intensity psychosocial intervention) sessions were provided during each visit to support participants in changing their behaviour and to enhance adherence to treatment. • Dose: a 7-week titration period during which the daily dose was gradually increased from 1 to 9 tablets; initial dose was provided twice a day (10 mg morning and evening) for 2 days, then 3 times/day and dose increased by 10 mg every 4 days; a 17-week maintenance period at dose reached at end of the titration period and a 2-week tapering-off period; up to 180 mg/day; mean dose administered by participants: 153.5 mg/day • Duration of treatment: 26 weeks • Length of follow-up: 30 weeks Placebo (162 participants) + BRENDA (a low-intensity psychosocial intervention) sessions were provided during each visit to support participants in changing their behaviour and to enhance adherence to treatment. • Dose: N/A • 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/day) • HDD (days/month) to month 6, change from baseline • Craving: OCDS change from baseline • CGI-S, change from baseline • CGI-I, change from baseline • Anxiety and depression: Hospital Anxiety and Depression scale, change from baseline • 9-item Alcohol Dependence Quality of Life, change from baseline • Adverse events
Identification	**Sponsorship source:** study was supported by Ethypharm SAS **Author's name:** Michel Reynaud **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	

Reynaud 2017 *(Continued)*

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. 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."
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."
Incomplete outcome data (attrition bias) All outcomes	Low 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." Quote: "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)	Unclear risk	Study protocol unavailable.

Rigal 2020

Study characteristics	
Methods	**Study design:** double-blind RCT **Country:** France
Participants	**Baseline characteristics** Baclofen • Age (years): median 46.0 (IQR 40–54) • Gender: 115 (71%) male • Sample size: 162 • Race: NR • Marital status: NR • Educational level: NR • Current use (daily alcohol consumption in g): mean 129 (SD 89) • Comorbidity: 37 (23%) attempted suicide Placebo • Age (years): median 47 (IQR 40–55) • Gender: 109 (69%) male • Sample size: 158 • Race: NR • Marital status: NR • Educational level: NR • Current use (daily alcohol consumption in g): mean 129 (SD 78) • Comorbidity: 30 (19%) attempted suicide **Inclusion criteria:** aged 18–65 years; at high-risk drinking during last 3 months (at least twice per month); for women, > 40 g/day or > 280 g/week or > 40 g in 1 session; for men, > 60 g/day or > 420 g/week, or > 60 g at in 1 session. **Exclusion criteria:** pregnant, nursing, or of childbearing age and not using effective contraception; serious psychiatric illness (psychosis, notably schizophrenia and bipolar disorders); sufficiently serious organic pathology interfering with his/her inclusion in the study in the investigator's opinion. **Detoxification:** sobriety was not required.
Interventions	Baclofen (162 participants) • Dose: 15–300 mg/day; median dose administered by participants: 180 mg/day • Duration of treatment: 12 months • Length of follow-up: 12 months Placebo (158 participants) • Dose: N/A • Duration of treatment: 12 months • Length of follow-up: 12 months
Outcomes	**Primary outcomes** • Null or low-risk alcohol consumption according to WHO criteria during month 12 (mean daily consumption ≤ 20 g/day for women or ≤ 40 g/day for men) **Secondary outcomes**

Rigal 2020 *(Continued)*

- Mean daily alcohol consumption throughout each month
- Number of days per month of abstinence
- Number of days per month of heavy drinking as a day alcohol consumption > 40 g for women

Identification		
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent statistician provided a computer generated randomization list, with permuted blocks of size 4 stratified by primary care center."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed by use of a Web-based inclusion system."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Patients, treating physicians, data collectors and statisticians were blinded to treatment allocation." Quote: "The appearance, size, weight and taste of the placebo tablets were identical to those of the 10-mg baclofen tablets and the scored tablets were provided in identical containers."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Patients, treating physicians, data collectors and statisticians were blinded to treatment allocation." Quote: "The appearance, size, weight and taste of the placebo tablets were identical to those of the 10-mg baclofen tablets and the scored tablets were provided in identical containers."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote: "Patients, treating physicians, data collectors and statisticians were blinded to treatment allocation."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Patients, treating physicians, data collectors and statisticians were blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Efficacy analyses were performed in the intent-to-treat (ITT) population (i.e. all randomized patients were analyzed in their randomization arm whatever the treatment actually received or any other deviation to the protocol). Safety analyses were performed in the ITT population and in the safety population, in which patients received baclofen whatever their randomization arm in the 'baclofen' group. We used multiple imputation of missing alcohol consumption during follow-up."
Selective reporting (reporting bias)	Unclear risk	Study protocol unavailable.

ADS: Alcohol Dependence Scale; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUD: alcohol use disorder; AUDIT-C: Alcohol Use Disorders Identification Test; BBCET: brief behavioral compliance enhancement treatment; BDI: Beck's Depression Inventory; BSI: Brief Symptom Inventory; CBT: cognitive behavioural therapy; CDT: carbohydrate-deficient transferrin; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th revision (text revision); DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GGT: gamma-glutamyl transferase; HCV: hepatitis C virus; HDD: heavy drinking day; ICD: International Classification of Diseases; IQR: interquartile range; N/A: not applicable; NIH: National Institutes of Health; 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 study < 12 weeks.
Flannery 2004	Study design not in the inclusion criteria: uncontrolled preliminary study on 14 participants.
Gupta 2017	Benfothiamine used as inactive medication for the control group has been found to have an effect on both alcohol consumption and anxiety (Manzardo 2013; Manzardo 2015).
Jose 2019	Study duration < 12 weeks.
Kumar 2020b	Both groups received baclofen.
Leggio 2011	Study objective not in the inclusion criteria: human laboratory study to investigate putative behavioural mechanisms by which baclofen reduces drinking.
Leggio 2013	Study objective not in the inclusion criteria: human laboratory study to investigate putative behavioural mechanisms by which baclofen reduces drinking.

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

Karthik 2018

Methods	
Participants	42 participants with severe alcohol dependence, after detoxification
Interventions	Baclofen 60–80 mg/day (16 participants) vs naltrexone 50–100 mg/day (16 participants)
Outcomes	Carving, abstinence
Notes	Conference abstract; insufficient information provided about study design and length of follow-up.

Sharma 2012

Methods	Randomised, double-blind, controlled trial
Participants	54 participants
Interventions	Baclofen 10 mg/day vs 12 mg/day for 12 weeks (18 participants) vs placebo (18 participants)
Outcomes	Daily number of drinks
Notes	Conference abstract without enough usable data

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

CTRI/2011/11/002154

Study name	CTRI/2011/11/002154
Methods	Randomised, phase III, parallel-group, placebo-controlled trial
Participants	180 men or women aged 21–75 years, meeting DSM-IV-TR criteria for current AD
Interventions	Baclofen vs placebo
Outcomes	• Time to relapse • Time to first lapse • Number of abstinent days • Number of drinks per drinking day • Number HDDs • Liver biomarkers • Alcohol dependence severity • Extent of craving for alcohol • Compliance to treatment • Compliance to study • Investigator's global impression of change and participant's global impression of change Safety variables • 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	

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 versus placebo (all studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Relapse: return to any drinking at end of treatment	12	1057	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
1.2 Frequency of use: % days abstinence at end of treatment	16	1273	Mean Difference (IV, Random, 95% CI)	9.07 [3.30, 14.85]

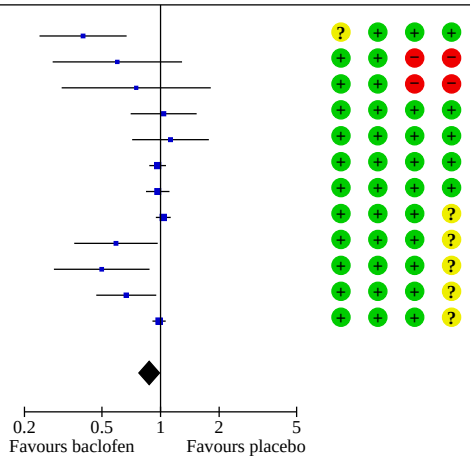
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Frequency of use: heavy drinking days at end of treatment	13	840	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.48, 0.11]
1.4 Amount of use: drinks per drinking days at end of treatment	9	392	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.20, 0.30]
1.5 Adverse events: number of participants with at least one adverse event at end of treatment	10	738	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
1.6 Dropouts at end of treatment	17	1563	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.03]
1.7 Dropouts due to adverse events	16	1499	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.89, 2.18]
1.8 Craving	17	1275	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.37, 0.04]
1.9 Anxiety	15	1127	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.14, 0.11]
1.10 Depression	12	1029	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.12, 0.27]
1.11 Adverse events: fatigue, tiredness	13	1311	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.09, 1.59]
1.12 Adverse events: insomnia	11	1100	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.62, 1.35]
1.13 Adverse events: pain (diverse)	3	98	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.19, 1.33]
1.14 Adverse events: vertigo, dizziness	15	1415	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.35, 2.13]
1.15 Adverse events: constipation	11	1124	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.61, 1.47]
1.16 Adverse events: somnolence, sleepiness, drowsiness or sedation	17	1543	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.19, 1.56]
1.17 Adverse events: muscle pain	5	594	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.38, 2.25]
1.18 Adverse events: dry mouth	8	933	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.01, 3.18]
1.19 Adverse events: nausea	10	1060	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.88, 1.54]
1.20 Adverse events: skin rash	7	446	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.33, 1.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21 Adverse events: headaches	13	1304	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.04, 1.64]
1.22 Adverse events: paraesthesia/numbness	6	914	Risk Ratio (M-H, Random, 95% CI)	2.87 [1.17, 7.06]
1.23 Adverse events: diarrhoea	3	816	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.40, 1.02]
1.24 Adverse events: tinnitus	2	496	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.16, 20.16]
1.25 Adverse events: muscle spasm/rigidity	3	552	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.07, 3.52]
1.26 Adverse events: hyperhidrosis	3	816	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.89, 2.51]
1.27 Adverse events: nasopharyngitis	4	872	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.40, 1.95]
1.28 Adverse events: decrease appetite/anorexia	3	816	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.31, 1.75]
1.29 Adverse events: dysgeusia/ageusia	3	816	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.57, 5.24]
1.30 Adverse events: tremor	3	816	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.42, 1.15]
1.31 Adverse events: weakness	3	552	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.70, 2.01]
1.32 Adverse events: vomiting	3	816	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.66, 1.71]
1.33 Adverse events: urinary frequency	4	340	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.45, 2.68]
1.34 Adverse events: shortness of breath	2	104	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.04, 22.31]

Analysis 1.1. Comparison 1: Baclofen versus placebo (all studies), Outcome 1: Relapse: return to any drinking at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	12	42	30	42	4.3%	0.40 [0.24 , 0.67]
Addolorato 2011-LD	6	14	5	7	2.2%	0.60 [0.28 , 1.29]
Addolorato 2011-MD	6	14	4	7	1.7%	0.75 [0.31 , 1.81]
Beraha 2016-HD	33	58	17	31	6.4%	1.04 [0.70 , 1.53]
Beraha 2016-LD	18	31	16	31	5.2%	1.13 [0.71 , 1.77]
Garbutt 2021-LD	41	43	20	20	16.3%	0.97 [0.88 , 1.07]
Garbutt 2021-MD	34	37	19	20	14.8%	0.97 [0.84 , 1.11]
Hauser 2017	82	88	83	92	16.7%	1.03 [0.95 , 1.13]
Morley 2018-LD	15	36	12	17	4.6%	0.59 [0.36 , 0.97]
Morley 2018-MD	12	35	11	16	3.7%	0.50 [0.28 , 0.88]
Muller 2015	16	28	24	28	7.2%	0.67 [0.47 , 0.95]
Reynaud 2017	139	158	145	162	17.0%	0.98 [0.91 , 1.06]
Total (95% CI)		**584**		**473**	**100.0%**	**0.87 [0.77 , 0.99]**
Total events:	414		386			

Heterogeneity: Tau² = 0.02; Chi² = 40.60, df = 11 (P < 0.0001); I² = 73%
Test for overall effect: Z = 2.16 (P = 0.03)
Test for subgroup differences: Not applicable

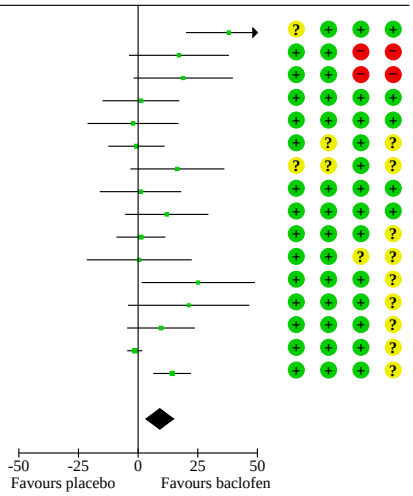


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 1.2. Comparison 1: Baclofen versus placebo (all studies), Outcome 2: Frequency of use: % days abstinence at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Addolorato 2007	74.7	41.5	42	36.7	42.4	42	5.6%	38.00 [20.06 , 55.94]
Addolorato 2011-LD	93.15	14.5	14	76.04	26.36	7	4.7%	17.11 [-3.84 , 38.06]
Addolorato 2011-MD	94.94	13.7	14	76.04	26.36	7	4.7%	18.90 [-1.90 , 39.70]
Beraha 2016-HD	70.98	35.89	58	69.82	37.41	31	6.2%	1.16 [-14.93 , 17.25]
Beraha 2016-LD	67.68	39.11	31	69.82	37.41	31	5.2%	-2.14 [-21.19 , 16.91]
Garbutt 2010a	49.9	27.9	40	50.6	25.9	40	8.0%	-0.70 [-12.50 , 11.10]
Garbutt 2010b1	62.6	30.68	20	46.15	32.82	20	5.0%	16.45 [-3.24 , 36.14]
Garbutt 2021-LD	48	30.68	43	47	32.82	20	5.9%	1.00 [-16.06 , 18.06]
Garbutt 2021-MD	59	30.68	37	47	32.82	20	5.7%	12.00 [-5.45 , 29.45]
Hauser 2017	32.3	35.633419	88	31.1	34.525362	92	8.7%	1.20 [-9.06 , 11.46]
Krupitskii 2017	94.2	30.68	16	93.7	32.82	16	4.4%	0.50 [-21.51 , 22.51]
Morley 2018-LD	68.54	35.4	36	43.35	43.658676	17	4.0%	25.19 [1.43 , 48.95]
Morley 2018-MD	64.56	41.412558	35	43.35	43.658676	16	3.6%	21.21 [-4.20 , 46.62]
Muller 2015	49.35	29.17	28	39.76	24.94	28	7.0%	9.59 [-4.63 , 23.81]
Ponizovsky 2015	46.1	5.3	32	47.5	7.5	32	11.6%	-1.40 [-4.58 , 1.78]
Rigal 2020	53.57	32.29	162	39.29	39.29	158	9.8%	14.28 [6.39 , 22.17]
Total (95% CI)			**696**			**577**	**100.0%**	**9.07 [3.30 , 14.85]**

Heterogeneity: Tau² = 72.19; Chi² = 43.69, df = 15 (P = 0.0001); I² = 66%
Test for overall effect: Z = 3.08 (P = 0.002)
Test for subgroup differences: Not applicable

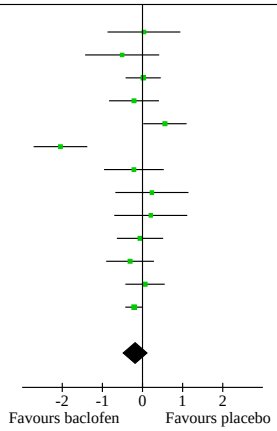


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 1.3. Comparison 1: Baclofen versus placebo (all studies), Outcome 3: Frequency of use: heavy drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D
Addolorato 2011-LD	1.67	5.2	14	1.5	2.83	7	5.7%	0.04 [-0.87 , 0.94]	+	+	−	−
Addolorato 2011-MD	0.5	1.24	14	1.5	2.83	7	5.6%	-0.51 [-1.43 , 0.42]	+	+	−	−
Garbutt 2010a	25.9	23.2	40	25.5	23.6	40	9.6%	0.02 [-0.42 , 0.46]	+	?	+	?
Garbutt 2010b1	13.25	5.28	20	14.4	5.35	20	7.9%	-0.21 [-0.83 , 0.41]	?	?	+	?
Garbutt 2021-LD	42	5.28	43	39	5.35	20	8.6%	0.56 [0.02 , 1.10]	+	+	+	+
Garbutt 2021-MD	28	5.28	37	39	5.35	20	7.5%	-2.05 [-2.71 , -1.38]	+	+	+	+
Krupitskii 2017	0.4	0.4	14	0.5	0.5	14	6.9%	-0.21 [-0.96 , 0.53]	+	+	?	?
Morley 2014-LD	2.07	3.134835	14	1.36	2.355456	7	5.7%	0.23 [-0.68 , 1.14]	+	+	?	?
Morley 2014-MD	1.89	2.519992	14	1.36	2.355456	7	5.7%	0.21 [-0.70 , 1.12]	+	+	?	?
Morley 2018-LD	2.28	2.89	36	2.46	2.77	17	8.3%	-0.06 [-0.64 , 0.51]	+	+	+	?
Morley 2018-MD	1.65	2.48	35	2.46	2.77	16	8.1%	-0.31 [-0.90 , 0.28]	+	+	+	?
Ponizovsky 2015	20.1	2.7	32	19.9	3.5	32	9.1%	0.06 [-0.43 , 0.55]	+	+	+	?
Rigal 2020	6	9	162	8	10	158	11.4%	-0.21 [-0.43 , 0.01]	+	+	+	?
Total (95% CI)			**475**			**365**	**100.0%**	**-0.18 [-0.48 , 0.11]**				

Heterogeneity: Tau² = 0.19; Chi² = 41.40, df = 12 (P < 0.0001); I² = 71%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable

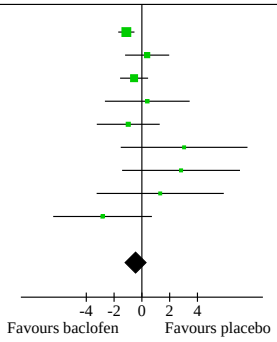


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 1.4. Comparison 1: Baclofen versus placebo (all studies), Outcome 4: Amount of use: drinks per drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D
Addolorato 2007	0.5781	1.06	42	1.6945	1.6099	42	34.6%	-1.12 [-1.70 , -0.53]	?	+	+	+
Addolorato 2011-LD	1.24	2.43	14	0.86	1.28	7	14.8%	0.38 [-1.21 , 1.97]	+	+	−	−
Addolorato 2011-MD	0.3	0.65	14	0.86	1.28	7	24.4%	-0.56 [-1.57 , 0.45]	+	+	−	−
Garbutt 2021-LD	7.64	8.11	43	7.25	4.22	20	5.3%	0.39 [-2.66 , 3.44]	+	+	+	+
Garbutt 2021-MD	6.27	4.05	37	7.25	4.22	20	8.8%	-0.98 [-3.24 , 1.28]	+	+	+	+
Morley 2014-LD	5.86	5.299777	14	2.82	4.884108	7	2.6%	3.04 [-1.52 , 7.60]	+	+	?	?
Morley 2014-MD	5.64	4.225966	14	2.82	4.884108	7	2.9%	2.82 [-1.42 , 7.06]	+	+	?	?
Morley 2018-LD	8.82	10.38	36	7.5	6.46	17	2.5%	1.32 [-3.25 , 5.89]	+	+	+	?
Morley 2018-MD	4.67	4.86	35	7.5	6.46	16	4.1%	-2.83 [-6.38 , 0.72]	+	+	+	?
Total (95% CI)			**249**			**143**	**100.0%**	**-0.45 [-1.20 , 0.30]**				

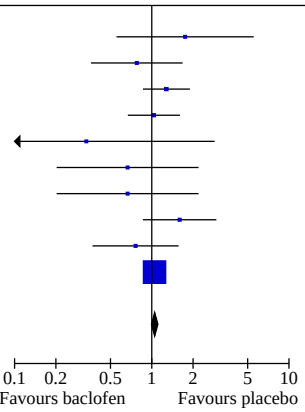
Heterogeneity: Tau² = 0.34; Chi² = 11.65, df = 8 (P = 0.17); I² = 31%
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable

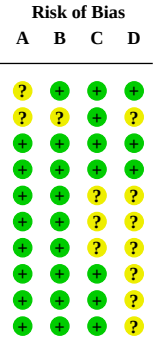


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

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

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	7	42	4	42	0.2%	1.75 [0.55 , 5.54]
Garbutt 2010b1	7	20	9	20	0.5%	0.78 [0.36 , 1.68]
Garbutt 2021-LD	33	43	12	20	1.9%	1.28 [0.86 , 1.90]
Garbutt 2021-MD	23	37	12	20	1.5%	1.04 [0.67 , 1.60]
Krupitskii 2017	1	16	3	16	0.1%	0.33 [0.04 , 2.87]
Morley 2014-LD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2014-MD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2018-LD	23	35	7	17	0.8%	1.60 [0.86 , 2.96]
Morley 2018-MD	12	36	7	16	0.6%	0.76 [0.37 , 1.57]
Reynaud 2017	151	157	146	159	94.0%	1.05 [0.99 , 1.11]
Total (95% CI)		**414**		**324**	**100.0%**	**1.05 [0.99 , 1.11]**
Total events:	265		206			



