**Baclofen: its effectiveness in reducing harmful drinking, craving, and negative mood. A meta-analysis**

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**Abstract**

**Background and Aims**: There are a limited number of pharmacotherapies licensed for alcohol use disorders (AUDs). Baclofen is a GABA-B agonist which is increasingly used as an off label treatment. A meta-analysis of randomized controlled trials (RCTs) was conducted to determine the efficacy of baclofen in reducing drinking behaviour, craving, depression, and anxiety, compared with placebo.

**Methods**: Random effects meta-analyses were computed on outcome data from 12 RCTs comparing baclofen with placebo. Included RCTs provided data on at least one of the primary outcome measures (drinking related: heavy drinking days, abstinent days, abstinence rates), or secondary outcome measures (craving, anxiety, depression).

**Results**: Baclofen had a significant effect on abstinence rates when using Intention to Treat analysis (Total N# Baclofen = 307, Total N# Control = 283: OR= 2.67 [95% CI 1.03, 6.93]; Z= 2.01, p = .04, I2= 76%, NNT = 8). No other significant effects of treatment efficacy (e.g. heavy drinking days: SMD= -.26 [95% CI -0.68, 0.15]; Z= 1.24, p= .21, I2= 95%) or mechanism of action (e.g. craving: SMD= -0.13 [95% CI = -0.36, 0.09]; Z= 1.18, p= .24, I2= 87%) were observed. There was substantial heterogeneity in effect sizes across each analysis.

**Conclusions**: As a treatment for AUDs, baclofen is associated with higher rates of abstinence than placebo. However, there is no superior effect of baclofen on increasing number of abstinent days, or decreasing heavy drinking, craving, anxiety or depression. These results suggest that the current increasing use of baclofen as a treatment for AUDs is premature.

**Key words**: Baclofen, Alcohol, Abstinence, Craving, Depression, Anxiety

**Introduction**

Alcohol consumption is associated with the most prominent non-communicable diseases including cancer, liver disease, and stroke. Overall, 5.1% of global burden of disease and 5.9% of global death is attributable to alcohol consumption[1]. Within the UK, the cost of alcohol-related harm is £21bn per year, £3.5bn of which is National Health Service costs[2]. Following treatment, relapse rates are high: up to 70% within 6 months of treatment[3]. Relapse rates do not mean that patients are lost to treatment, but it highlights the complexity of alcohol use disorders (AUD) and the need for multiple treatment pathways to help improve patient outcomes. Given the serious health and socioeconomic consequences of AUDs, identifying efficacious treatments is a high priority, and the National Institute for Care and Clinical Excellence (NICE) recommends that a combination of psychosocial treatments and pharmacotherapies be used where possible[4].

There are currently three licensed pharmacotherapies for the treatment of AUDs in the UK: naltrexone (opioid antagonist), acamprosate (mechanism unclear), and disulfiram (aldehyde dehydrogenase inhibitor). Cochrane reviews show that, compared with placebo, naltrexone reduces the risk of heavy drinking (RR 0.83 [95% CI 0.76-0.90]) and number of drinking days (MD -3.89 [95% CI -5.75- -2.04]) [5]. Similarly, acamprosate reduces the risk of any drinking (RR 0.86 [95% CI 0.81-.91])[6]. Disulfiram also shows efficacy compared with placebo in a meta-analysis of open label trials (g = .58 [95%CI = .35-.82]) (as disulfiram works via expectancy of negative effects, blinded trials maybe an unsuitable assessment method) [7]. However, these drugs are often contraindicated in those with the most severe forms of alcohol-related disease. Naltrexone and disulfiram cannot be used in those with alcohol-related liver disease (ALD), and acamprosate should be avoided in those with renal impairment.

Baclofen is a γ-aminobutyric acid B (GABA-B) receptor agonist extensively used as an anti-spasticity agent since the 1970s. More recently it has attracted interest as a pharmacotherapy for AUDs. Importantly, baclofen is excreted largely through the kidneys so is a potential pharmacotherapy for some of the most high need AUD patients (i.e. those with ALD). Therefore, baclofen may provide a pharmacotherapy for high need patients and those who have already failed to respond to other drug treatments.

Baclofen stimulates GABA-B receptors which are prolific within the limbic system, a key area for regulating emotion. The stimulation of these receptors inhibits the release of excitatory amino acids (glutamate, aspartate), as well as decreasing serotonin and noradrenalin, and dopamine activity within the mesolimbic dopamine system[8]. These actions may reduce anxiety, alcohol withdrawal, and the rewarding and/or pleasurable effects of alcohol[9]. Although the psychological mechanisms by which baclofen work are unknown, based on its pharmacological profile its impact on mood and alcohol reinforcement are potential candidates.