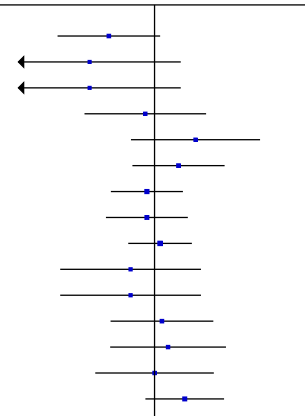


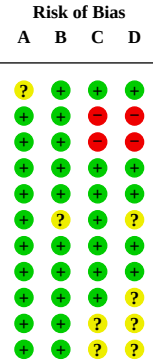
Heterogeneity: Tau² = 0.00; Chi² = 7.06, df = 9 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 1.6. Comparison 1: Baclofen versus placebo (all studies), Outcome 6: Dropouts at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	6	42	13	42	3.3%	0.46 [0.19 , 1.10]
Addolorato 2011-LD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Addolorato 2011-MD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Beraha 2016-HD	8	58	5	31	2.4%	0.86 [0.31 , 2.39]
Beraha 2016-LD	8	31	4	31	2.2%	2.00 [0.67 , 5.96]
Garbutt 2010a	12	40	8	40	4.0%	1.50 [0.69 , 3.27]
Garbutt 2021-LD	17	43	9	20	6.2%	0.88 [0.48 , 1.62]
Garbutt 2021-MD	13	37	8	20	5.0%	0.88 [0.44 , 1.76]
Hauser 2017	21	88	20	92	7.6%	1.10 [0.64 , 1.88]
Morley 2014-LD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2014-MD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2018-LD	12	36	5	17	3.3%	1.13 [0.48 , 2.70]
Morley 2018-MD	11	35	4	16	2.7%	1.26 [0.47 , 3.35]
Muller 2015	6	28	6	28	2.5%	1.00 [0.37 , 2.73]
Ponizovsky 2015	15	32	9	32	5.3%	1.67 [0.86 , 3.24]
Reynaud 2017	59	158	71	162	19.5%	0.85 [0.65 , 1.11]
Rigal 2020	95	162	127	158	29.9%	0.73 [0.63 , 0.85]
Total (95% CI)		**846**		**717**	**100.0%**	**0.88 [0.74 , 1.03]**
Total events:	295		301			





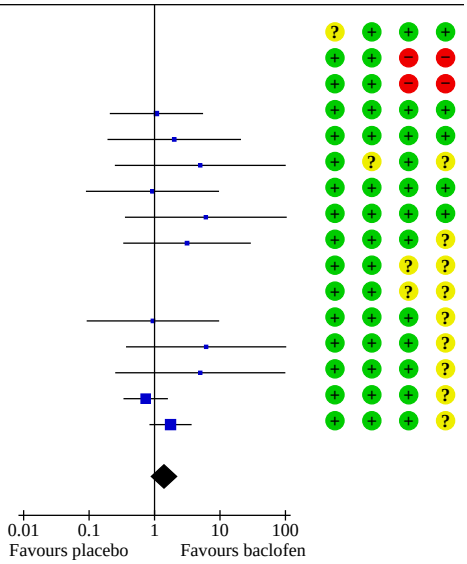
Heterogeneity: Tau² = 0.02; Chi² = 19.55, df = 16 (P = 0.24); I² = 18%
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 1.7. Comparison 1: Baclofen versus placebo (all studies), Outcome 7: Dropouts due to adverse events

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	0	42	0	42		Not estimable
Addolorato 2011-LD	0	14	0	7		Not estimable
Addolorato 2011-MD	0	14	0	7		Not estimable
Beraha 2016-HD	4	58	2	31	7.4%	1.07 [0.21 , 5.51]
Beraha 2016-LD	2	31	1	31	3.6%	2.00 [0.19 , 20.93]
Garbutt 2010a	2	40	0	40	2.2%	5.00 [0.25 , 100.97]
Garbutt 2021-LD	2	43	1	20	3.6%	0.93 [0.09 , 9.67]
Garbutt 2021-MD	5	37	0	20	2.4%	6.08 [0.35 , 104.63]
Hauser 2017	3	88	1	92	3.9%	3.14 [0.33 , 29.59]
Morley 2014-LD	0	14	0	7		Not estimable
Morley 2014-MD	0	14	0	7		Not estimable
Morley 2018-LD	2	36	1	17	3.6%	0.94 [0.09 , 9.71]
Morley 2018-MD	6	35	0	16	2.5%	6.14 [0.37 , 102.79]
Muller 2015	2	28	0	28	2.2%	5.00 [0.25 , 99.67]
Reynaud 2017	10	158	14	162	32.5%	0.73 [0.34 , 1.60]
Rigal 2020	18	162	10	158	36.1%	1.76 [0.84 , 3.68]
Total (95% CI)		**814**		**685**	**100.0%**	**1.39 [0.89 , 2.18]**
Total events:	56		30			

Heterogeneity: Tau² = 0.00; Chi² = 7.55, df = 10 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

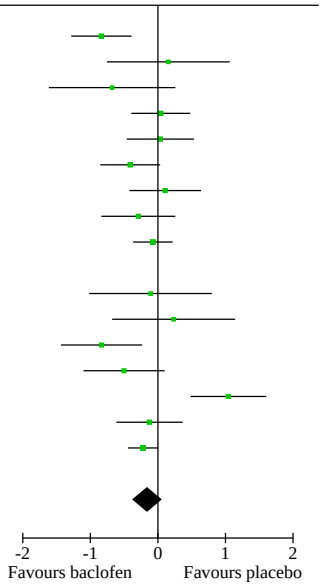


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 1.8. Comparison 1: Baclofen versus placebo (all studies), Outcome 8: Craving

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addolorato 2007	3.1	4.5	42	6.9	4.5	42	7.4%	-0.84 [-1.28 , -0.39]
Addolorato 2011-LD	7.83	10.9	14	6.25	6.94	7	3.5%	0.15 [-0.75 , 1.06]
Addolorato 2011-MD	3	2.95	14	6.25	6.94	7	3.4%	-0.68 [-1.61 , 0.26]
Beraha 2016-HD	12.4	4.9	58	12.2	4.3	31	7.5%	0.04 [-0.39 , 0.48]
Beraha 2016-LD	12.4	6.4	31	12.2	4.3	31	6.8%	0.04 [-0.46 , 0.53]
Garbutt 2010a	9.65	6.65	40	12.68	7.93	40	7.5%	-0.41 [-0.85 , 0.03]
Garbutt 2021-LD	10.51	6.86	43	9.75	7.04	20	6.5%	0.11 [-0.42 , 0.64]
Garbutt 2021-MD	7.78	6.53	37	9.75	7.04	20	6.3%	-0.29 [-0.84 , 0.26]
Hauser 2017	8.79	9.81	88	9.52	9.7	92	9.3%	-0.07 [-0.37 , 0.22]
Krupitskii 2017	1.6	3.794733	16	0	0	16		Not estimable
Morley 2014-LD	11.01	6.2	14	11.64	3.77	7	3.5%	-0.11 [-1.02 , 0.80]
Morley 2014-MD	12.69	4.57	14	11.64	3.77	7	3.5%	0.23 [-0.68 , 1.14]
Morley 2018-LD	9.26	8.14	36	16	7.57	17	5.8%	-0.83 [-1.43 , -0.23]
Morley 2018-MD	12.13	7.61	35	16	7.57	16	5.8%	-0.50 [-1.10 , 0.10]
Muller 2015	9.3	8.8	28	2.3	3.2	28	6.2%	1.04 [0.48 , 1.60]
Ponizovsky 2015	11.5	9.3	32	12.8	11.2	32	6.9%	-0.12 [-0.62 , 0.37]
Rigal 2020	12	9	162	14	9	158	10.1%	-0.22 [-0.44 , -0.00]
Total (95% CI)			**704**			**571**	**100.0%**	**-0.16 [-0.37 , 0.04]**

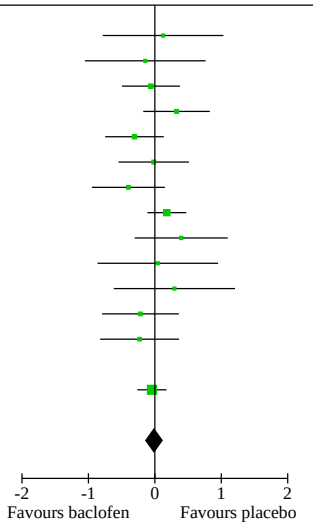
Heterogeneity: Tau² = 0.09; Chi² = 39.36, df = 15 (P = 0.0006); I² = 62%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Baclofen versus placebo (all studies), Outcome 9: Anxiety

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addolorato 2011-LD	40.5	14.92	14	38.5	16.51	7	1.8%	0.12 [-0.78 , 1.03]
Addolorato 2011-MD	36.58	10.56	14	38.5	16.51	7	1.8%	-0.14 [-1.05 , 0.76]
Beraha 2016-HD	37.3	12.1	58	38	11.1	31	7.9%	-0.06 [-0.50 , 0.38]
Beraha 2016-LD	42.2	14.1	31	38	11.1	31	6.0%	0.33 [-0.17 , 0.83]
Garbutt 2010a	27.5	13.5	40	32.2	16.7	40	7.7%	-0.31 [-0.75 , 0.13]
Garbutt 2021-LD	43.1	11.07	43	43.3	12.64	20	5.3%	-0.02 [-0.55 , 0.51]
Garbutt 2021-MD	38.6	11.07	37	43.3	12.64	20	5.0%	-0.40 [-0.95 , 0.15]
Hauser 2017	29.9	15.9	88	27.04	15.6	92	17.6%	0.18 [-0.11 , 0.47]
Krupitskii 2017	34.8	8.979978	16	32	3.741657	16	3.1%	0.40 [-0.30 , 1.10]
Morley 2014-LD	33.18	15.665517	14	32.44	17	7	1.8%	0.04 [-0.86 , 0.95]
Morley 2014-MD	36.61	11.700453	14	32.44	17	7	1.8%	0.29 [-0.62 , 1.21]
Morley 2018-LD	7.65	9.72	36	9.91	11.4	17	4.5%	-0.22 [-0.80 , 0.36]
Morley 2018-MD	7.83	7.55	35	9.91	11.4	16	4.3%	-0.23 [-0.82 , 0.36]
Muller 2015	1.9	5	28	0	0	28		Not estimable
Rigal 2020	7.6	4.2	162	7.8	4.8	158	31.3%	-0.04 [-0.26 , 0.17]
Total (95% CI)			**630**			**497**	**100.0%**	**-0.01 [-0.14 , 0.11]**

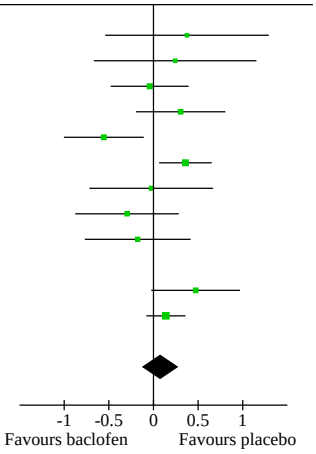
Heterogeneity: Tau² = 0.00; Chi² = 10.09, df = 13 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Baclofen versus placebo (all studies), Outcome 10: Depression

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addolorato 2011-LD	35.42	11.83	14	31.25	7.55	7	3.7%	0.38 [-0.54 , 1.29]
Addolorato 2011-MD	33.58	9.89	14	31.25	7.55	7	3.7%	0.24 [-0.67 , 1.15]
Beraha 2016-HD	5.8	7.3	58	6.1	6.6	31	10.6%	-0.04 [-0.48 , 0.39]
Beraha 2016-LD	8.8	10.5	31	6.1	6.6	31	9.0%	0.30 [-0.20 , 0.80]
Garbutt 2010a	30.33	8.71	40	35.54	9.81	40	10.3%	-0.56 [-1.00 , -0.11]
Hauser 2017	9.63	10.1	88	6.02	10	92	15.1%	0.36 [0.06 , 0.65]
Krupitskii 2017	1.2	4.489989	16	1.3	3.367492	16	5.8%	-0.02 [-0.72 , 0.67]
Morley 2018-LD	10.17	11.09	36	14	15.74	17	7.5%	-0.30 [-0.88 , 0.28]
Morley 2018-MD	11.83	10.11	35	14	15.74	16	7.2%	-0.18 [-0.77 , 0.42]
Muller 2015	2.1	5.4	28	0	0	28		Not estimable
Ponizovsky 2015	13.41	1.3	32	10.3	9.1	32	9.1%	0.47 [-0.02 , 0.97]
Rigal 2020	6.4	4.4	162	5.8	4.2	158	18.0%	0.14 [-0.08 , 0.36]
Total (95% CI)			**554**			**475**	**100.0%**	**0.07 [-0.12 , 0.27]**

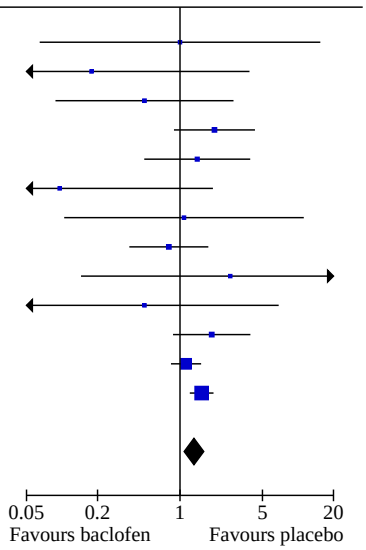
Heterogeneity: Tau² = 0.04; Chi² = 17.73, df = 10 (P = 0.06); I² = 44%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Baclofen versus placebo (all studies), Outcome 11: Adverse events: fatigue, tiredness

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	1	42	1	42	0.5%	1.00 [0.06 , 15.47]
Addolorato 2011-LD	0	14	1	7	0.4%	0.18 [0.01 , 3.88]
Addolorato 2011-MD	2	14	2	7	1.2%	0.50 [0.09 , 2.84]
Beraha 2016-HD	22	58	6	31	5.5%	1.96 [0.89 , 4.32]
Beraha 2016-LD	7	31	5	31	3.3%	1.40 [0.50 , 3.94]
Garbutt 2021-LD	0	43	2	20	0.4%	0.10 [0.00 , 1.90]
Garbutt 2021-MD	2	37	1	20	0.7%	1.08 [0.10 , 11.20]
Hauser 2017	10	88	13	92	5.8%	0.80 [0.37 , 1.74]
Morley 2014-LD	2	14	0	7	0.4%	2.67 [0.14 , 49.08]
Morley 2014-MD	1	14	1	7	0.5%	0.50 [0.04 , 6.86]
Muller 2015	13	28	7	28	6.1%	1.86 [0.87 , 3.95]
Reynaud 2017	60	157	54	159	31.3%	1.13 [0.84 , 1.51]
Rigal 2020	97	162	62	158	43.9%	1.53 [1.21 , 1.92]
Total (95% CI)		**702**		**609**	**100.0%**	**1.31 [1.09 , 1.59]**
Total events:	217		155			

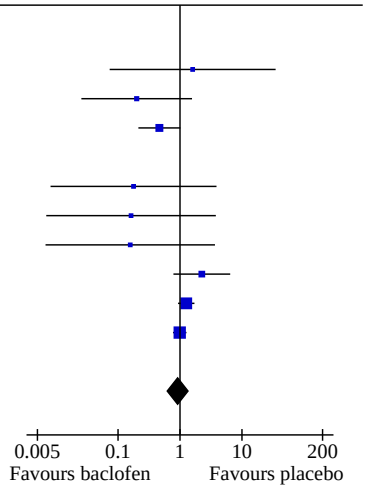
Heterogeneity: Tau² = 0.01; Chi² = 12.71, df = 12 (P = 0.39); I² = 6%
Test for overall effect: Z = 2.80 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Baclofen versus placebo (all studies), Outcome 12: Adverse events: insomnia

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2011-LD	0	14	0	7		Not estimable
Addolorato 2011-MD	1	14	0	7	1.5%	1.60 [0.07 , 34.93]
Garbutt 2010b1	1	20	5	20	3.2%	0.20 [0.03 , 1.56]
Hauser 2017	8	88	18	92	15.1%	0.46 [0.21 , 1.01]
Morley 2014-LD	0	14	0	7		Not estimable
Morley 2014-MD	0	14	1	7	1.5%	0.18 [0.01 , 3.88]
Morley 2018-LD	0	36	1	17	1.4%	0.16 [0.01 , 3.79]
Morley 2018-MD	0	35	1	16	1.4%	0.16 [0.01 , 3.67]
Muller 2015	9	28	4	28	10.0%	2.25 [0.78 , 6.46]
Reynaud 2017	61	157	49	159	31.8%	1.26 [0.93 , 1.71]
Rigal 2020	70	162	69	158	34.0%	0.99 [0.77 , 1.27]
Total (95% CI)		**582**		**518**	**100.0%**	**0.92 [0.62 , 1.35]**
Total events:	150		148			

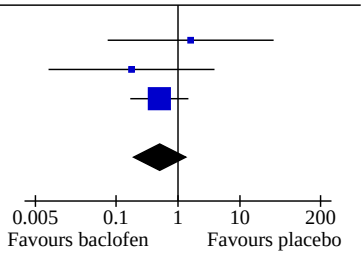
Heterogeneity: Tau² = 0.10; Chi² = 14.52, df = 8 (P = 0.07); I² = 45%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2011-LD	1	14	0	7	9.8%	1.60 [0.07 , 34.93]
Addolorato 2011-MD	0	14	1	7	9.8%	0.18 [0.01 , 3.88]
Muller 2015	4	28	8	28	80.3%	0.50 [0.17 , 1.47]
Total (95% CI)		**56**		**42**	**100.0%**	**0.51 [0.19 , 1.33]**
Total events:	5		9			

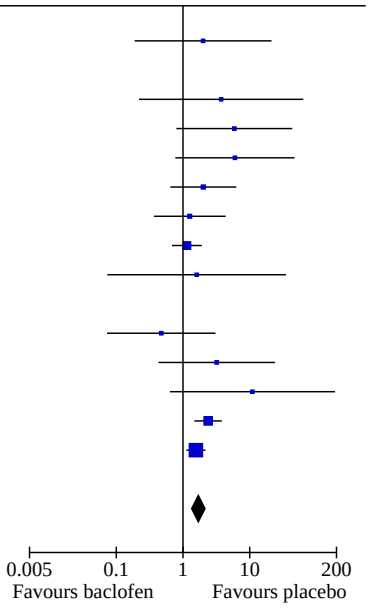
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Baclofen versus placebo (all studies), Outcome 14: Adverse events: vertigo, dizziness

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	2	42	1	42	0.9%	2.00 [0.19 , 21.23]
Addolorato 2011-LD	0	14	0	7		Not estimable
Addolorato 2011-MD	3	14	0	7	0.7%	3.73 [0.22 , 63.66]
Beraha 2016-HD	11	58	1	31	1.3%	5.88 [0.80 , 43.45]
Beraha 2016-LD	6	31	1	31	1.2%	6.00 [0.77 , 46.96]
Garbutt 2021-LD	13	43	3	20	4.0%	2.02 [0.65 , 6.29]
Garbutt 2021-MD	7	37	3	20	3.4%	1.26 [0.37 , 4.35]
Hauser 2017	23	88	21	92	18.9%	1.15 [0.68 , 1.92]
Morley 2014-LD	1	14	0	7	0.6%	1.60 [0.07 , 34.93]
Morley 2014-MD	0	14	0	7		Not estimable
Morley 2018-LD	2	36	2	17	1.5%	0.47 [0.07 , 3.07]
Morley 2018-MD	7	35	1	16	1.3%	3.20 [0.43 , 23.88]
Muller 2015	5	28	0	28	0.6%	11.00 [0.64 , 189.96]
Reynaud 2017	47	157	20	159	22.1%	2.38 [1.48 , 3.83]
Rigal 2020	64	162	40	158	43.4%	1.56 [1.12 , 2.17]
Total (95% CI)		**773**		**642**	**100.0%**	**1.70 [1.35 , 2.13]**
Total events:	191		93			

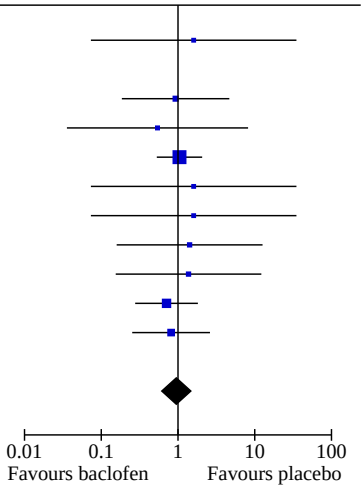
Heterogeneity: Tau² = 0.00; Chi² = 12.19, df = 12 (P = 0.43); I² = 2%
Test for overall effect: Z = 4.52 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Baclofen versus placebo (all studies), Outcome 15: Adverse events: constipation

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2011-LD	1	14	0	7	2.0%	1.60 [0.07 , 34.93]
Addolorato 2011-MD	0	14	0	7		Not estimable
Garbutt 2021-LD	4	43	2	20	7.3%	0.93 [0.19 , 4.66]
Garbutt 2021-MD	1	37	1	20	2.6%	0.54 [0.04 , 8.19]
Hauser 2017	14	88	14	92	40.9%	1.05 [0.53 , 2.07]
Morley 2014-LD	1	14	0	7	2.0%	1.60 [0.07 , 34.93]
Morley 2014-MD	1	14	0	7	2.0%	1.60 [0.07 , 34.93]
Morley 2018-LD	3	36	1	17	4.0%	1.42 [0.16 , 12.64]
Morley 2018-MD	3	35	1	16	4.0%	1.37 [0.15 , 12.19]
Reynaud 2017	7	157	10	159	21.4%	0.71 [0.28 , 1.82]
Rigal 2020	5	162	6	158	13.9%	0.81 [0.25 , 2.61]
Total (95% CI)		**614**		**510**	**100.0%**	**0.95 [0.61 , 1.47]**
Total events:	40		35			

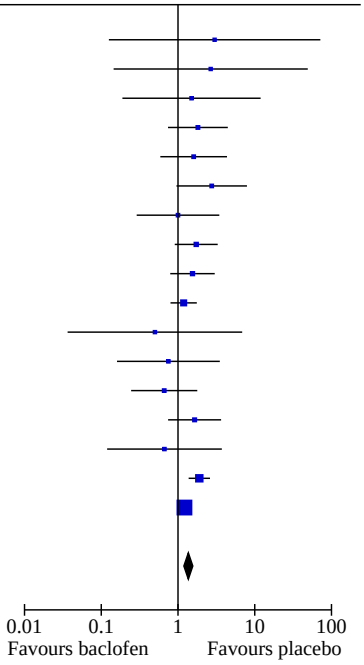
Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 9 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Baclofen versus placebo (all studies), Outcome 16: Adverse events: somnolence, sleepiness, drowsiness or sedation

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	1	42	0	42	0.2%	3.00 [0.13 , 71.61]
Addolorato 2011-LD	2	14	0	7	0.2%	2.67 [0.14 , 49.08]
Addolorato 2011-MD	3	14	1	7	0.4%	1.50 [0.19 , 11.93]
Beraha 2016-HD	17	58	5	31	2.2%	1.82 [0.74 , 4.46]
Beraha 2016-LD	8	31	5	31	1.8%	1.60 [0.59 , 4.35]
Garbutt 2010a	11	40	4	40	1.6%	2.75 [0.96 , 7.91]
Garbutt 2010b1	4	20	4	20	1.2%	1.00 [0.29 , 3.45]
Garbutt 2021-LD	26	43	7	20	4.3%	1.73 [0.91 , 3.29]
Garbutt 2021-MD	20	37	7	20	4.0%	1.54 [0.79 , 3.01]
Hauser 2017	34	88	30	92	11.5%	1.18 [0.80 , 1.76]
Morley 2014-LD	1	14	1	7	0.3%	0.50 [0.04 , 6.86]
Morley 2014-MD	3	14	2	7	0.8%	0.75 [0.16 , 3.51]
Morley 2018-LD	7	36	5	17	1.8%	0.66 [0.25 , 1.78]
Morley 2018-MD	18	35	5	16	2.8%	1.65 [0.74 , 3.64]
Ponizovsky 2015	2	32	3	32	0.6%	0.67 [0.12 , 3.73]
Reynaud 2017	73	157	39	159	17.4%	1.90 [1.38 , 2.61]
Rigal 2020	102	162	82	158	49.0%	1.21 [1.00 , 1.47]
Total (95% CI)		**837**		**706**	**100.0%**	**1.36 [1.19 , 1.56]**
Total events:	332		200			

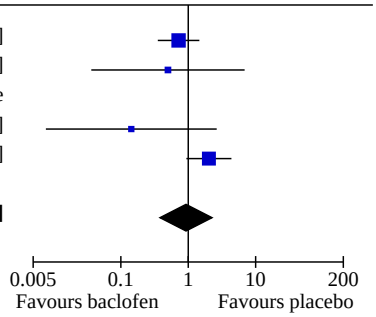
Heterogeneity: Tau² = 0.00; Chi² = 13.85, df = 16 (P = 0.61); I² = 0%
Test for overall effect: Z = 4.55 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Baclofen versus placebo (all studies), Outcome 17: Adverse events: muscle pain

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	11	88	16	92	42.2%	0.72 [0.35 , 1.46]
Morley 2014-LD	1	14	1	7	9.6%	0.50 [0.04 , 6.86]
Morley 2014-MD	0	14	0	7		Not estimable
Muller 2015	0	28	3	28	8.0%	0.14 [0.01 , 2.64]
Reynaud 2017	18	157	9	159	40.3%	2.03 [0.94 , 4.37]
Total (95% CI)		**301**		**293**	**100.0%**	**0.93 [0.38 , 2.25]**
Total events:	30		29			

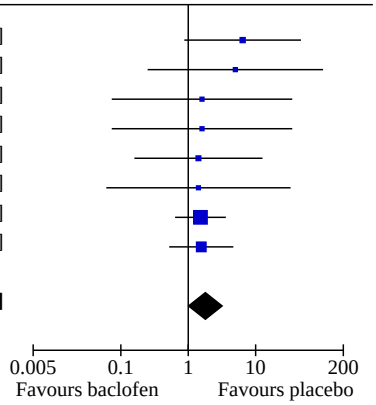
Heterogeneity: Tau² = 0.35; Chi² = 6.00, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Baclofen versus placebo (all studies), Outcome 18: Adverse events: dry mouth

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Beraha 2016-HD	12	58	1	31	8.3%	6.41 [0.87 , 47.05]
Beraha 2016-LD	2	31	0	31	3.7%	5.00 [0.25 , 100.08]
Morley 2014-LD	1	14	0	7	3.5%	1.60 [0.07 , 34.93]
Morley 2014-MD	1	14	0	7	3.5%	1.60 [0.07 , 34.93]
Morley 2018-LD	3	36	1	17	6.9%	1.42 [0.16 , 12.64]
Morley 2018-MD	1	35	0	16	3.3%	1.42 [0.06 , 33.00]
Reynaud 2017	12	157	8	159	43.7%	1.52 [0.64 , 3.62]
Rigal 2020	8	162	5	158	27.3%	1.56 [0.52 , 4.67]
Total (95% CI)		**507**		**426**	**100.0%**	**1.79 [1.01 , 3.18]**
Total events:	40		15			

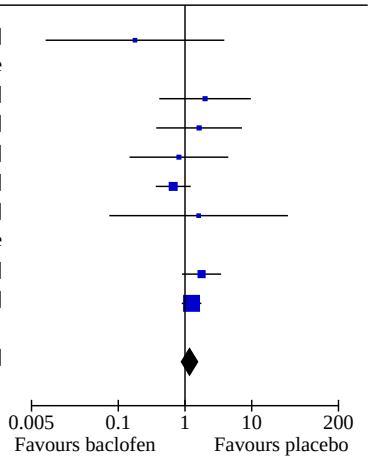
Heterogeneity: Tau² = 0.00; Chi² = 2.40, df = 7 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Baclofen versus placebo (all studies), Outcome 19: Adverse events: nausea

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2011-LD	0	14	1	7	0.8%	0.18 [0.01 , 3.88]
Addolorato 2011-MD	0	14	0	7		Not estimable
Garbutt 2010b1	4	20	2	20	3.1%	2.00 [0.41 , 9.71]
Garbutt 2021-LD	7	43	2	20	3.5%	1.63 [0.37 , 7.15]
Garbutt 2021-MD	3	37	2	20	2.6%	0.81 [0.15 , 4.46]
Hauser 2017	14	88	22	92	19.6%	0.67 [0.36 , 1.22]
Morley 2014-LD	1	14	0	7	0.8%	1.60 [0.07 , 34.93]
Morley 2014-MD	0	14	0	7		Not estimable
Reynaud 2017	21	157	12	159	16.0%	1.77 [0.90 , 3.48]
Rigal 2020	54	162	42	158	53.6%	1.25 [0.89 , 1.76]
Total (95% CI)		**563**		**497**	**100.0%**	**1.17 [0.88 , 1.54]**
Total events:	104		83			

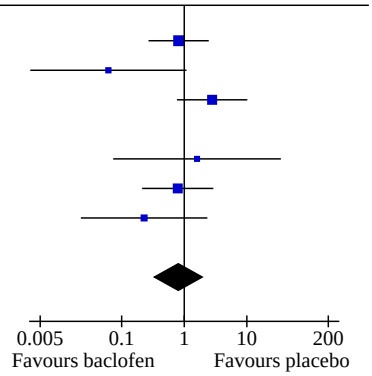
Heterogeneity: Tau² = 0.01; Chi² = 7.27, df = 7 (P = 0.40); I² = 4%
Test for overall effect: Z = 1.09 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Baclofen versus placebo (all studies), Outcome 20: Adverse events: skin rash

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Garbutt 2021-LD	7	43	4	20	27.3%	0.81 [0.27 , 2.46]
Garbutt 2021-MD	0	37	4	20	7.8%	0.06 [0.00 , 1.09]
Hauser 2017	8	88	3	92	23.6%	2.79 [0.76 , 10.17]
Morley 2014-LD	0	14	0	7		Not estimable
Morley 2014-MD	1	14	0	7	6.9%	1.60 [0.07 , 34.93]
Morley 2018-LD	5	36	3	17	23.3%	0.79 [0.21 , 2.92]
Morley 2018-MD	1	35	2	16	11.0%	0.23 [0.02 , 2.34]
Total (95% CI)		**267**		**179**	**100.0%**	**0.80 [0.33 , 1.93]**
Total events:	22		16			

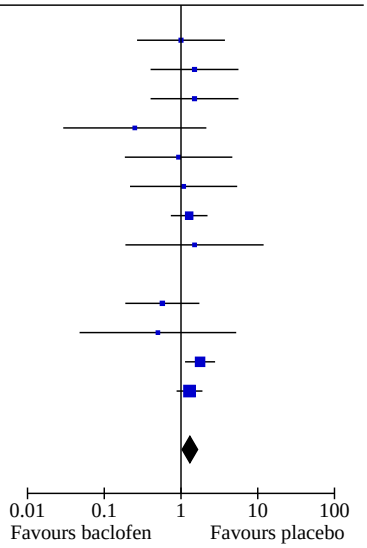
Heterogeneity: Tau² = 0.42; Chi² = 7.89, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 0.49 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Baclofen versus placebo (all studies), Outcome 21: Adverse events: headaches

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Addolorato 2007	4	42	4	42	3.1%	1.00 [0.27 , 3.74]
Addolorato 2011-LD	6	14	2	7	3.1%	1.50 [0.40 , 5.61]
Addolorato 2011-MD	6	14	2	7	3.1%	1.50 [0.40 , 5.61]
Garbutt 2010a	1	40	4	40	1.2%	0.25 [0.03 , 2.14]
Garbutt 2021-LD	4	43	2	20	2.0%	0.93 [0.19 , 4.66]
Garbutt 2021-MD	4	37	2	20	2.1%	1.08 [0.22 , 5.40]
Hauser 2017	22	88	18	92	17.6%	1.28 [0.74 , 2.21]
Morley 2014-LD	3	14	1	7	1.2%	1.50 [0.19 , 11.93]
Morley 2014-MD	0	14	0	7		Not estimable
Muller 2015	4	28	7	28	4.3%	0.57 [0.19 , 1.74]
Ponizovsky 2015	1	32	2	32	1.0%	0.50 [0.05 , 5.24]
Reynaud 2017	42	157	24	159	26.2%	1.77 [1.13 , 2.78]
Rigal 2020	45	162	34	158	35.3%	1.29 [0.88 , 1.90]
Total (95% CI)		**685**		**619**	**100.0%**	**1.31 [1.04 , 1.64]**
Total events:	142		102			

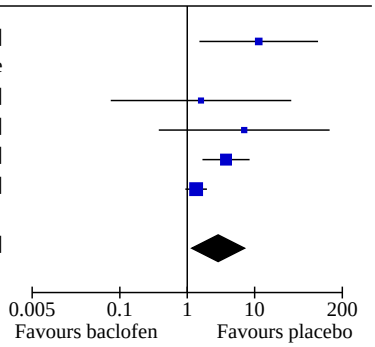
Heterogeneity: Tau² = 0.00; Chi² = 7.32, df = 11 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Baclofen versus placebo (all studies), Outcome 22: Adverse events: paraesthesia/numbness

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	11	88	1	92	13.5%	11.50 [1.52 , 87.23]
Morley 2014-LD	0	14	0	7		Not estimable
Morley 2014-MD	1	14	0	7	7.1%	1.60 [0.07 , 34.93]
Muller 2015	3	28	0	28	7.8%	7.00 [0.38 , 129.55]
Reynaud 2017	26	157	7	159	31.8%	3.76 [1.68 , 8.41]
Rigal 2020	50	162	36	158	39.9%	1.35 [0.94 , 1.96]
Total (95% CI)		**463**		**451**	**100.0%**	**2.87 [1.17 , 7.06]**
Total events:	91		44			

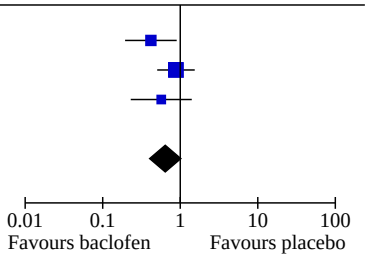
Heterogeneity: Tau² = 0.49; Chi² = 10.29, df = 4 (P = 0.04); I² = 61%
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Baclofen versus placebo (all studies), Outcome 23: Adverse events: diarrhoea

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	8	88	20	92	29.6%	0.42 [0.19 , 0.90]
Reynaud 2017	20	157	23	159	48.0%	0.88 [0.50 , 1.54]
Rigal 2020	7	162	12	158	22.4%	0.57 [0.23 , 1.41]
Total (95% CI)		**407**		**409**	**100.0%**	**0.64 [0.40 , 1.02]**
Total events:	35		55			

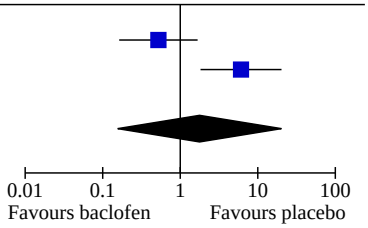
Heterogeneity: Tau² = 0.03; Chi² = 2.50, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: Baclofen versus placebo (all studies), Outcome 24: Adverse events: tinnitus

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	4	88	8	92	50.2%	0.52 [0.16 , 1.67]
Reynaud 2017	18	157	3	159	49.8%	6.08 [1.83 , 20.22]
Total (95% CI)		**245**		**251**	**100.0%**	**1.77 [0.16 , 20.16]**
Total events:	22		11			

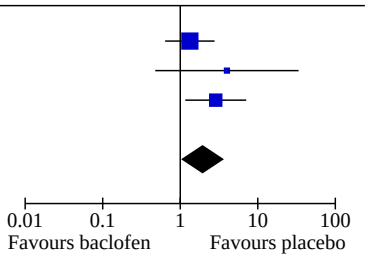
Heterogeneity: Tau² = 2.71; Chi² = 8.44, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: Baclofen versus placebo (all studies), Outcome 25: Adverse events: muscle spasm/rigidity

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	14	88	11	92	54.3%	1.33 [0.64 , 2.77]
Muller 2015	4	28	1	28	7.6%	4.00 [0.48 , 33.58]
Reynaud 2017	17	157	6	159	38.0%	2.87 [1.16 , 7.09]
Total (95% CI)		**273**		**279**	**100.0%**	**1.94 [1.07 , 3.52]**
Total events:	35		18			

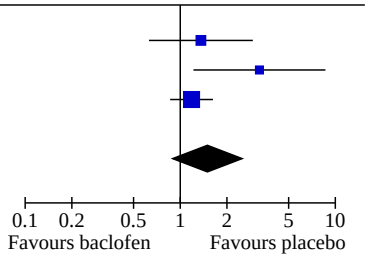
Heterogeneity: Tau² = 0.03; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Baclofen versus placebo (all studies), Outcome 26: Adverse events: hyperhidrosis

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	13	88	10	92	26.9%	1.36 [0.63 , 2.94]
Reynaud 2017	16	157	5	159	19.6%	3.24 [1.22 , 8.63]
Rigal 2020	57	162	47	158	53.5%	1.18 [0.86 , 1.63]
Total (95% CI)		**407**		**409**	**100.0%**	**1.50 [0.89 , 2.51]**
Total events:	86		62			

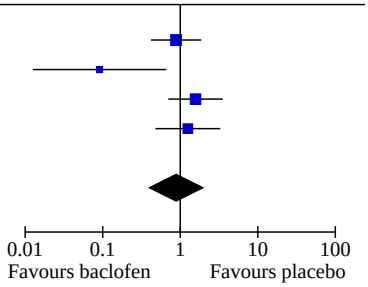
Heterogeneity: Tau² = 0.10; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: Baclofen versus placebo (all studies), Outcome 27: Adverse events: nasopharyngitis

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	11	88	13	92	31.6%	0.88 [0.42 , 1.87]
Muller 2015	1	28	11	28	11.7%	0.09 [0.01 , 0.66]
Reynaud 2017	14	157	9	159	30.1%	1.58 [0.70 , 3.53]
Rigal 2020	9	162	7	158	26.6%	1.25 [0.48 , 3.29]
Total (95% CI)		**435**		**437**	**100.0%**	**0.89 [0.40 , 1.95]**
Total events:	35		40			

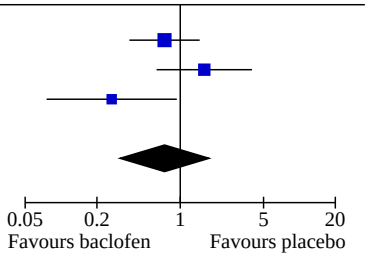
Heterogeneity: Tau² = 0.37; Chi² = 7.53, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Baclofen versus placebo (all studies), Outcome 28: Adverse events: decrease appetite/anorexia

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	12	88	17	92	41.0%	0.74 [0.37 , 1.45]
Reynaud 2017	11	157	7	159	33.7%	1.59 [0.63 , 4.00]
Rigal 2020	3	162	11	158	25.3%	0.27 [0.08 , 0.94]
Total (95% CI)		**407**		**409**	**100.0%**	**0.74 [0.31 , 1.75]**
Total events:	26		35			

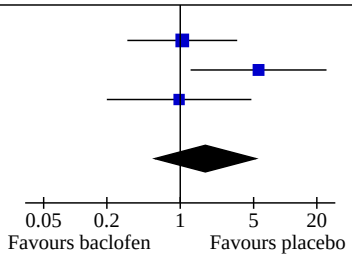
Heterogeneity: Tau² = 0.35; Chi² = 5.16, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1: Baclofen versus placebo (all studies), Outcome 29: Adverse events: dysgeusia/ageusia

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	5	88	5	92	39.3%	1.05 [0.31 , 3.49]
Reynaud 2017	11	157	2	159	31.5%	5.57 [1.25 , 24.73]
Rigal 2020	3	162	3	158	29.3%	0.98 [0.20 , 4.76]
Total (95% CI)		**407**		**409**	**100.0%**	**1.73 [0.57 , 5.24]**
Total events:	19		10			

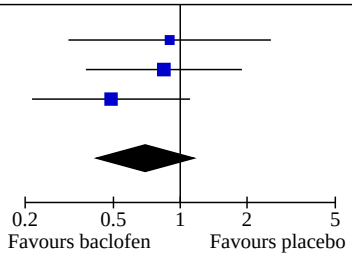
Heterogeneity: Tau² = 0.43; Chi² = 3.65, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 1.30. Comparison 1: Baclofen versus placebo (all studies), Outcome 30: Adverse events: tremor

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	6	88	7	92	23.1%	0.90 [0.31 , 2.56]
Reynaud 2017	10	157	12	159	38.9%	0.84 [0.38 , 1.90]
Rigal 2020	8	162	16	158	38.0%	0.49 [0.21 , 1.11]
Total (95% CI)		**407**		**409**	**100.0%**	**0.69 [0.42 , 1.15]**
Total events:	24		35			

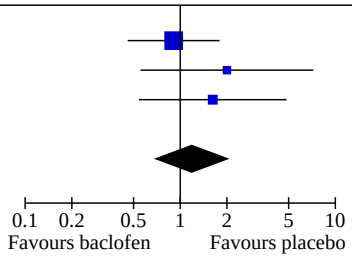
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 1.31. Comparison 1: Baclofen versus placebo (all studies), Outcome 31: Adverse events: weakness

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	13	88	15	92	59.8%	0.91 [0.46 , 1.79]
Muller 2015	6	28	3	28	16.9%	2.00 [0.55 , 7.22]
Reynaud 2017	8	157	5	159	23.2%	1.62 [0.54 , 4.85]
Total (95% CI)		**273**		**279**	**100.0%**	**1.19 [0.70 , 2.01]**
Total events:	27		23			