Preclinical work shows that pre-treatment with baclofen suppresses acquisition of alcohol administration[10], attenuates the alcohol deprivation effect (high intake following a period of abstinence)[11], reduces established intake and withdrawal symptoms[12], and cue induced self-administration[13].

Human research has also produced numerous favourable findings from open-label and case studies. A retrospective cohort study assessing the impact of high doses of baclofen (M=129 mg/day at 12 months) found that 80% of patients assessed at 1 year follow-up (58% of the original sample) were abstinent or had significantly reduced their drinking levels[14]. We conducted a prospective cohort study investigating the effects of baclofen on 219 dependent patients[15]. At 12 month follow-up, 53% were abstinent. Severity of alcohol dependence (SADQ) scores and alcohol consumption were significantly reduced, as were biochemical markers of GGT and bilirubin (indicating improved liver function).

Baclofen’s first open label study found that after 4 weeks of treatment (30mg/day) alcohol craving was reduced and 7 of the 10 patients were abstinent, with a further two significantly reducing their intake[16]. A recent open label study found a significant effect of baclofen, relative to a nutritional supplement, in improving drinking outcomes, and reducing craving and anxiety[17]. Imbert and colleagues [18] followed patients for 3 months; baclofen doses up to 180mg/d decreased craving, although some patients responded more quickly than others. In an observational study of 100 dependent participants, 92 claimed that baclofen suppressed craving and motivation to drink. Sixty-two percent were labelled as low-moderate risk from alcohol harm at a 2 year follow-up[19].

Several studies have reported a decrease (or suppression) in craving following baclofen administration[20] which is equivalent to other licensed pharmacotherapies but with fewer adverse effects[21]. Within randomised control trials (RCTs), Addolorato et al[22, 23] found a decrease in compulsive craving relative to placebo within a sample of cirrhotic patients[23]. Kruptisky et al[24] found decreases in craving, anxiety, and depression more frequently in the baclofen relative to placebo groups. Although, overall, these measures did not differ between groups.

Baclofen has also been shown to reduce alcohol withdrawal symptoms in a way that is comparable with diazepam [25], although its effects on delirium tremens and withdrawal seizures is unclear. Therefore, unlike other AUD pharmacotherapies, baclofen appears to have a mixed pharmacological profile and may benefit patients via several pathways.

However, there have been negative results. Garbutt and colleagues [26] failed to find an effect of baclofen over a 12 week treatment regime. Although they found a reduction in state anxiety compared with placebo, drink-related measures showed no difference. It was suggested that these results may be due to the stringent exclusion criteria and the fact that participants were not heavily alcohol dependent[9]. Given its increasing use as an AUD drug treatment (in France off label prescriptions of baclofen for AUD in 2011 were three times that of 2007), it is important to assess baclofen’s effectiveness through RCTs. However, current RCTs have led to mixed findings, therefore, a meta-analysis of the data will provide more useful indications into baclofen’s efficacy.

In terms of safety, baclofen is often reported as generally safe and well-tolerated [9, 27]. A well-cited self-case study reported that doses of 270mg/d did not result in severe adverse effects (AE) but did suppress all symptoms of alcohol dependence [20]. When heavy social drinkers treated with baclofen consumed alcohol (0.75g/kg), no AEs were reported [28]. However, some studies report high drop-out rates [29], and recent, larger studies have reported rates of 53% for persistent AEs and 7-21.5% for cessation of baclofen treatment due to AEs [30, 31]. The most common AEs concern sleep issues and headaches [26], which may increase as a function of concurrent alcohol consumption [31]. Importantly off-label prescribing is associated with real health concerns, including a lack of, or delay in, reporting adverse drug reactions [32]. This may result in overestimating baclofen’s safety and tolerability, thus increasing its use in a wider range of AUD patients without sufficient evidence. There are also a growing number of studies incorporating higher doses of baclofen. Therefore, the current analysis provides a summary of (serious) adverse events as reported in the RCTs (see Supplemental doc).

The aim of the current paper was to provide a meta-analytic investigation of RCTs. Outcome measures were baclofen’s effect (vs placebo) on drinking behaviour, craving, and mood. Our drinking behaviour outcomes were number of heavy drinking days and number of abstinent days during treatment as these were most commonly reported across studies, and are often used as outcomes for AUD treatments[33]. However, we also looked at rates of abstinence given the promising results using this outcome in several studies. Finally, we examined any reductions in craving, anxiety and depression, which are potential psychological mechanisms of effect. Our hypotheses were directional: baclofen, compared to placebo, would increase abstinent rates and reduce all other outcome measures.