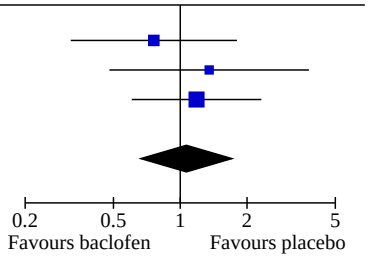
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.32. Comparison 1: Baclofen versus placebo (all studies), Outcome 32: Adverse events: vomiting

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	8	88	11	92	29.9%	0.76 [0.32 , 1.80]
Reynaud 2017	8	157	6	159	20.8%	1.35 [0.48 , 3.80]
Rigal 2020	17	162	14	158	49.3%	1.18 [0.60 , 2.32]
Total (95% CI)		**407**		**409**	**100.0%**	**1.07 [0.66 , 1.71]**
Total events:	33		31			

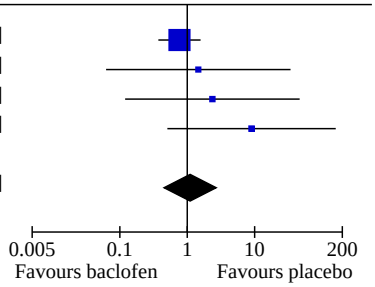
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 1.33. Comparison 1: Baclofen versus placebo (all studies), Outcome 33: Adverse events: urinary frequency

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauser 2017	11	88	15	92	75.1%	0.77 [0.37 , 1.58]
Morley 2018-LD	1	36	0	17	7.6%	1.46 [0.06 , 34.08]
Morley 2018-MD	2	35	0	16	8.4%	2.36 [0.12 , 46.54]
Muller 2015	4	28	0	28	9.0%	9.00 [0.51 , 159.70]
Total (95% CI)		**187**		**153**	**100.0%**	**1.10 [0.45 , 2.68]**
Total events:	18		15			

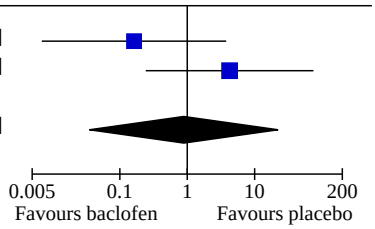
Heterogeneity: Tau² = 0.14; Chi² = 3.32, df = 3 (P = 0.34); I² = 10%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



Analysis 1.34. Comparison 1: Baclofen versus placebo (all studies), Outcome 34: Adverse events: shortness of breath

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Morley 2018-LD	0	36	1	17	47.9%	0.16 [0.01 , 3.79]
Morley 2018-MD	4	35	0	16	52.1%	4.25 [0.24 , 74.53]
Total (95% CI)		**71**		**33**	**100.0%**	**0.89 [0.04 , 22.31]**
Total events:	4		1			

Heterogeneity: Tau² = 3.06; Chi² = 2.30, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Comparison 2. Baclofen versus placebo (divided into low, medium and high doses of baclofen)

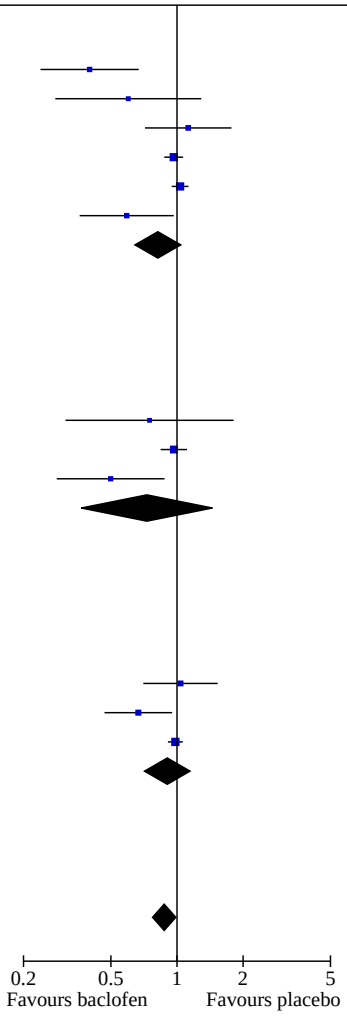
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Relapse: return to any drinking at end of treatment	12	1057	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 Low doses	6	463	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.64, 1.04]
2.1.2 Medium doses	3	129	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.37, 1.45]
2.1.3 High doses	3	465	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.15]
2.2 Frequency of use: % days abstinence at end of treatment	16	1273	Mean Difference (IV, Random, 95% CI)	9.07 [3.30, 14.85]
2.2.1 Low doses	8	583	Mean Difference (IV, Random, 95% CI)	10.59 [0.77, 20.41]
2.2.2 Medium doses	5	225	Mean Difference (IV, Random, 95% CI)	7.14 [-3.10, 17.38]
2.2.3 High doses	3	465	Mean Difference (IV, Random, 95% CI)	11.09 [4.39, 17.80]
2.3 Frequency of use: % of heavy drinking days at end of treatment	13	840	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.48, 0.11]
2.3.1 Low doses	6	278	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.15, 0.34]
2.3.2 Medium doses	6	242	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-1.15, 0.20]
2.3.3 High doses	1	320	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.43, 0.01]
2.4 Amount of use: drinks per drinking days at end of treatment	9	392	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.20, 0.30]
2.4.1 Low doses	5	242	Mean Difference (IV, Random, 95% CI)	-0.06 [-1.33, 1.22]
2.4.2 Medium doses	4	150	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.95, 0.68]
2.5 Adverse events: number of participants with at least one adverse event at end of treatment	10	738	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
2.5.1 Low doses	5	260	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.92, 1.64]
2.5.2 Medium doses	4	162	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.63, 1.28]
2.5.3 High doses	1	316	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
2.6 Dropouts at end of treatment	17	1563	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.1 Low doses	8	564	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.32]
2.6.2 Medium doses	5	214	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.65, 1.61]
2.6.3 High doses	4	785	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.67, 0.87]
2.7 Dropouts due to adverse events	16	1499	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.89, 2.18]
2.7.1 Low doses	8	564	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.61, 5.32]
2.7.2 Medium doses	4	150	Risk Ratio (M-H, Random, 95% CI)	6.11 [0.82, 45.25]
2.7.3 High doses	4	785	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.68, 2.13]

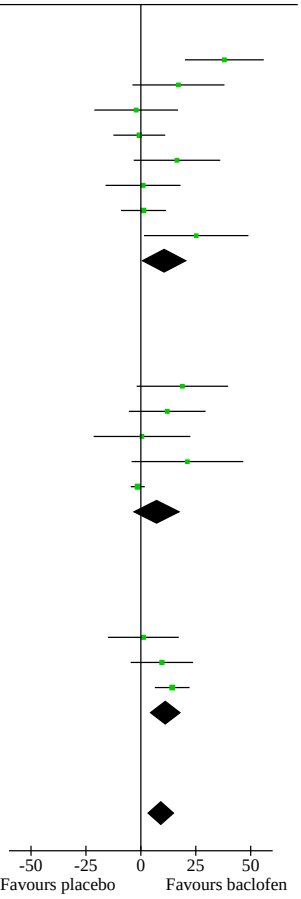
Analysis 2.1. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 1: Relapse: return to any drinking at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Low doses						
Addolorato 2007	12	42	30	42	4.3%	0.40 [0.24 , 0.67]
Addolorato 2011-LD	6	14	5	7	2.2%	0.60 [0.28 , 1.29]
Beraha 2016-LD	18	31	16	31	5.2%	1.13 [0.71 , 1.77]
Garbutt 2021-LD	41	43	20	20	16.3%	0.97 [0.88 , 1.07]
Hauser 2017	82	88	83	92	16.7%	1.03 [0.95 , 1.13]
Morley 2018-LD	15	36	12	17	4.6%	0.59 [0.36 , 0.97]
Subtotal (95% CI)		**254**		**209**	**49.3%**	**0.82 [0.64 , 1.04]**
Total events:	174		166			
Heterogeneity: Tau² = 0.05; Chi² = 32.98, df = 5 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 1.64 (P = 0.10)						
2.1.2 Medium doses						
Addolorato 2011-MD	6	14	4	7	1.7%	0.75 [0.31 , 1.81]
Garbutt 2021-MD	34	37	19	20	14.8%	0.97 [0.84 , 1.11]
Morley 2018-MD	12	35	11	16	3.7%	0.50 [0.28 , 0.88]
Subtotal (95% CI)		**86**		**43**	**20.2%**	**0.73 [0.37 , 1.45]**
Total events:	52		34			
Heterogeneity: Tau² = 0.29; Chi² = 11.20, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.1.3 High doses						
Beraha 2016-HD	33	58	17	31	6.4%	1.04 [0.70 , 1.53]
Muller 2015	16	28	24	28	7.2%	0.67 [0.47 , 0.95]
Reynaud 2017	139	158	145	162	17.0%	0.98 [0.91 , 1.06]
Subtotal (95% CI)		**244**		**221**	**30.5%**	**0.90 [0.71 , 1.15]**
Total events:	188		186			
Heterogeneity: Tau² = 0.03; Chi² = 4.78, df = 2 (P = 0.09); I² = 58%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**584**		**473**	**100.0%**	**0.87 [0.77 , 0.99]**
Total events:	414		386			
Heterogeneity: Tau² = 0.02; Chi² = 40.60, df = 11 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 2.16 (P = 0.03)						
Test for subgroup differences: Chi² = 0.54, df = 2 (P = 0.77), I² = 0%						



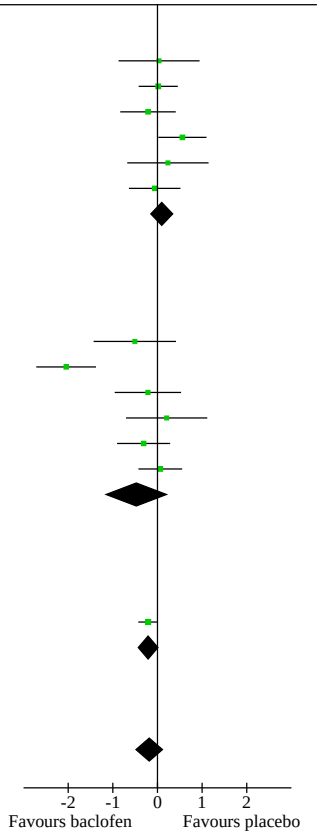
Analysis 2.2. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 2: Frequency of use: % days abstinence at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Low doses								
Addolorato 2007	74.7	41.5	42	36.7	42.4	42	5.6%	38.00 [20.06 , 55.94]
Addolorato 2011-LD	93.15	14.5	14	76.04	26.36	7	4.7%	17.11 [-3.84 , 38.06]
Beraha 2016-LD	67.68	39.11	31	69.82	37.41	31	5.2%	-2.14 [-21.19 , 16.91]
Garbutt 2010a	49.9	27.9	40	50.6	25.9	40	8.0%	-0.70 [-12.50 , 11.10]
Garbutt 2010b1	62.6	30.68	20	46.15	32.82	20	5.0%	16.45 [-3.24 , 36.14]
Garbutt 2021-LD	48	30.68	43	47	32.82	20	5.9%	1.00 [-16.06 , 18.06]
Hauser 2017	32.3	35.633419	88	31.1	34.525362	92	8.7%	1.20 [-9.06 , 11.46]
Morley 2018-LD	68.54	35.4	36	43.35	43.658676	17	4.0%	25.19 [1.43 , 48.95]
Subtotal (95% CI)			**314**			**269**	**47.0%**	**10.59 [0.77 , 20.41]**
Heterogeneity: Tau² = 122.61; Chi² = 19.68, df = 7 (P = 0.006); I² = 64%								
Test for overall effect: Z = 2.11 (P = 0.03)								
2.2.2 Medium doses								
Addolorato 2011-MD	94.94	13.7	14	76.04	26.36	7	4.7%	18.90 [-1.90 , 39.70]
Garbutt 2021-MD	59	30.68	37	47	32.82	20	5.7%	12.00 [-5.45 , 29.45]
Krupitskii 2017	94.2	30.68	16	93.7	32.82	16	4.4%	0.50 [-21.51 , 22.51]
Morley 2018-MD	64.56	41.412558	35	43.35	43.658676	16	3.6%	21.21 [-4.20 , 46.62]
Ponizovsky 2015	46.1	5.3	32	47.5	7.5	32	11.6%	-1.40 [-4.58 , 1.78]
Subtotal (95% CI)			**134**			**91**	**30.0%**	**7.14 [-3.10 , 17.38]**
Heterogeneity: Tau² = 65.64; Chi² = 8.39, df = 4 (P = 0.08); I² = 52%								
Test for overall effect: Z = 1.37 (P = 0.17)								
2.2.3 High doses								
Beraha 2016-HD	70.98	35.89	58	69.82	37.41	31	6.2%	1.16 [-14.93 , 17.25]
Muller 2015	49.35	29.17	28	39.76	24.94	28	7.0%	9.59 [-4.63 , 23.81]
Rigal 2020	53.57	32.29	162	39.29	39.29	158	9.8%	14.28 [6.39 , 22.17]
Subtotal (95% CI)			**248**			**217**	**23.0%**	**11.09 [4.39 , 17.80]**
Heterogeneity: Tau² = 2.62; Chi² = 2.13, df = 2 (P = 0.34); I² = 6%								
Test for overall effect: Z = 3.24 (P = 0.001)								
Total (95% CI)			**696**			**577**	**100.0%**	**9.07 [3.30 , 14.85]**
Heterogeneity: Tau² = 72.19; Chi² = 43.69, df = 15 (P = 0.0001); I² = 66%								
Test for overall effect: Z = 3.08 (P = 0.002)								
Test for subgroup differences: Chi² = 0.42, df = 2 (P = 0.81), I² = 0%								



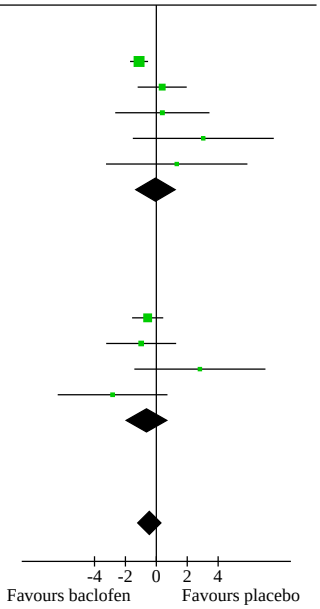
Analysis 2.3. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 3: Frequency of use: % of heavy drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.3.1 Low doses								
Addolorato 2011-LD	1.67	5.2	14	1.5	2.83	7	5.7%	0.04 [-0.87 , 0.94]
Garbutt 2010a	25.9	23.2	40	25.5	23.6	40	9.6%	0.02 [-0.42 , 0.46]
Garbutt 2010b1	13.25	5.28	20	14.4	5.35	20	7.9%	-0.21 [-0.83 , 0.41]
Garbutt 2021-LD	42	5.28	43	39	5.35	20	8.6%	0.56 [0.02 , 1.10]
Morley 2014-LD	2.07	3.134835	14	1.36	2.355456	7	5.7%	0.23 [-0.68 , 1.14]
Morley 2018-LD	2.28	2.89	36	2.46	2.77	17	8.3%	-0.06 [-0.64 , 0.51]
Subtotal (95% CI)			**167**			**111**	**45.8%**	**0.10 [-0.15 , 0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.28, df = 5 (P = 0.51); I² = 0%								
Test for overall effect: Z = 0.77 (P = 0.44)								
2.3.2 Medium doses								
Addolorato 2011-MD	0.5	1.24	14	1.5	2.83	7	5.6%	-0.51 [-1.43 , 0.42]
Garbutt 2021-MD	28	5.28	37	39	5.35	20	7.5%	-2.05 [-2.71 , -1.38]
Krupitskii 2017	0.4	0.4	14	0.5	0.5	14	6.9%	-0.21 [-0.96 , 0.53]
Morley 2014-MD	1.89	2.519992	14	1.36	2.355456	7	5.7%	0.21 [-0.70 , 1.12]
Morley 2018-MD	1.65	2.48	35	2.46	2.77	16	8.1%	-0.31 [-0.90 , 0.28]
Ponizovsky 2015	20.1	2.7	32	19.9	3.5	32	9.1%	0.06 [-0.43 , 0.55]
Subtotal (95% CI)			**146**			**96**	**42.9%**	**-0.47 [-1.15 , 0.20]**
Heterogeneity: Tau² = 0.58; Chi² = 28.68, df = 5 (P < 0.0001); I² = 83%								
Test for overall effect: Z = 1.38 (P = 0.17)								
2.3.3 High doses								
Rigal 2020	6	9	162	8	10	158	11.4%	-0.21 [-0.43 , 0.01]
Subtotal (95% CI)			**162**			**158**	**11.4%**	**-0.21 [-0.43 , 0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								
Total (95% CI)			**475**			**365**	**100.0%**	**-0.18 [-0.48 , 0.11]**
Heterogeneity: Tau² = 0.19; Chi² = 41.40, df = 12 (P < 0.0001); I² = 71%								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: Chi² = 4.59, df = 2 (P = 0.10), I² = 56.4%								



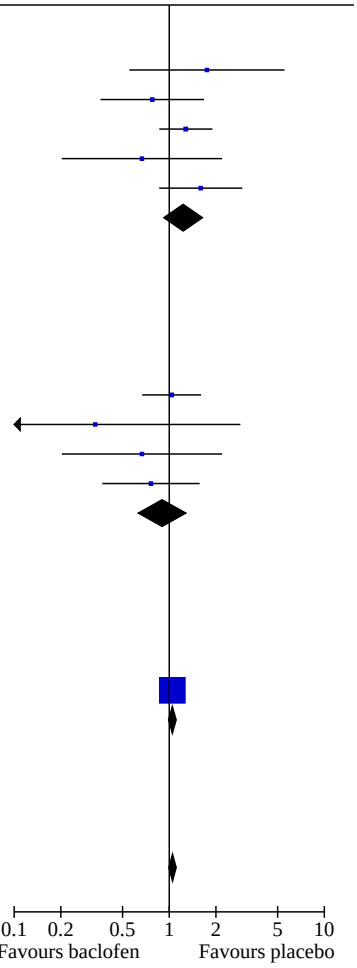
Analysis 2.4. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 4: Amount of use: drinks per drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Low doses								
Addolorato 2007	0.5781	1.06	42	1.6945	1.6099	42	34.6%	-1.12 [-1.70 , -0.53]
Addolorato 2011-LD	1.24	2.43	14	0.86	1.28	7	14.8%	0.38 [-1.21 , 1.97]
Garbutt 2021-LD	7.64	8.11	43	7.25	4.22	20	5.3%	0.39 [-2.66 , 3.44]
Morley 2014-LD	5.86	5.299777	14	2.82	4.884108	7	2.6%	3.04 [-1.52 , 7.60]
Morley 2018-LD	8.82	10.38	36	7.5	6.46	17	2.5%	1.32 [-3.25 , 5.89]
Subtotal (95% CI)			**149**			**93**	**59.8%**	**-0.06 [-1.33 , 1.22]**
Heterogeneity: Tau² = 0.84; Chi² = 7.39, df = 4 (P = 0.12); I² = 46%								
Test for overall effect: Z = 0.09 (P = 0.93)								
2.4.2 Medium doses								
Addolorato 2011-MD	0.3	0.65	14	0.86	1.28	7	24.4%	-0.56 [-1.57 , 0.45]
Garbutt 2021-MD	6.27	4.05	37	7.25	4.22	20	8.8%	-0.98 [-3.24 , 1.28]
Morley 2014-MD	5.64	4.225966	14	2.82	4.884108	7	2.9%	2.82 [-1.42 , 7.06]
Morley 2018-MD	4.67	4.86	35	7.5	6.46	16	4.1%	-2.83 [-6.38 , 0.72]
Subtotal (95% CI)			**100**			**50**	**40.2%**	**-0.64 [-1.95 , 0.68]**
Heterogeneity: Tau² = 0.54; Chi² = 4.13, df = 3 (P = 0.25); I² = 27%								
Test for overall effect: Z = 0.95 (P = 0.34)								
Total (95% CI)			**249**			**143**	**100.0%**	**-0.45 [-1.20 , 0.30]**
Heterogeneity: Tau² = 0.34; Chi² = 11.65, df = 8 (P = 0.17); I² = 31%								
Test for overall effect: Z = 1.18 (P = 0.24)								
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%								



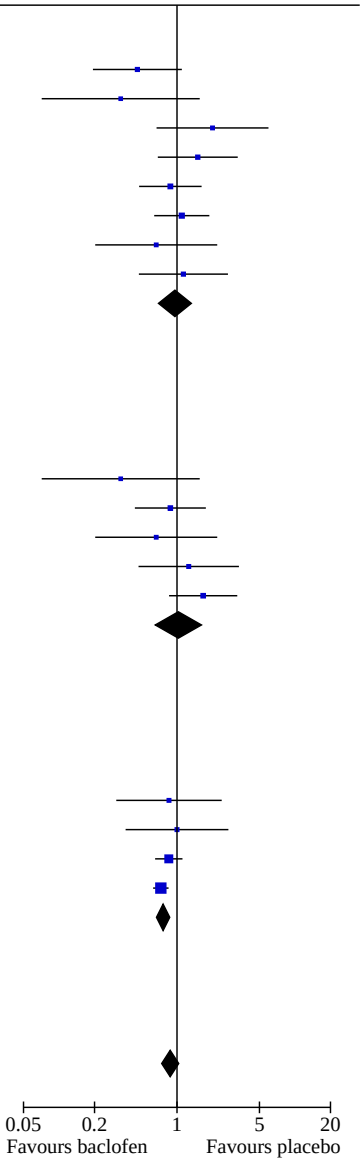
Analysis 2.5. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 5: Adverse events: number of participants with at least one adverse event at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Low doses						
Addolorato 2007	7	42	4	42	0.2%	1.75 [0.55 , 5.54]
Garbutt 2010b1	7	20	9	20	0.5%	0.78 [0.36 , 1.68]
Garbutt 2021-LD	33	43	12	20	1.9%	1.28 [0.86 , 1.90]
Morley 2014-LD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2018-LD	23	35	7	17	0.8%	1.60 [0.86 , 2.96]
Subtotal (95% CI)		**154**		**106**	**3.6%**	**1.23 [0.92 , 1.64]**
Total events:	74		35			
Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 4 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
2.5.2 Medium doses						
Garbutt 2021-MD	23	37	12	20	1.5%	1.04 [0.67 , 1.60]
Krupitskii 2017	1	16	3	16	0.1%	0.33 [0.04 , 2.87]
Morley 2014-MD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2018-MD	12	36	7	16	0.6%	0.76 [0.37 , 1.57]
Subtotal (95% CI)		**103**		**59**	**2.4%**	**0.90 [0.63 , 1.28]**
Total events:	40		25			
Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 3 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.55)						
2.5.3 High doses						
Reynaud 2017	151	157	146	159	94.0%	1.05 [0.99 , 1.11]
Subtotal (95% CI)		**157**		**159**	**94.0%**	**1.05 [0.99 , 1.11]**
Total events:	151		146			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Total (95% CI)		**414**		**324**	**100.0%**	**1.05 [0.99 , 1.11]**
Total events:	265		206			
Heterogeneity: Tau² = 0.00; Chi² = 7.06, df = 9 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 1.93, df = 2 (P = 0.38), I² = 0%						



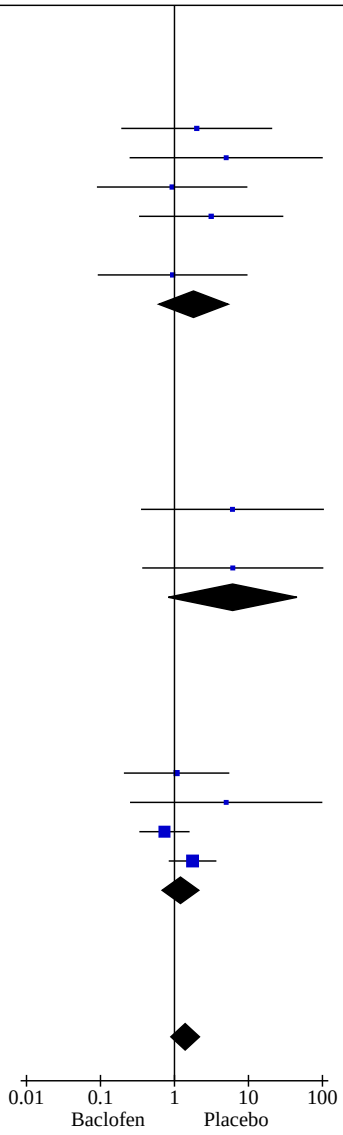
Analysis 2.6. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 6: Dropouts at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Low doses						
Addolorato 2007	6	42	13	42	3.3%	0.46 [0.19 , 1.10]
Addolorato 2011-LD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Beraha 2016-LD	8	31	4	31	2.2%	2.00 [0.67 , 5.96]
Garbutt 2010a	12	40	8	40	4.0%	1.50 [0.69 , 3.27]
Garbutt 2021-LD	17	43	9	20	6.2%	0.88 [0.48 , 1.62]
Hauser 2017	21	88	20	92	7.6%	1.10 [0.64 , 1.88]
Morley 2014-LD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2018-LD	12	36	5	17	3.3%	1.13 [0.48 , 2.70]
Subtotal (95% CI)		**308**		**256**	**29.7%**	**0.96 [0.70 , 1.32]**
Total events:	82		65			
Heterogeneity: Tau² = 0.03; Chi² = 8.36, df = 7 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.25 (P = 0.80)						
2.6.2 Medium doses						
Addolorato 2011-MD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Garbutt 2021-MD	13	37	8	20	5.0%	0.88 [0.44 , 1.76]
Morley 2014-MD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2018-MD	11	35	4	16	2.7%	1.26 [0.47 , 3.35]
Ponizovsky 2015	15	32	9	32	5.3%	1.67 [0.86 , 3.24]
Subtotal (95% CI)		**132**		**82**	**16.0%**	**1.03 [0.65 , 1.61]**
Total events:	45		27			
Heterogeneity: Tau² = 0.05; Chi² = 4.92, df = 4 (P = 0.30); I² = 19%						
Test for overall effect: Z = 0.12 (P = 0.91)						
2.6.3 High doses						
Beraha 2016-HD	8	58	5	31	2.4%	0.86 [0.31 , 2.39]
Muller 2015	6	28	6	28	2.5%	1.00 [0.37 , 2.73]
Reynaud 2017	59	158	71	162	19.5%	0.85 [0.65 , 1.11]
Rigal 2020	95	162	127	158	29.9%	0.73 [0.63 , 0.85]
Subtotal (95% CI)		**406**		**379**	**54.4%**	**0.76 [0.67 , 0.87]**
Total events:	168		209			
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
Total (95% CI)		**846**		**717**	**100.0%**	**0.88 [0.74 , 1.03]**
Total events:	295		301			
Heterogeneity: Tau² = 0.02; Chi² = 19.55, df = 16 (P = 0.24); I² = 18%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 2.97, df = 2 (P = 0.23), I² = 32.6%						



Analysis 2.7. Comparison 2: Baclofen versus placebo (divided into low, medium and high doses of baclofen), Outcome 7: Dropouts due to adverse events

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Low doses						
Addolorato 2007	0	42	0	42		Not estimable
Addolorato 2011-LD	0	14	0	7		Not estimable
Beraha 2016-LD	2	31	1	31	3.6%	2.00 [0.19 , 20.93]
Garbutt 2010a	2	40	0	40	2.2%	5.00 [0.25 , 100.97]
Garbutt 2021-LD	2	43	1	20	3.6%	0.93 [0.09 , 9.67]
Hauser 2017	3	88	1	92	3.9%	3.14 [0.33 , 29.59]
Morley 2014-LD	0	14	0	7		Not estimable
Morley 2018-LD	2	36	1	17	3.6%	0.94 [0.09 , 9.71]
Subtotal (95% CI)		**308**		**256**	**17.0%**	**1.81 [0.61 , 5.32]**
Total events:	11		4			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
2.7.2 Medium doses						
Addolorato 2011-MD	0	14	0	7		Not estimable
Garbutt 2021-MD	5	37	0	20	2.4%	6.08 [0.35 , 104.63]
Morley 2014-MD	0	14	0	7		Not estimable
Morley 2018-MD	6	35	0	16	2.5%	6.14 [0.37 , 102.79]
Subtotal (95% CI)		**100**		**50**	**4.9%**	**6.11 [0.82 , 45.25]**
Total events:	11		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
2.7.3 High doses						
Beraha 2016-HD	4	58	2	31	7.4%	1.07 [0.21 , 5.51]
Muller 2015	2	28	0	28	2.2%	5.00 [0.25 , 99.67]
Reynaud 2017	10	158	14	162	32.5%	0.73 [0.34 , 1.60]
Rigal 2020	18	162	10	158	36.1%	1.76 [0.84 , 3.68]
Subtotal (95% CI)		**406**		**379**	**78.1%**	**1.21 [0.68 , 2.13]**
Total events:	34		26			
Heterogeneity: Tau² = 0.05; Chi² = 3.45, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**814**		**685**	**100.0%**	**1.39 [0.89 , 2.18]**
Total events:	56		30			
Heterogeneity: Tau² = 0.00; Chi² = 7.55, df = 10 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
Test for subgroup differences: Chi² = 2.54, df = 2 (P = 0.28), I² = 21.4%						



Comparison 3. Baclofen versus placebo (divided into 12-week and longer than 12-week studies)

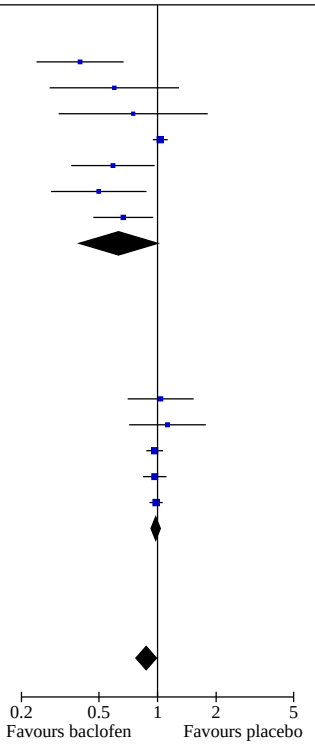
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Relapse: return to any drinking at end of treatment	12	1057	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
3.1.1 12-week studies	7	466	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.2 Longer than 12-week studies	5	591	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
3.2 Frequency of use: % days abstinence at end of treatment	16	1273	Mean Difference (IV, Random, 95% CI)	9.07 [3.30, 14.85]
3.2.1 12-week studies	11	682	Mean Difference (IV, Random, 95% CI)	10.90 [3.17, 18.62]
3.2.2 Longer than 12-week studies	5	591	Mean Difference (IV, Random, 95% CI)	8.05 [1.09, 15.01]
3.3 Frequency of use: % of heavy drinking days at end of treatment	13	840	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.48, 0.11]
3.3.1 12-week studies	10	400	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.27, 0.13]
3.3.2 Longer than 12-week studies	3	440	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.68, 0.60]
3.4 Amount of use: drink per drinking days at end of treatment	9	392	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.20, 0.30]
3.4.1 12-week studies	7	272	Mean Difference (IV, Random, 95% CI)	-0.36 [-1.29, 0.57]
3.4.2 Longer than 12-week studies	2	120	Mean Difference (IV, Random, 95% CI)	-0.49 [-2.31, 1.32]
3.5 Adverse events: number of participants with at least one adverse event at end of treatment	10	738	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
3.5.1 12-week studies	7	302	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.70, 1.39]
3.5.2 Longer than 12-week studies	3	436	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.00, 1.11]
3.6 Dropouts at end of treatment	17	1563	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.03]
3.6.1 12-week studies	11	652	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.73, 1.31]
3.6.2 Longer than 12-week studies	6	911	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.88]
3.7 Dropout due to adverse events	16	1499	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.89, 2.18]
3.7.1 12-week studies	10	588	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.93, 9.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7.2 Longer than 12-week studies	6	911	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.98]

Analysis 3.1. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 1: Relapse: return to any drinking at end of treatment

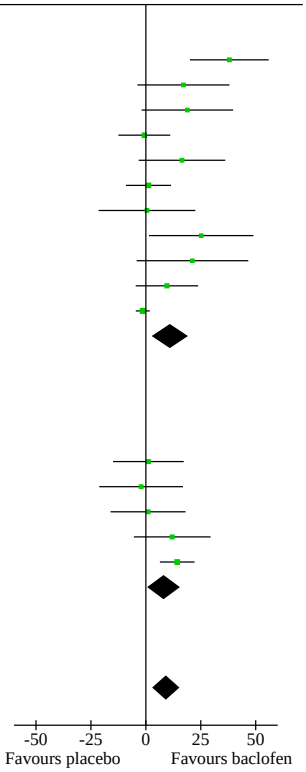
Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
3.1.1 12-week studies										
Addolorato 2007	12	42	30	42	4.3%	0.40 [0.24 , 0.67]	?	+	+	+
Addolorato 2011-LD	6	14	5	7	2.2%	0.60 [0.28 , 1.29]	+	+	−	−
Addolorato 2011-MD	6	14	4	7	1.7%	0.75 [0.31 , 1.81]	+	+	−	−
Hauser 2017	82	88	83	92	16.7%	1.03 [0.95 , 1.13]	+	+	+	?
Morley 2018-LD	15	36	12	17	4.6%	0.59 [0.36 , 0.97]	+	+	+	?
Morley 2018-MD	12	35	11	16	3.7%	0.50 [0.28 , 0.88]	+	+	+	?
Muller 2015	16	28	24	28	7.2%	0.67 [0.47 , 0.95]	+	+	+	?
Subtotal (95% CI)		**257**		**209**	**40.4%**	**0.63 [0.40 , 1.00]**				
Total events:	149		169							
Heterogeneity: Tau² = 0.32; Chi² = 54.47, df = 6 (P < 0.00001); I² = 89%										
Test for overall effect: Z = 1.95 (P = 0.05)										
3.1.2 Longer than 12-week studies										
Beraha 2016-HD	33	58	17	31	6.4%	1.04 [0.70 , 1.53]	+	+	+	+
Beraha 2016-LD	18	31	16	31	5.2%	1.13 [0.71 , 1.77]	+	+	+	+
Garbutt 2021-LD	41	43	20	20	16.3%	0.97 [0.88 , 1.07]	+	+	+	+
Garbutt 2021-MD	34	37	19	20	14.8%	0.97 [0.84 , 1.11]	+	+	+	+
Reynaud 2017	139	158	145	162	17.0%	0.98 [0.91 , 1.06]	+	+	+	?
Subtotal (95% CI)		**327**		**264**	**59.6%**	**0.98 [0.93 , 1.03]**				
Total events:	265		217							
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 4 (P = 0.93); I² = 0%										
Test for overall effect: Z = 0.79 (P = 0.43)										
Total (95% CI)		**584**		**473**	**100.0%**	**0.87 [0.77 , 0.99]**				
Total events:	414		386							
Heterogeneity: Tau² = 0.02; Chi² = 40.60, df = 11 (P < 0.0001); I² = 73%										
Test for overall effect: Z = 2.16 (P = 0.03)										
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.5%										



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

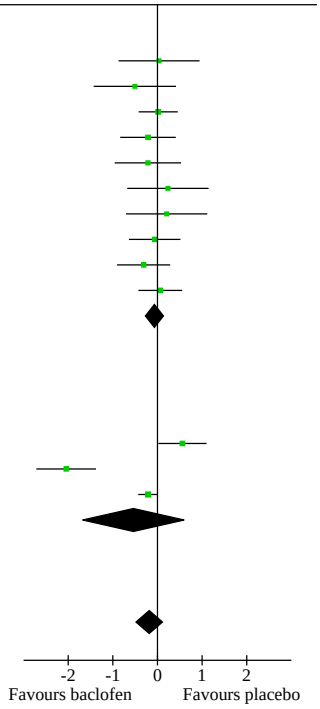
Analysis 3.2. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 2: Frequency of use: % days abstinence at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 12-week studies								
Addolorato 2007	74.7	41.5	42	36.7	42.4	42	5.6%	38.00 [20.06 , 55.94]
Addolorato 2011-LD	93.15	14.5	14	76.04	26.36	7	4.7%	17.11 [-3.84 , 38.06]
Addolorato 2011-MD	94.94	13.7	14	76.04	26.36	7	4.7%	18.90 [-1.90 , 39.70]
Garbutt 2010a	49.9	27.9	40	50.6	25.9	40	8.0%	-0.70 [-12.50 , 11.10]
Garbutt 2010b1	62.6	30.68	20	46.15	32.82	20	5.0%	16.45 [-3.24 , 36.14]
Hauser 2017	32.3	35.633419	88	31.1	34.525362	92	8.7%	1.20 [-9.06 , 11.46]
Krupitskii 2017	94.2	30.68	16	93.7	32.82	16	4.4%	0.50 [-21.51 , 22.51]
Morley 2018-LD	68.54	35.4	36	43.35	43.658676	17	4.0%	25.19 [1.43 , 48.95]
Morley 2018-MD	64.56	41.412558	35	43.35	43.658676	16	3.6%	21.21 [-4.20 , 46.62]
Muller 2015	49.35	29.17	28	39.76	24.94	28	7.0%	9.59 [-4.63 , 23.81]
Ponizovsky 2015	46.1	5.3	32	47.5	7.5	32	11.6%	-1.40 [-4.58 , 1.78]
Subtotal (95% CI)			**365**			**317**	**67.2%**	**10.90 [3.17 , 18.62]**
Heterogeneity: Tau² = 97.74; Chi² = 33.61, df = 10 (P = 0.0002); I² = 70%								
Test for overall effect: Z = 2.77 (P = 0.006)								
3.2.2 Longer than 12-week studies								
Beraha 2016-HD	70.98	35.89	58	69.82	37.41	31	6.2%	1.16 [-14.93 , 17.25]
Beraha 2016-LD	67.68	39.11	31	69.82	37.41	31	5.2%	-2.14 [-21.19 , 16.91]
Garbutt 2021-LD	48	30.68	43	47	32.82	20	5.9%	1.00 [-16.06 , 18.06]
Garbutt 2021-MD	59	30.68	37	47	32.82	20	5.7%	12.00 [-5.45 , 29.45]
Rigal 2020	53.57	32.29	162	39.29	39.29	158	9.8%	14.28 [6.39 , 22.17]
Subtotal (95% CI)			**331**			**260**	**32.8%**	**8.05 [1.09 , 15.01]**
Heterogeneity: Tau² = 12.27; Chi² = 4.90, df = 4 (P = 0.30); I² = 18%								
Test for overall effect: Z = 2.27 (P = 0.02)								
Total (95% CI)			**696**			**577**	**100.0%**	**9.07 [3.30 , 14.85]**
Heterogeneity: Tau² = 72.19; Chi² = 43.69, df = 15 (P = 0.0001); I² = 66%								
Test for overall effect: Z = 3.08 (P = 0.002)								
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%								



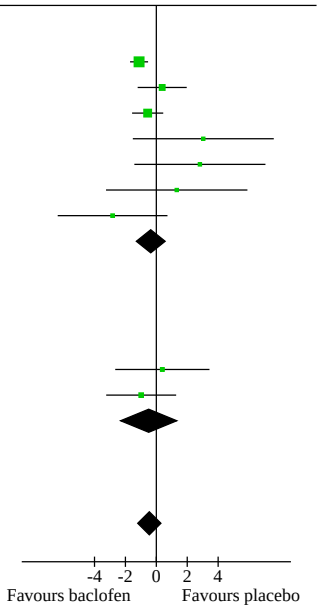
Analysis 3.3. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 3: Frequency of use: % of heavy drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.1 12-week studies								
Addolorato 2011-LD	1.67	5.2	14	1.5	2.83	7	5.7%	0.04 [-0.87 , 0.94]
Addolorato 2011-MD	0.5	1.24	14	1.5	2.83	7	5.6%	-0.51 [-1.43 , 0.42]
Garbutt 2010a	25.9	23.2	40	25.5	23.6	40	9.6%	0.02 [-0.42 , 0.46]
Garbutt 2010b1	13.25	5.28	20	14.4	5.35	20	7.9%	-0.21 [-0.83 , 0.41]
Krupitskii 2017	0.4	0.4	14	0.5	0.5	14	6.9%	-0.21 [-0.96 , 0.53]
Morley 2014-LD	2.07	3.134835	14	1.36	2.355456	7	5.7%	0.23 [-0.68 , 1.14]
Morley 2014-MD	1.89	2.519992	14	1.36	2.355456	7	5.7%	0.21 [-0.70 , 1.12]
Morley 2018-LD	2.28	2.89	36	2.46	2.77	17	8.3%	-0.06 [-0.64 , 0.51]
Morley 2018-MD	1.65	2.48	35	2.46	2.77	16	8.1%	-0.31 [-0.90 , 0.28]
Ponizovsky 2015	20.1	2.7	32	19.9	3.5	32	9.1%	0.06 [-0.43 , 0.55]
Subtotal (95% CI)			**233**			**167**	**72.5%**	**-0.07 [-0.27 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 9 (P = 0.96); I² = 0%								
Test for overall effect: Z = 0.66 (P = 0.51)								
3.3.2 Longer than 12-week studies								
Garbutt 2021-LD	42	5.28	43	39	5.35	20	8.6%	0.56 [0.02 , 1.10]
Garbutt 2021-MD	28	5.28	37	39	5.35	20	7.5%	-2.05 [-2.71 , -1.38]
Rigal 2020	6	9	162	8	10	158	11.4%	-0.21 [-0.43 , 0.01]
Subtotal (95% CI)			**242**			**198**	**27.5%**	**-0.54 [-1.68 , 0.60]**
Heterogeneity: Tau² = 0.94; Chi² = 36.40, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Total (95% CI)			**475**			**365**	**100.0%**	**-0.18 [-0.48 , 0.11]**
Heterogeneity: Tau² = 0.19; Chi² = 41.40, df = 12 (P < 0.0001); I² = 71%								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%								



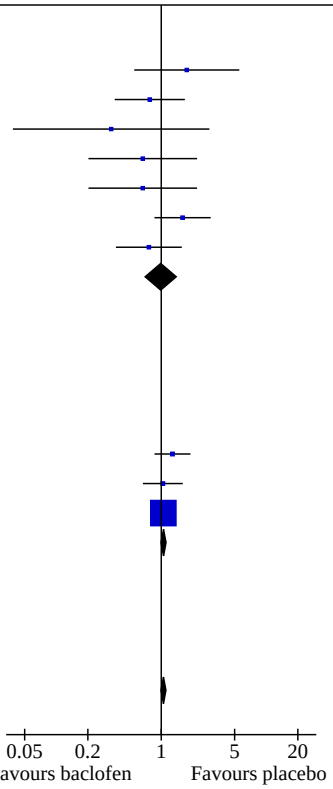
Analysis 3.4. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 4: Amount of use: drink per drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 12-week studies								
Addolorato 2007	0.5781	1.06	42	1.6945	1.6099	42	34.6%	-1.12 [-1.70 , -0.53]
Addolorato 2011-LD	1.24	2.43	14	0.86	1.28	7	14.8%	0.38 [-1.21 , 1.97]
Addolorato 2011-MD	0.3	0.65	14	0.86	1.28	7	24.4%	-0.56 [-1.57 , 0.45]
Morley 2014-LD	5.86	5.299777	14	2.82	4.884108	7	2.6%	3.04 [-1.52 , 7.60]
Morley 2014-MD	5.64	4.225966	14	2.82	4.884108	7	2.9%	2.82 [-1.42 , 7.06]
Morley 2018-LD	8.82	10.38	36	7.5	6.46	17	2.5%	1.32 [-3.25 , 5.89]
Morley 2018-MD	4.67	4.86	35	7.5	6.46	16	4.1%	-2.83 [-6.38 , 0.72]
Subtotal (95% CI)			**169**			**103**	**85.9%**	**-0.36 [-1.29 , 0.57]**
Heterogeneity: Tau² = 0.55; Chi² = 11.07, df = 6 (P = 0.09); I² = 46%								
Test for overall effect: Z = 0.76 (P = 0.45)								
3.4.2 Longer than 12-week studies								
Garbutt 2021-LD	7.64	8.11	43	7.25	4.22	20	5.3%	0.39 [-2.66 , 3.44]
Garbutt 2021-MD	6.27	4.05	37	7.25	4.22	20	8.8%	-0.98 [-3.24 , 1.28]
Subtotal (95% CI)			**80**			**40**	**14.1%**	**-0.49 [-2.31 , 1.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 0.53 (P = 0.59)								
Total (95% CI)			**249**			**143**	**100.0%**	**-0.45 [-1.20 , 0.30]**
Heterogeneity: Tau² = 0.34; Chi² = 11.65, df = 8 (P = 0.17); I² = 31%								
Test for overall effect: Z = 1.18 (P = 0.24)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%								



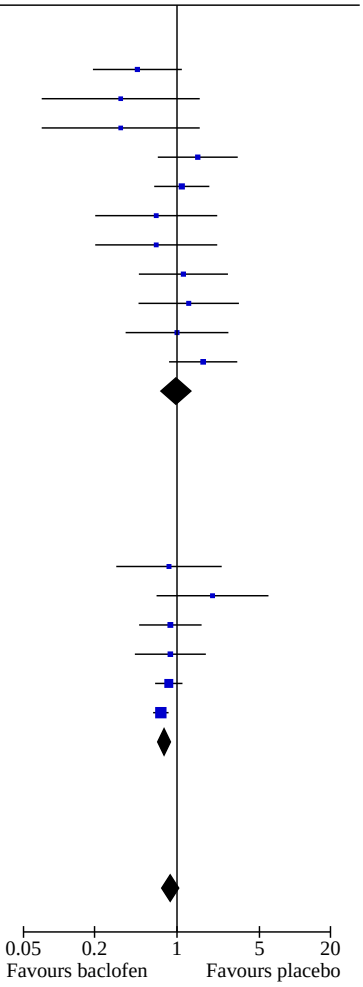
Analysis 3.5. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 5: Adverse events: number of participants with at least one adverse event at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 12-week studies						
Addolorato 2007	7	42	4	42	0.2%	1.75 [0.55 , 5.54]
Garbutt 2010b1	7	20	9	20	0.5%	0.78 [0.36 , 1.68]
Krupitskii 2017	1	16	3	16	0.1%	0.33 [0.04 , 2.87]
Morley 2014-LD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2014-MD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2018-LD	23	35	7	17	0.8%	1.60 [0.86 , 2.96]
Morley 2018-MD	12	36	7	16	0.6%	0.76 [0.37 , 1.57]
Subtotal (95% CI)		**177**		**125**	**2.5%**	**0.99 [0.70 , 1.39]**
Total events:	58		36			
Heterogeneity: Tau² = 0.00; Chi² = 5.96, df = 6 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
3.5.2 Longer than 12-week studies						
Garbutt 2021-LD	33	43	12	20	1.9%	1.28 [0.86 , 1.90]
Garbutt 2021-MD	23	37	12	20	1.5%	1.04 [0.67 , 1.60]
Reynaud 2017	151	157	146	159	94.0%	1.05 [0.99 , 1.11]
Subtotal (95% CI)		**237**		**199**	**97.5%**	**1.05 [1.00 , 1.11]**
Total events:	207		170			
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						
Total (95% CI)		**414**		**324**	**100.0%**	**1.05 [0.99 , 1.11]**
Total events:	265		206			
Heterogeneity: Tau² = 0.00; Chi² = 7.06, df = 9 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.72), I² = 0%						



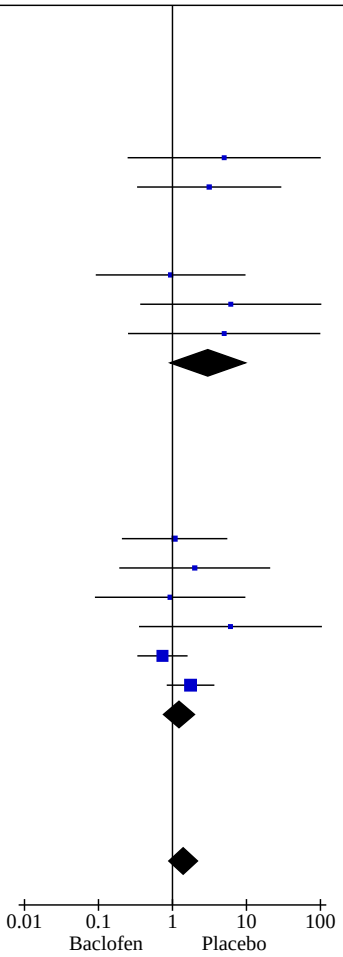
Analysis 3.6. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 6: Dropouts at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 12-week studies						
Addolorato 2007	6	42	13	42	3.3%	0.46 [0.19 , 1.10]
Addolorato 2011-LD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Addolorato 2011-MD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Garbutt 2010a	12	40	8	40	4.0%	1.50 [0.69 , 3.27]
Hauser 2017	21	88	20	92	7.6%	1.10 [0.64 , 1.88]
Morley 2014-LD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2014-MD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2018-LD	12	36	5	17	3.3%	1.13 [0.48 , 2.70]
Morley 2018-MD	11	35	4	16	2.7%	1.26 [0.47 , 3.35]
Muller 2015	6	28	6	28	2.5%	1.00 [0.37 , 2.73]
Ponizovsky 2015	15	32	9	32	5.3%	1.67 [0.86 , 3.24]
Subtotal (95% CI)		**357**		**295**	**34.8%**	**0.98 [0.73 , 1.31]**
Total events:	95		77			
Heterogeneity: Tau² = 0.03; Chi² = 11.55, df = 10 (P = 0.32); I² = 13%						
Test for overall effect: Z = 0.15 (P = 0.88)						
3.6.2 Longer than 12-week studies						
Beraha 2016-HD	8	58	5	31	2.4%	0.86 [0.31 , 2.39]
Beraha 2016-LD	8	31	4	31	2.2%	2.00 [0.67 , 5.96]
Garbutt 2021-LD	17	43	9	20	6.2%	0.88 [0.48 , 1.62]
Garbutt 2021-MD	13	37	8	20	5.0%	0.88 [0.44 , 1.76]
Reynaud 2017	59	158	71	162	19.5%	0.85 [0.65 , 1.11]
Rigal 2020	95	162	127	158	29.9%	0.73 [0.63 , 0.85]
Subtotal (95% CI)		**489**		**422**	**65.2%**	**0.78 [0.69 , 0.88]**
Total events:	200		224			
Heterogeneity: Tau² = 0.00; Chi² = 4.67, df = 5 (P = 0.46); I² = 0%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
Total (95% CI)		**846**		**717**	**100.0%**	**0.88 [0.74 , 1.03]**
Total events:	295		301			
Heterogeneity: Tau² = 0.02; Chi² = 19.55, df = 16 (P = 0.24); I² = 18%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 2.03, df = 1 (P = 0.15), I² = 50.8%						



Analysis 3.7. Comparison 3: Baclofen versus placebo (divided into 12-week and longer than 12-week studies), Outcome 7: Dropout due to adverse events

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 12-week studies						
Addolorato 2007	0	42	0	42		Not estimable
Addolorato 2011-LD	0	14	0	7		Not estimable
Addolorato 2011-MD	0	14	0	7		Not estimable
Garbutt 2010a	2	40	0	40	2.2%	5.00 [0.25 , 100.97]
Hauser 2017	3	88	1	92	3.9%	3.14 [0.33 , 29.59]
Morley 2014-LD	0	14	0	7		Not estimable
Morley 2014-MD	0	14	0	7		Not estimable
Morley 2018-LD	2	36	1	17	3.6%	0.94 [0.09 , 9.71]
Morley 2018-MD	6	35	0	16	2.5%	6.14 [0.37 , 102.79]
Muller 2015	2	28	0	28	2.2%	5.00 [0.25 , 99.67]
Subtotal (95% CI)		**325**		**263**	**14.5%**	**3.00 [0.93 , 9.66]**
Total events:	15		2			
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
3.7.2 Longer than 12-week studies						
Beraha 2016-HD	4	58	2	31	7.4%	1.07 [0.21 , 5.51]
Beraha 2016-LD	2	31	1	31	3.6%	2.00 [0.19 , 20.93]
Garbutt 2021-LD	2	43	1	20	3.6%	0.93 [0.09 , 9.67]
Garbutt 2021-MD	5	37	0	20	2.4%	6.08 [0.35 , 104.63]
Reynaud 2017	10	158	14	162	32.5%	0.73 [0.34 , 1.60]
Rigal 2020	18	162	10	158	36.1%	1.76 [0.84 , 3.68]
Subtotal (95% CI)		**489**		**422**	**85.5%**	**1.22 [0.76 , 1.98]**
Total events:	41		28			
Heterogeneity: Tau² = 0.00; Chi² = 4.07, df = 5 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**814**		**685**	**100.0%**	**1.39 [0.89 , 2.18]**
Total events:	56		30			
Heterogeneity: Tau² = 0.00; Chi² = 7.55, df = 10 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
Test for subgroup differences: Chi² = 1.93, df = 1 (P = 0.17), I² = 48.1%						



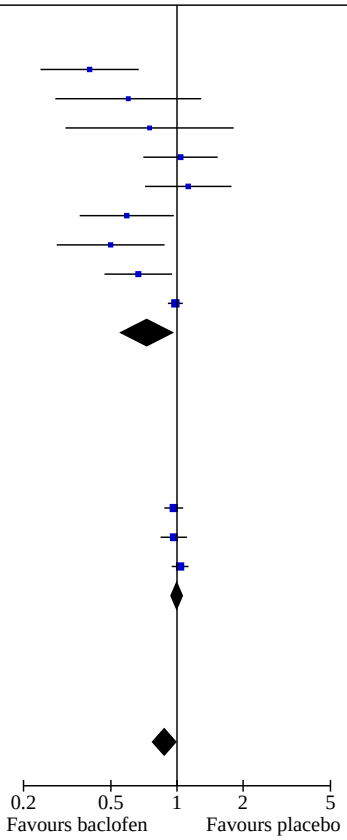
Comparison 4. Baclofen versus placebo (divided into detoxified and non-detoxified participants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Relapse: return to any drinking at end of treatment	12	1057	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.99]
4.1.1 Detoxified participants	9	757	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.95]
4.1.2 Non-detoxified participants	3	300	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
4.2 Frequency of use: % days abstinence at end of treatment	16	1273	Mean Difference (IV, Random, 95% CI)	9.07 [3.30, 14.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.1 Detoxified participants	10	549	Mean Difference (IV, Random, 95% CI)	11.76 [3.22, 20.29]
4.2.2 Non-detoxified participants	6	724	Mean Difference (IV, Random, 95% CI)	6.03 [-1.59, 13.64]
4.3 Frequency of use: % of heavy drinking days at end of treatment	13	840	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.48, 0.11]
4.3.1 Detoxified participants	8	296	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.32, 0.16]
4.3.2 Non-detoxified participants	5	544	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.98, 0.30]
4.4 Amount of use: drink per drinking days at end of treatment	9	392	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.20, 0.30]
4.4.1 Detoxified participants	7	272	Mean Difference (IV, Random, 95% CI)	-0.36 [-1.29, 0.57]
4.4.2 Non-detoxified participants	2	120	Mean Difference (IV, Random, 95% CI)	-0.49 [-2.31, 1.32]
4.5 Adverse events: number of participants with at least one adverse event at end of treatment	10	738	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
4.5.1 Detoxified participants	7	578	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
4.5.2 Non-detoxified participants	3	160	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.45]
4.6 Dropouts at end of treatment	17	1563	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.03]
4.6.1 Detoxified participants	12	879	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
4.6.2 No-detoxified participants	5	684	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.28]
4.7 Dropouts due to adverse events	16	1499	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.89, 2.18]
4.7.1 Detoxified participants	12	879	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.59, 1.98]
4.7.2 No-detoxified participants	4	620	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.97, 3.61]

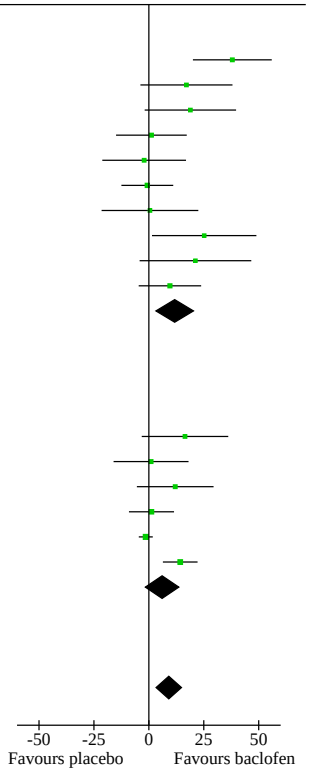
Analysis 4.1. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 1: Relapse: return to any drinking at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Detoxified participants						
Addolorato 2007	12	42	30	42	4.3%	0.40 [0.24 , 0.67]
Addolorato 2011-LD	6	14	5	7	2.2%	0.60 [0.28 , 1.29]
Addolorato 2011-MD	6	14	4	7	1.7%	0.75 [0.31 , 1.81]
Beraha 2016-HD	33	58	17	31	6.4%	1.04 [0.70 , 1.53]
Beraha 2016-LD	18	31	16	31	5.2%	1.13 [0.71 , 1.77]
Morley 2018-LD	15	36	12	17	4.6%	0.59 [0.36 , 0.97]
Morley 2018-MD	12	35	11	16	3.7%	0.50 [0.28 , 0.88]
Muller 2015	16	28	24	28	7.2%	0.67 [0.47 , 0.95]
Reynaud 2017	139	158	145	162	17.0%	0.98 [0.91 , 1.06]
Subtotal (95% CI)		**416**		**341**	**52.3%**	**0.73 [0.55 , 0.95]**
Total events:	257		264			
Heterogeneity: Tau² = 0.11; Chi² = 33.42, df = 8 (P < 0.0001); I² = 76%						
Test for overall effect: Z = 2.30 (P = 0.02)						
4.1.2 Non-detoxified participants						
Garbutt 2021-LD	41	43	20	20	16.3%	0.97 [0.88 , 1.07]
Garbutt 2021-MD	34	37	19	20	14.8%	0.97 [0.84 , 1.11]
Hauser 2017	82	88	83	92	16.7%	1.03 [0.95 , 1.13]
Subtotal (95% CI)		**168**		**132**	**47.7%**	**1.00 [0.94 , 1.06]**
Total events:	157		122			
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**584**		**473**	**100.0%**	**0.87 [0.77 , 0.99]**
Total events:	414		386			
Heterogeneity: Tau² = 0.02; Chi² = 40.60, df = 11 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 2.16 (P = 0.03)						
Test for subgroup differences: Chi² = 4.94, df = 1 (P = 0.03), I² = 79.8%						



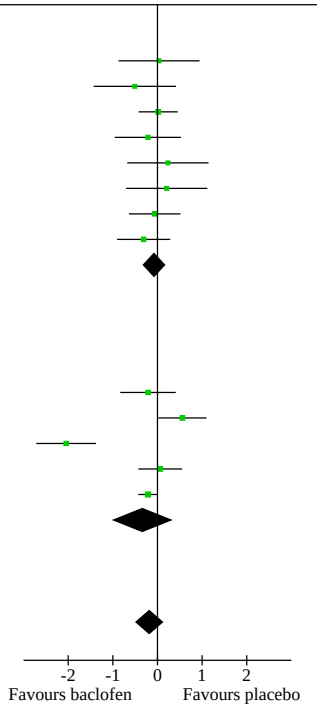
Analysis 4.2. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 2: Frequency of use: % days abstinence at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
4.2.1 Detoxified participants								
Addolorato 2007	74.7	41.5	42	36.7	42.4	42	5.6%	38.00 [20.06 , 55.94]
Addolorato 2011-LD	93.15	14.5	14	76.04	26.36	7	4.7%	17.11 [-3.84 , 38.06]
Addolorato 2011-MD	94.94	13.7	14	76.04	26.36	7	4.7%	18.90 [-1.90 , 39.70]
Beraha 2016-HD	70.98	35.89	58	69.82	37.41	31	6.2%	1.16 [-14.93 , 17.25]
Beraha 2016-LD	67.68	39.11	31	69.82	37.41	31	5.2%	-2.14 [-21.19 , 16.91]
Garbutt 2010a	49.9	27.9	40	50.6	25.9	40	8.0%	-0.70 [-12.50 , 11.10]
Krupitskii 2017	94.2	30.68	16	93.7	32.82	16	4.4%	0.50 [-21.51 , 22.51]
Morley 2018-LD	68.54	35.4	36	43.35	43.658676	17	4.0%	25.19 [1.43 , 48.95]
Morley 2018-MD	64.56	41.412558	35	43.35	43.658676	16	3.6%	21.21 [-4.20 , 46.62]
Muller 2015	49.35	29.17	28	39.76	24.94	28	7.0%	9.59 [-4.63 , 23.81]
Subtotal (95% CI)			**314**			**235**	**53.3%**	**11.76 [3.22 , 20.29]**
Heterogeneity: Tau² = 97.56; Chi² = 19.42, df = 9 (P = 0.02); I² = 54%								
Test for overall effect: Z = 2.70 (P = 0.007)								
4.2.2 Non-detoxified participants								
Garbutt 2010b1	62.6	30.68	20	46.15	32.82	20	5.0%	16.45 [-3.24 , 36.14]
Garbutt 2021-LD	48	30.68	43	47	32.82	20	5.9%	1.00 [-16.06 , 18.06]
Garbutt 2021-MD	59	30.68	37	47	32.82	20	5.7%	12.00 [-5.45 , 29.45]
Hauser 2017	32.3	35.633419	88	31.1	34.525362	92	8.7%	1.20 [-9.06 , 11.46]
Ponizovsky 2015	46.1	5.3	32	47.5	7.5	32	11.6%	-1.40 [-4.58 , 1.78]
Rigal 2020	53.57	32.29	162	39.29	39.29	158	9.8%	14.28 [6.39 , 22.17]
Subtotal (95% CI)			**382**			**342**	**46.7%**	**6.03 [-1.59 , 13.64]**
Heterogeneity: Tau² = 53.48; Chi² = 16.88, df = 5 (P = 0.005); I² = 70%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Total (95% CI)			**696**			**577**	**100.0%**	**9.07 [3.30 , 14.85]**
Heterogeneity: Tau² = 72.19; Chi² = 43.69, df = 15 (P = 0.0001); I² = 66%								
Test for overall effect: Z = 3.08 (P = 0.002)								
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%								



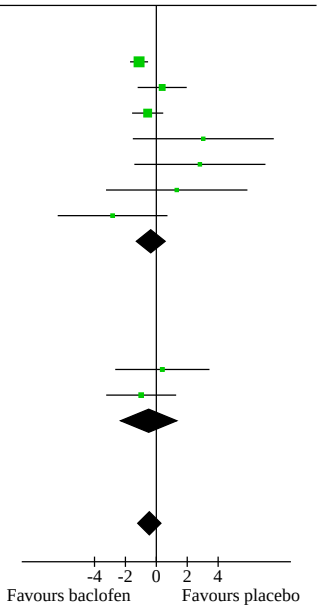
Analysis 4.3. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 3: Frequency of use: % of heavy drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.3.1 Detoxified participants								
Addolorato 2011-LD	1.67	5.2	14	1.5	2.83	7	5.7%	0.04 [-0.87 , 0.94]
Addolorato 2011-MD	0.5	1.24	14	1.5	2.83	7	5.6%	-0.51 [-1.43 , 0.42]
Garbutt 2010a	25.9	23.2	40	25.5	23.6	40	9.6%	0.02 [-0.42 , 0.46]
Krupitskii 2017	0.4	0.4	14	0.5	0.5	14	6.9%	-0.21 [-0.96 , 0.53]
Morley 2014-LD	2.07	3.134835	14	1.36	2.355456	7	5.7%	0.23 [-0.68 , 1.14]
Morley 2014-MD	1.89	2.519992	14	1.36	2.355456	7	5.7%	0.21 [-0.70 , 1.12]
Morley 2018-LD	2.28	2.89	36	2.46	2.77	17	8.3%	-0.06 [-0.64 , 0.51]
Morley 2018-MD	1.65	2.48	35	2.46	2.77	16	8.1%	-0.31 [-0.90 , 0.28]
Subtotal (95% CI)			**181**			**115**	**55.5%**	**-0.08 [-0.32 , 0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 2.61, df = 7 (P = 0.92); I² = 0%								
Test for overall effect: Z = 0.65 (P = 0.52)								
4.3.2 Non-detoxified participants								
Garbutt 2010b1	13.25	5.28	20	14.4	5.35	20	7.9%	-0.21 [-0.83 , 0.41]
Garbutt 2021-LD	42	5.28	43	39	5.35	20	8.6%	0.56 [0.02 , 1.10]
Garbutt 2021-MD	28	5.28	37	39	5.35	20	7.5%	-2.05 [-2.71 , -1.38]
Ponizovsky 2015	20.1	2.7	32	19.9	3.5	32	9.1%	0.06 [-0.43 , 0.55]
Rigal 2020	6	9	162	8	10	158	11.4%	-0.21 [-0.43 , 0.01]
Subtotal (95% CI)			**294**			**250**	**44.5%**	**-0.34 [-0.98 , 0.30]**
Heterogeneity: Tau² = 0.47; Chi² = 37.90, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 1.04 (P = 0.30)								
Total (95% CI)			**475**			**365**	**100.0%**	**-0.18 [-0.48 , 0.11]**
Heterogeneity: Tau² = 0.19; Chi² = 41.40, df = 12 (P < 0.0001); I² = 71%								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%								



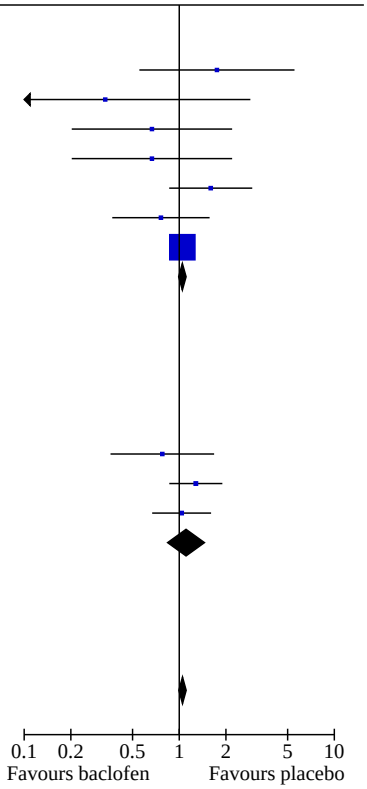
Analysis 4.4. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 4: Amount of use: drink per drinking days at end of treatment

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
4.4.1 Detoxified participants								
Addolorato 2007	0.5781	1.06	42	1.6945	1.6099	42	34.6%	-1.12 [-1.70 , -0.53]
Addolorato 2011-LD	1.24	2.43	14	0.86	1.28	7	14.8%	0.38 [-1.21 , 1.97]
Addolorato 2011-MD	0.3	0.65	14	0.86	1.28	7	24.4%	-0.56 [-1.57 , 0.45]
Morley 2014-LD	5.86	5.299777	14	2.82	4.884108	7	2.6%	3.04 [-1.52 , 7.60]
Morley 2014-MD	5.64	4.225966	14	2.82	4.884108	7	2.9%	2.82 [-1.42 , 7.06]
Morley 2018-LD	8.82	10.38	36	7.5	6.46	17	2.5%	1.32 [-3.25 , 5.89]
Morley 2018-MD	4.67	4.86	35	7.5	6.46	16	4.1%	-2.83 [-6.38 , 0.72]
Subtotal (95% CI)			**169**			**103**	**85.9%**	**-0.36 [-1.29 , 0.57]**
Heterogeneity: Tau² = 0.55; Chi² = 11.07, df = 6 (P = 0.09); I² = 46%								
Test for overall effect: Z = 0.76 (P = 0.45)								
4.4.2 Non-detoxified participants								
Garbutt 2021-LD	7.64	8.11	43	7.25	4.22	20	5.3%	0.39 [-2.66 , 3.44]
Garbutt 2021-MD	6.27	4.05	37	7.25	4.22	20	8.8%	-0.98 [-3.24 , 1.28]
Subtotal (95% CI)			**80**			**40**	**14.1%**	**-0.49 [-2.31 , 1.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 0.53 (P = 0.59)								
Total (95% CI)			**249**			**143**	**100.0%**	**-0.45 [-1.20 , 0.30]**
Heterogeneity: Tau² = 0.34; Chi² = 11.65, df = 8 (P = 0.17); I² = 31%								
Test for overall effect: Z = 1.18 (P = 0.24)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%								

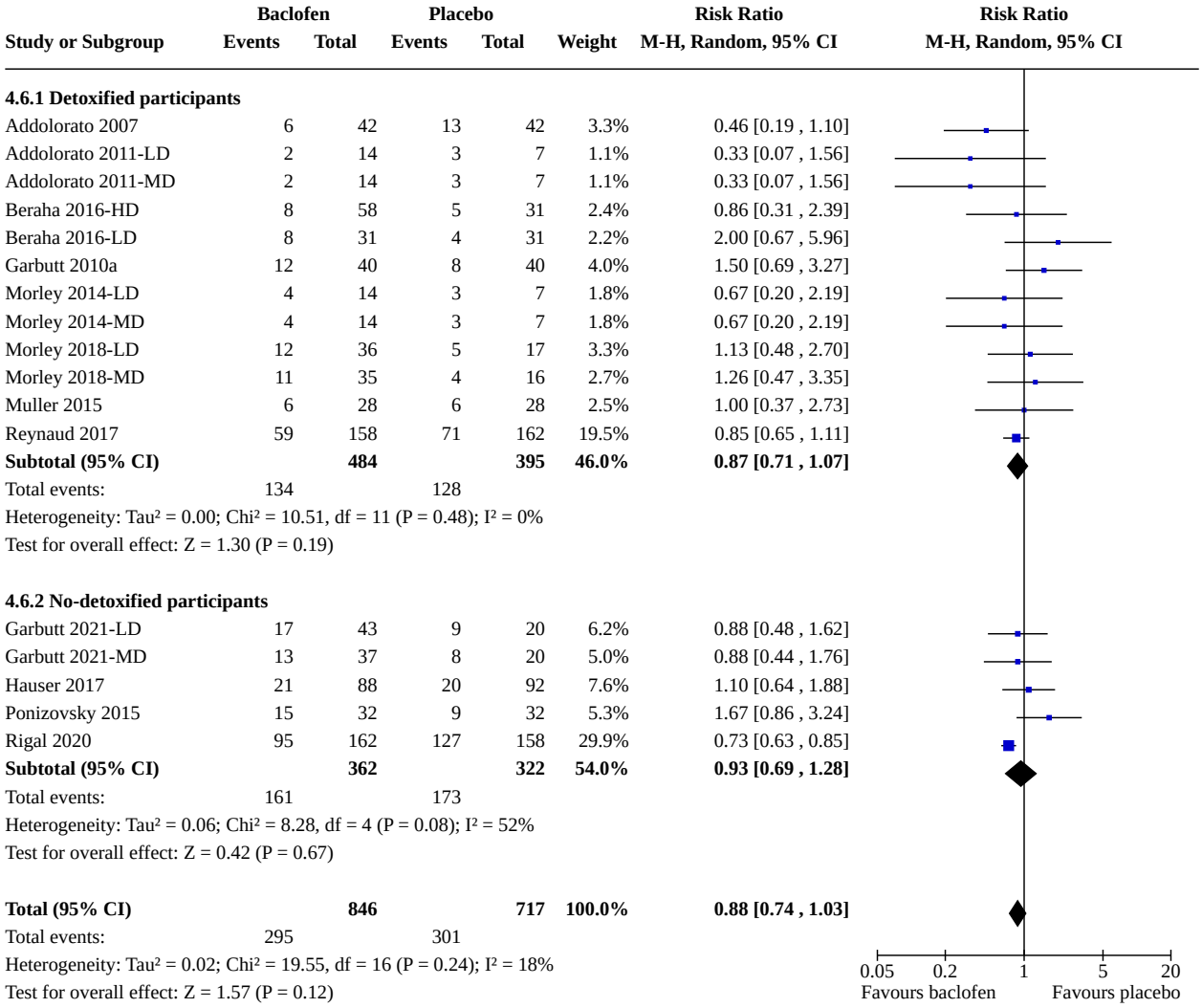


Analysis 4.5. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 5: Adverse events: number of participants with at least one adverse event at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 Detoxified participants						
Addolorato 2007	7	42	4	42	0.2%	1.75 [0.55 , 5.54]
Krupitskii 2017	1	16	3	16	0.1%	0.33 [0.04 , 2.87]
Morley 2014-LD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2014-MD	4	14	3	7	0.2%	0.67 [0.20 , 2.19]
Morley 2018-LD	23	35	7	17	0.8%	1.60 [0.86 , 2.96]
Morley 2018-MD	12	36	7	16	0.6%	0.76 [0.37 , 1.57]
Reynaud 2017	151	157	146	159	94.0%	1.05 [0.99 , 1.11]
Subtotal (95% CI)		**314**		**264**	**96.1%**	**1.05 [0.99 , 1.11]**
Total events:	202		173			
Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 6 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
4.5.2 Non-detoxified participants						
Garbutt 2010b1	7	20	9	20	0.5%	0.78 [0.36 , 1.68]
Garbutt 2021-LD	33	43	12	20	1.9%	1.28 [0.86 , 1.90]
Garbutt 2021-MD	23	37	12	20	1.5%	1.04 [0.67 , 1.60]
Subtotal (95% CI)		**100**		**60**	**3.9%**	**1.11 [0.84 , 1.45]**
Total events:	63		33			
Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (95% CI)		**414**		**324**	**100.0%**	**1.05 [0.99 , 1.11]**
Total events:	265		206			
Heterogeneity: Tau² = 0.00; Chi² = 7.06, df = 9 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						

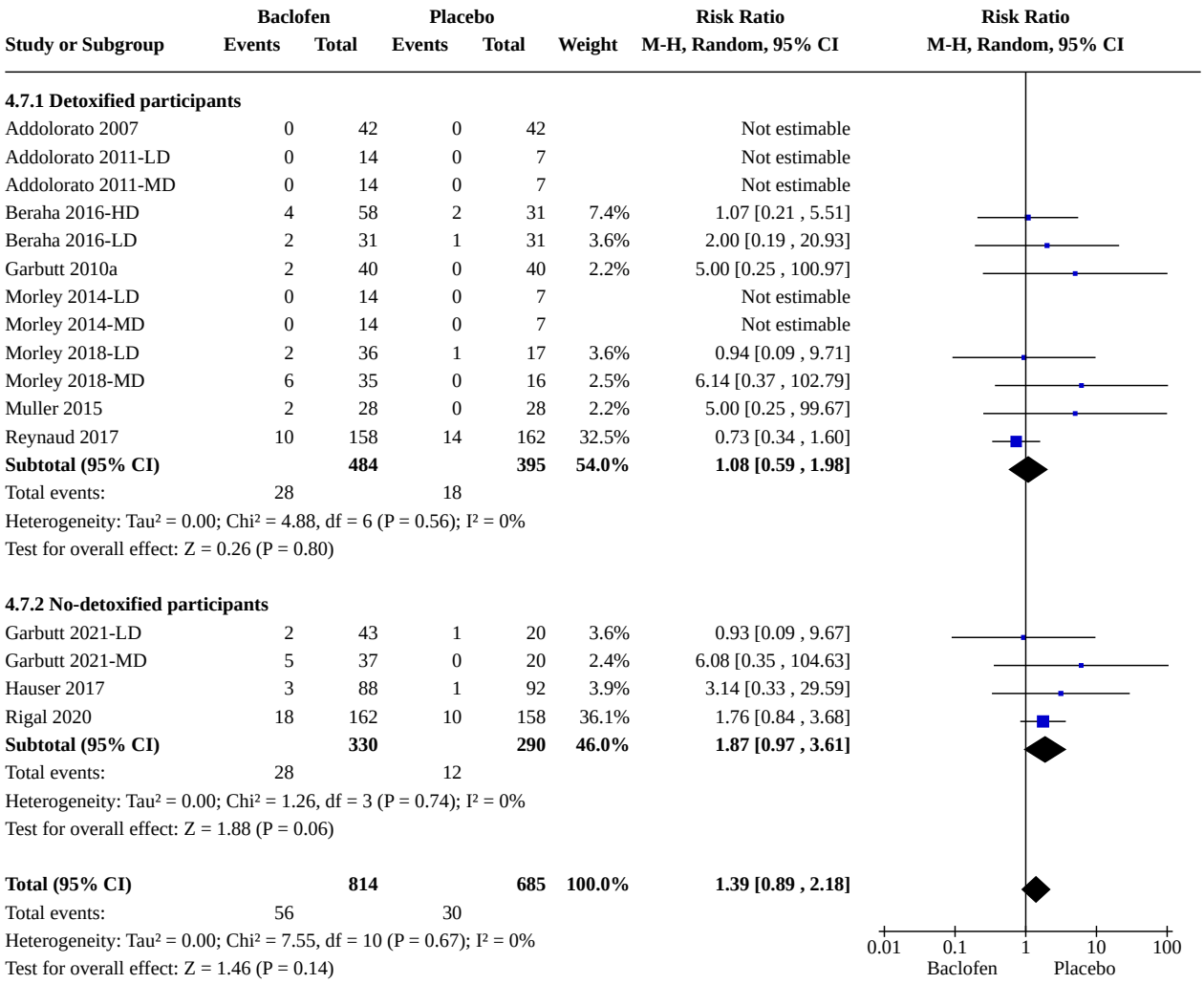


Analysis 4.6. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 6: Dropouts at end of treatment



Study or Subgroup	Baclofen Events	Baclofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Detoxified participants						
Addolorato 2007	6	42	13	42	3.3%	0.46 [0.19 , 1.10]
Addolorato 2011-LD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Addolorato 2011-MD	2	14	3	7	1.1%	0.33 [0.07 , 1.56]
Beraha 2016-HD	8	58	5	31	2.4%	0.86 [0.31 , 2.39]
Beraha 2016-LD	8	31	4	31	2.2%	2.00 [0.67 , 5.96]
Garbutt 2010a	12	40	8	40	4.0%	1.50 [0.69 , 3.27]
Morley 2014-LD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2014-MD	4	14	3	7	1.8%	0.67 [0.20 , 2.19]
Morley 2018-LD	12	36	5	17	3.3%	1.13 [0.48 , 2.70]
Morley 2018-MD	11	35	4	16	2.7%	1.26 [0.47 , 3.35]
Muller 2015	6	28	6	28	2.5%	1.00 [0.37 , 2.73]
Reynaud 2017	59	158	71	162	19.5%	0.85 [0.65 , 1.11]
Subtotal (95% CI)		**484**		**395**	**46.0%**	**0.87 [0.71 , 1.07]**
Total events:	134		128			
Heterogeneity: Tau² = 0.00; Chi² = 10.51, df = 11 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
4.6.2 No-detoxified participants						
Garbutt 2021-LD	17	43	9	20	6.2%	0.88 [0.48 , 1.62]
Garbutt 2021-MD	13	37	8	20	5.0%	0.88 [0.44 , 1.76]
Hauser 2017	21	88	20	92	7.6%	1.10 [0.64 , 1.88]
Ponizovsky 2015	15	32	9	32	5.3%	1.67 [0.86 , 3.24]
Rigal 2020	95	162	127	158	29.9%	0.73 [0.63 , 0.85]
Subtotal (95% CI)		**362**		**322**	**54.0%**	**0.93 [0.69 , 1.28]**
Total events:	161		173			
Heterogeneity: Tau² = 0.06; Chi² = 8.28, df = 4 (P = 0.08); I² = 52%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Total (95% CI)		**846**		**717**	**100.0%**	**0.88 [0.74 , 1.03]**
Total events:	295		301			
Heterogeneity: Tau² = 0.02; Chi² = 19.55, df = 16 (P = 0.24); I² = 18%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.72), I² = 0%						

Analysis 4.7. Comparison 4: Baclofen versus placebo (divided into detoxified and non-detoxified participants), Outcome 7: Dropouts due to adverse events



Comparison 5. Baclofen versus acamprosate

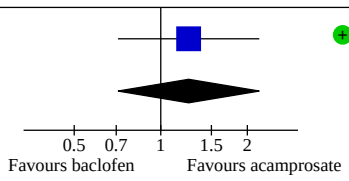
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Relapse: return to any drinking at end of treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.71, 2.20]
5.2 Adverse events: number of participants with at least one adverse event at end of treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.23, 1.69]
5.3 Dropouts at end of treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.21, 1.46]
5.4 Dropouts due to adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Craving	2	109	Mean Difference (IV, Random, 95% CI)	5.80 [-11.84, 23.44]
5.6 Adverse events: fatigue, tiredness	1	60	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.83]
5.7 Adverse events: vertigo, dizziness	1	60	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.90]
5.8 Adverse events: nausea	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
5.9 Adverse events: skin rash	1	60	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.00]
5.10 Adverse events: decrease appetite/anorexia	1	60	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.15, 6.64]
5.11 Adverse events: acidity	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
5.12 Adverse events: palpitations	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]

Analysis 5.1. Comparison 5: Baclofen versus acamprosate, Outcome 1: Relapse: return to any drinking at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
Kumar 2020a	15	30	12	30	100.0%	1.25 [0.71 , 2.20]	+	?	−	?
Total (95% CI)		**30**		**30**	**100.0%**	**1.25 [0.71 , 2.20]**				
Total events:	15		12							

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable

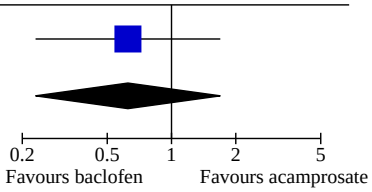


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 5.2. Comparison 5: Baclofen versus acamprosate, Outcome 2: Adverse events: number of participants with at least one adverse event at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	5	30	8	30	100.0%	0.63 [0.23 , 1.69]
Total (95% CI)		**30**		**30**	**100.0%**	**0.63 [0.23 , 1.69]**
Total events:	5		8			

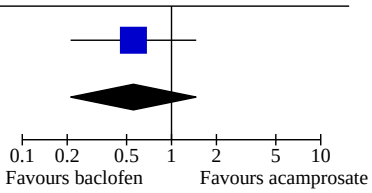
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Baclofen versus acamprosate, Outcome 3: Dropouts at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	5	30	9	30	100.0%	0.56 [0.21 , 1.46]
Total (95% CI)		**30**		**30**	**100.0%**	**0.56 [0.21 , 1.46]**
Total events:	5		9			

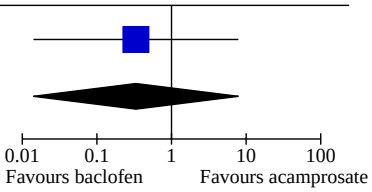
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Baclofen versus acamprosate, Outcome 4: Dropouts due to adverse events

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

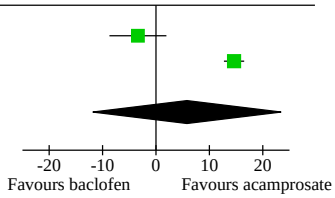
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Baclofen versus acamprosate, Outcome 5: Craving

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Acamprosate Mean	Acamprosate SD	Acamprosate Total	Weight	Mean Difference IV, Random, 95% CI
Kumar 2020a	11.79	10.62	30	15.17	10.45	30	49.0%	-3.38 [-8.71 , 1.95]
Mishra 2010	35.32	3.9	25	20.7	2.8	24	51.0%	14.62 [12.72 , 16.52]
Total (95% CI)			**55**			**54**	**100.0%**	**5.80 [-11.84 , 23.44]**

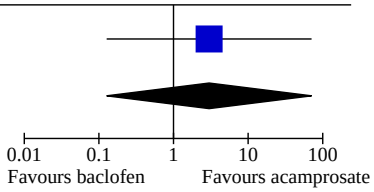
Heterogeneity: Tau² = 157.83; Chi² = 38.87, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Baclofen versus acamprosate, Outcome 6: Adverse events: fatigue, tiredness

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	1	30	0	30	100.0%	3.00 [0.13 , 70.83]
Total (95% CI)		**30**		**30**	**100.0%**	**3.00 [0.13 , 70.83]**
Total events:	1		0			

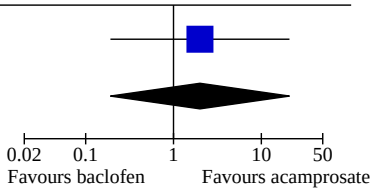
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 5.7. Comparison 5: Baclofen versus acamprosate, Outcome 7: Adverse events: vertigo, dizziness

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	2	30	1	30	100.0%	2.00 [0.19 , 20.90]
Total (95% CI)		**30**		**30**	**100.0%**	**2.00 [0.19 , 20.90]**
Total events:	2		1			

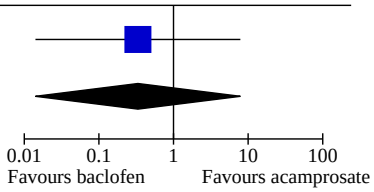
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 5.8. Comparison 5: Baclofen versus acamprosate, Outcome 8: Adverse events: nausea

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

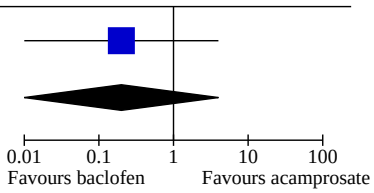
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 5.9. Comparison 5: Baclofen versus acamprosate, Outcome 9: Adverse events: skin rash

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	2	30	100.0%	0.20 [0.01 , 4.00]
Total (95% CI)		**30**		**30**	**100.0%**	**0.20 [0.01 , 4.00]**
Total events:	0		2			

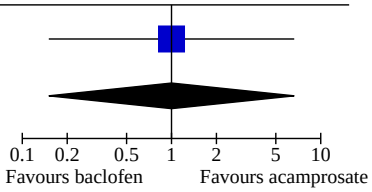
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 5.10. Comparison 5: Baclofen versus acamprosate, Outcome 10: Adverse events: decrease appetite/anorexia

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	2	30	2	30	100.0%	1.00 [0.15 , 6.64]
Total (95% CI)		**30**		**30**	**100.0%**	**1.00 [0.15 , 6.64]**
Total events:	2		2			

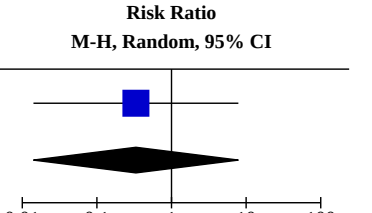
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 5.11. Comparison 5: Baclofen versus acamprosate, Outcome 11: Adverse events: acidity

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

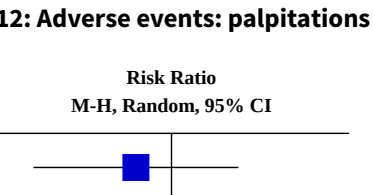
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 5.12. Comparison 5: Baclofen versus acamprosate, Outcome 12: Adverse events: palpitations

Study or Subgroup	Baclofen Events	Baclofen Total	Acamprosate Events	Acamprosate Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

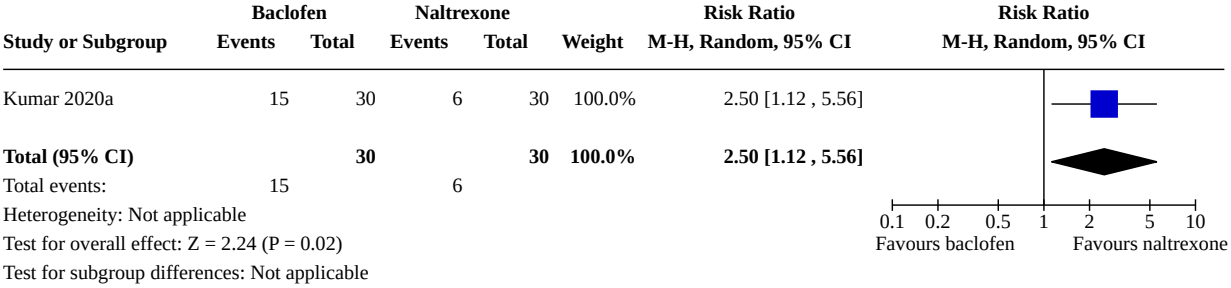


Comparison 6. Baclofen versus naltrexone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Relapse: return to any drinking at end of treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	2.50 [1.12, 5.56]
6.2 Adverse events: number of participants with at least one adverse event at end of treatment	2	80	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.80]
6.3 Dropouts at end of treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.32, 3.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Craving	1	60	Mean Difference (IV, Random, 95% CI)	2.08 [-3.71, 7.87]
6.5 Adverse events: fatigue, tiredness	1	60	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.83]
6.6 Adverse events: insomnia	1	20	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.45]
6.7 Adverse events: vertigo, dizziness	1	60	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 1.90]
6.8 Adverse events: somnolence, sleepiness, drowsiness or sedation	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.69]
6.9 Adverse events: nausea	2	80	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.20]
6.10 Adverse events: decrease appetite/anorexia	1	60	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.90]
6.11 Adverse events: tremor	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
6.12 Adverse events: acidity	1	60	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.00]
6.13 Adverse events: erectile dysfunction	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]

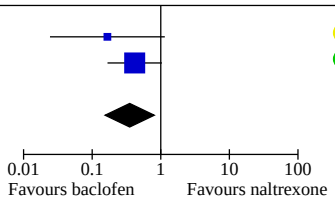
Analysis 6.1. Comparison 6: Baclofen versus naltrexone, Outcome 1: Relapse: return to any drinking at end of treatment

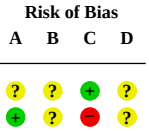


Analysis 6.2. Comparison 6: Baclofen versus naltrexone, Outcome 2: Adverse events: number of participants with at least one adverse event at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Garbutt 2010b1	1	10	6	10	18.3%	0.17 [0.02 , 1.14]
Kumar 2020a	5	30	12	30	81.7%	0.42 [0.17 , 1.04]
Total (95% CI)		**40**		**40**	**100.0%**	**0.35 [0.15 , 0.80]**
Total events:	6		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Not applicable



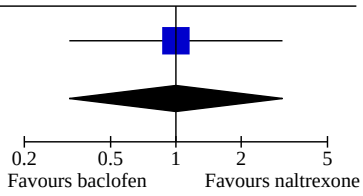


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Incomplete outcome data (attrition bias)
(D) Selective reporting (reporting bias)

Analysis 6.3. Comparison 6: Baclofen versus naltrexone, Outcome 3: Dropouts at end of treatment

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	5	30	5	30	100.0%	1.00 [0.32 , 3.10]
Total (95% CI)		**30**		**30**	**100.0%**	**1.00 [0.32 , 3.10]**
Total events:	5		5			

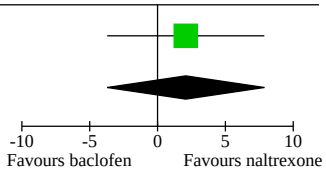
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Baclofen versus naltrexone, Outcome 4: Craving

Study or Subgroup	Baclofen Mean	Baclofen SD	Baclofen Total	Naltrexone Mean	Naltrexone SD	Naltrexone Total	Weight	Mean Difference IV, Random, 95% CI
Kumar 2020a	11.79	10.62	30	9.71	12.21	30	100.0%	2.08 [-3.71 , 7.87]
Total (95% CI)			**30**			**30**	**100.0%**	**2.08 [-3.71 , 7.87]**

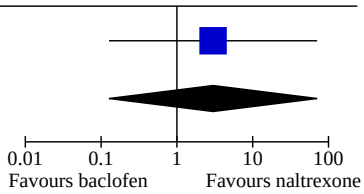
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Baclofen versus naltrexone, Outcome 5: Adverse events: fatigue, tiredness

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	1	30	0	30	100.0%	3.00 [0.13 , 70.83]
Total (95% CI)		**30**		**30**	**100.0%**	**3.00 [0.13 , 70.83]**
Total events:	1		0			

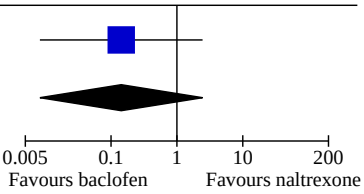
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Baclofen versus naltrexone, Outcome 6: Adverse events: insomnia

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Garbutt 2010b1	0	10	3	10	100.0%	0.14 [0.01 , 2.45]
Total (95% CI)		**10**		**10**	**100.0%**	**0.14 [0.01 , 2.45]**
Total events:	0		3			

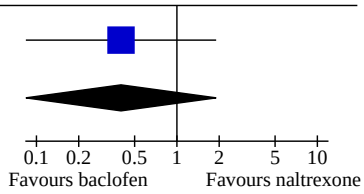
Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 6.7. Comparison 6: Baclofen versus naltrexone, Outcome 7: Adverse events: vertigo, dizziness

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	2	30	5	30	100.0%	0.40 [0.08 , 1.90]
Total (95% CI)		**30**		**30**	**100.0%**	**0.40 [0.08 , 1.90]**
Total events:	2		5			

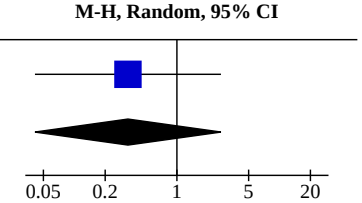
Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 6.8. Comparison 6: Baclofen versus naltrexone, Outcome 8: Adverse events: somnolence, sleepiness, drowsiness or sedation

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Garbutt 2010b1	1	10	3	10	100.0%	0.33 [0.04 , 2.69]
Total (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.04 , 2.69]**
Total events:	1		3			

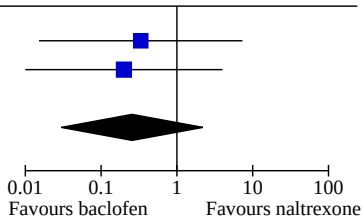
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 6.9. Comparison 6: Baclofen versus naltrexone, Outcome 9: Adverse events: nausea

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Garbutt 2010b1	0	10	1	10	48.5%	0.33 [0.02 , 7.32]
Kumar 2020a	0	30	2	30	51.5%	0.20 [0.01 , 4.00]
Total (95% CI)		**40**		**40**	**100.0%**	**0.26 [0.03 , 2.20]**
Total events:	0		3			

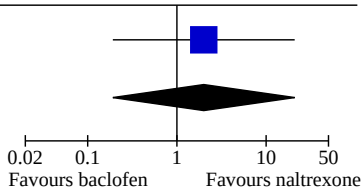
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 6.10. Comparison 6: Baclofen versus naltrexone, Outcome 10: Adverse events: decrease appetite/anorexia

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	2	30	1	30	100.0%	2.00 [0.19 , 20.90]
Total (95% CI)		**30**		**30**	**100.0%**	**2.00 [0.19 , 20.90]**
Total events:	2		1			

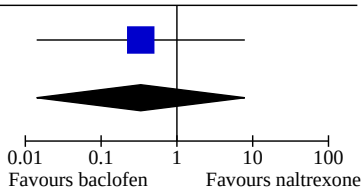
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 6.11. Comparison 6: Baclofen versus naltrexone, Outcome 11: Adverse events: tremor

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

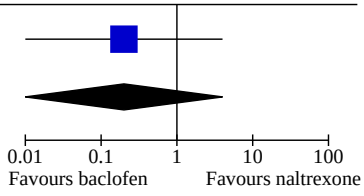
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 6.12. Comparison 6: Baclofen versus naltrexone, Outcome 12: Adverse events: acidity

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	2	30	100.0%	0.20 [0.01 , 4.00]
Total (95% CI)		**30**		**30**	**100.0%**	**0.20 [0.01 , 4.00]**
Total events:	0		2			

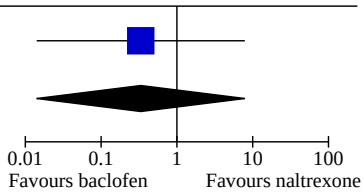
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 6.13. Comparison 6: Baclofen versus naltrexone, Outcome 13: Adverse events: erectile dysfunction

Study or Subgroup	Baclofen Events	Baclofen Total	Naltrexone Events	Naltrexone Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2020a	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



APPENDICES

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

CDAG Specialised Register (via CRSLive)

From 2018 to 22 November 2021 (53 hits)

baclofen (all fields)

Appendix 2. CENTRAL search

Cochrane Central Register of Controlled Trials (CENTRAL) (via onlinelibrary.wiley.com)

2021, issue 11 (46 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 with Publication Year from 2018 to present, in Trials

Appendix 3. MEDLINE (Ovid) search strategy

From January 2018 to 22 November (41 hits)

1. exp Alcohol-Related Disorders/
2. ((alcohol$ or drink$) adj5 (abstinen$ or abstain$ or abus$ or addict$ or crav$ or dependen$ or detox$ or disease$ or disorder$ or excessiv$ or heavy or intoxicat$ or misus$ or overdos$ or problem$ or rehab$ or relaps$ or treatment$ or withdraw$)).mp.
3. 1 or 2
4. BACLOFEN.mp. or exp Baclofen/
5. Lioresal.mp.
6. 4 or 5
7. 3 and 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. random*.ab.
11. placebo.ab.
12. clinical trials as topic.sh.
13. random allocation.sh.
14. trial.ti.
15. 8 or 9 or 10 or 11 or 12 or 13 or 14

16.exp animals/ not humans.sh.
17.15 not 16
18.7 and 17
19.limit 18 to yr="2018 -Current"

Appendix 4. Embase (Ovid) search strategy

From January 2018 to 22 November 2021 (78 hits)

1. exp alcoholism/
2. exp drinking behavior/
3. alcohol.mp.
4. (abuse* or addict* or dependen* or disorder* or drink* or consumption or treatment).ti,ab.
5. 3 and 4
6. 1 or 2 or 5
7. exp baclofen/ or baclofen.mp.
8. 6 and 7
9. exp randomized controlled trial/
10. exp randomization/
11. exp double blind procedure/
12. exp single blind procedure/
13. random$.tw.
14. 9 or 10 or 11 or 12 or 13
15. (animal or animal experiment).sh.
16. human.sh.
17. 15 and 16
18. 15 not 17
19. 14 not 18
20. exp clinical trial/
21. (clin$ adj3 trial$).tw.
22. exp crossover procedure/
23. exp double blind procedure/
24. exp controlled clinical trial/
25. (placebo or assign* or allocat* or volunteer* or random* or factorial* or crossover).ti,ab.
26. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
27. 20 or 21 or 22 or 23 or 24 or 25
28. 27 not 18
29. 19 or 28
30. 8 and 29

Appendix 5. PsycINFO (Ovid)

from January 2018 to 22 November (82 hits)

1. exp Alcoholism/
2. (alcohol$ or drink$) adj5 (abstinen$ or abstain$ or abus$ or addict$ or crav$ or dependen$ or detox$ or disease$ or disorder$ or excessiv$ or heavy or intoxicat$ or misus$ or overdos$ or problem$ or rehab$ or relaps$ or treatment$ or withdraw$)).mp.
3. 1 or 2
4. exp Baclofen/ or baclofen.mp.
5. 3 and 4
6. limit 5 to yr="2018 -Current"

Appendix 6. Web of Science search strategy

From January 2018 to 22 November 2021 (62 hits)

1. TOPIC: (((alcohol$ or drink$) NEAR/5 (abstinen$ or abstain$ or abus$ or addict$ or crav$ or dependen$ or detox$ or disease$ or disorder $ or excessiv$ or heavy or intoxicat$ or misus$ or overdos$ or problem$ or rehab$ or relaps$ or treatment$ or withdraw$)))
2. TOPIC: (baclofen)
3. TOPIC: (randomi* OR randomly OR trial*)
4. #3 AND #2 AND #1

Appendix 7. CINAHL (EBSCOhost) search strategy

from January 2018 to 22 November 2021 (25 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	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators described 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 described a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because 1 of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because 1 of the following methods was used: open random allocation sched-

(Continued)

		ule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non--opaque 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 was not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judged that the outcome was unlikely 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 was 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 was 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 was 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 was 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 judged that the outcome measurement was unlikely 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 was 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 was 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 was 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 was likely to be influenced by lack of blinding.

(Continued)

	Unclear risk	Insufficient information to permit judgement of low or high risk.
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or dropout	Low risk	No missing outcome data. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (mean differences or standardised mean differences) among missing outcomes not enough to have a clinically relevant impact on observed effect size. Missing data had been imputed using appropriate methods. All randomised participants were reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat).
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size. 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	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).
8. Selective reporting (reporting bias)	Low risk	The study protocol was available and all the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way. The study protocol was unavailable but it was clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	High risk	Not all the study's prespecified primary outcomes were reported. ≥ 1 primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified. ≥ 1 reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect). ≥ 1 outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis.

(Continued)

	The study report failed 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

22 November 2021

3 new records from January 2018 for: baclofen | Interventional Studies | alcohol (www.clinicaltrials.gov)

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

22 November 2021

3 new records from January 2018 for: baclofen AND alcohol (apps.who.int/trialsearch/)

WHAT'S NEW

Date	Event	Description
5 May 2022	New search has been performed	The latest search was conducted on 22 November 2021 and identified five new studies. These studies were added to the previously identified 12 studies. Meta-analyses of these 17 studies were updated and subgroups analyses were conducted.
5 May 2022	New citation required and conclusions have changed	Baclofen likely reduces the risk of relapse to any drinking and increases the percentage of abstinent days, mainly among detoxified participants. It does not increase the number of participants with at least one adverse event, those who dropout for any reason, and those who dropout due to adverse events. It probably does not reduce heavy drinking days and the number of drinks per drinking days. Current evidence suggests that baclofen may help people with alcohol use disorder in maintaining abstinence. The results of comparisons of baclofen with naltrexone and acamprosate were mainly based on a single study and do not allow conclusions.

HISTORY

Protocol first published: Issue 2, 2017
Review first published: Issue 11, 2018

CONTRIBUTIONS OF AUTHORS

RA and SR wrote the background section.

SM, RS and RA wrote the methods section.

RA, SM and RS conducted screening, extracted data, completed the risk of bias assessment and undertook data analysis.

All review authors contributed to writing the discussion and conclusion sections and revised the final report.

DECLARATIONS OF INTEREST

RA: none.

RS: none.

SR: none.

SM: none.

SOURCES OF SUPPORT

Internal sources

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

Sources of support

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The updated review differs from the previous version (Minozzi 2018) and the protocol (Minozzi 2017) for the following reasons.

- We did not investigate 'Cumulative abstinence duration' as planned as a secondary outcome in the protocol in either the previous version or updated review because we evaluated the rate of abstinent days as a primary outcome considered that the cumulative abstinence duration would add no further information.
- We added one study that was previously awaiting classification to the included studies section (Addolorato 2011-LD; Addolorato 2011-MD). This was a post-hoc analysis and data were unavailable despite us requesting them from the study authors for the previous version of this review. However, for this update, the authors allowed us to use the original database (see Included studies and Characteristics of included studies table for further details).
- In the previous version of this review, none of the subgroup analyses planned in the protocol were conducted because of the limited number of included studies; in this update, the larger number of included studies allowed us to perform one of the planned subgroup analyses (i.e. the daily doses of baclofen).
- In this update, we did not perform the other two subgroup analyses planned in the protocol (i.e. according to the presence of concomitant substance use disorders and other comorbid psychiatric disorders) because all studies excluded people with substance use disorders other than alcohol or nicotine except for one study that recruited participants dependent on both alcohol and nicotine (Leggio 2015). In addition, all studies excluded people with comorbid severe mental disorders.
- In this update, we performed subgroup analyses according to other variables (i.e. the duration of the studies and the consumption of alcohol at the beginning of treatment) (see Why it is important to do this review; Subgroup analysis and investigation of heterogeneity for further details).
- In the previous version of this review, we combined data of multiple-armed studies (e.g. two different doses of baclofen) into a single group and compared it to the placebo group. In this update, we did not combine the data of multiple-armed studies preferring to compare them each with placebo in the meta-analyses. To do so we divided the control group into two different subgroups to avoid double counting of participants in the control group (see Included studies; Subgroup analysis and investigation of heterogeneity for further details).

INDEX TERMS

Medical Subject Headings (MeSH)

Acamprosate [adverse effects] [therapeutic use]; Alcohol Drinking [drug therapy]; *Alcoholism [drug therapy]; *Baclofen [adverse effects] [therapeutic use]; Chronic Disease; Naltrexone [adverse effects] [therapeutic use]

MeSH check words

Adult; Female; Humans; Male; Middle Aged