**Methods**

Data sources and search strategy: Three electronic databases were searched during February 2017: SCOPUS, PsycINFO, PubMed. Searches included the key words ‘Baclofen’ AND ‘Alcohol’. Both authors performed independent searches. Formal electronic searches were supplemented by a manual search of reference sections in eligible articles. Corresponding authors of eligible articles were contacted to inquire if they had conducted any additional relevant work, published or unpublished, to reduce risk of publication bias. Supplementary searchers were conducted in October (2017) and identified two further articles[34, 35].

Study selection and Eligibility Criteria: For inclusion, studies had to be RCTs, comparing baclofen treatment with placebo, and published as a peer-reviewed journal article. There had to be at least one outcome measure which corresponded to our primary outcomes (abstinence days, drinking days, abstinence rate) and/or secondary outcomes (craving, anxiety, depression). Articles were evaluated for inclusion based on screening the titles, abstracts and full texts that appeared to meet criteria. See figure 1 for study search and selection flow chart.

*Insert Figure 1*

Data extraction: AKR/AJ performed the searches and extracted data. Authors were given one month to respond to data requests. If authors did not respond within one month, we estimated data from the text and available figures using Webplot Digitizer 3.1 (<http://arohatgi.info/WebPlotDigitizer>). Some studies reported means and SDs/SEs of 0 for some outcomes in both conditions (e.g. HDD[24]), these were not included as we were unable to generate effect sizes.

Quality assessment: We examined the methodological qualities of the studies using the Cochrane Collaboration’s Risk of Bias assessment tools. Each study was assessed by the authors (disagreements were resolved without arbitration) as low, unclear, or high risk on the following (for full definitions see [36]): 1. Random sequence generation, 2. Allocation concealment, 3. Blinding of participants/personnel, 4. Attrition data, 5. Selective reporting, 6. Matching of groups, 7. Performance bias.

Individual study ratings and justifications are included in supplementary materials.

Statistical analyses: For abstinence rates, we calculated odds ratios using the total number of participants reported abstinent at the end of treatment and the total number of participants randomised to that treatment arm [37]. Intention to treat (ITT) analysis was used for the primary analysis, in which all individuals randomly allocated to a treatment were included [38]. Drop outs and non-compliance were coded as relapse. We also computed number needed to treat (NNT) for abstinence following medication [39]. We conducted complete cases approach, as a secondary analysis, in which participants who completed treatment were included in the analysis.

We used SMD (MeanBaclofen - MeanPlacebo/Pooled Standard Deviation) as our outcome when measures varied across studies (i.e. craving). We converted standard errors to standard deviations by multiplying them by the **√**N[36]. These effect sizes were used for generic inverse variance meta-analyses methods, conducted in RevMan 5.3 (Cochrane, 2014). SMDs are commonly interpreted as 0.2 = small effect, 0.5 =moderate effect, and 0.8 = large effect. A positive SMD in this case would represent a *larger* score/number in the baclofen group compared to placebo/control. Despite treatment duration ranging across the studies, we estimated effect sizes from outcomes taken at the end of treatment in each study for consistency. Some studies [38-39] had two treatment conditions, in which baclofen was administered at different doses (e.g. 30mg vs 60mg). In this case we pooled the effect size across the different doses. Three studies [24, 25, 42] included multiple measures of anxiety, craving and depression, in this case we took the pooled effect size for each. We used an a-priori random effects model throughout.

Heterogeneity, or the variability in the study outcomes not due to sampling error, was assessed using the I2 statistic. The I2 statistic was calculated as ([Q-df]/Q) X 100%, where Q is the chi-squared statistic and df its degrees of freedom. Larger percentages are indicative of higher variability in effect sizes with >50% representative of substantial heterogeneity. Due to the small number of identified studies we did not conduct moderator analyses. This meta-analysis was not preregistered.

See supplementary materials for all forest and funnel plots.

**Results**

Trial overview: Table 1 provides key information on the studies, including participant characteristics, recruitment, drug treatment and psychosocial therapy details. Twelve RCTs were found to meet criteria to contribute to at least one of the current outcome measures.

*Insert Table 1*

Quality of included studies (see Figure 2): The quality of the studies was generally acceptable. There were limited instances >20% in which there was a high risk of bias for any criteria, with the highest being performance bias.

*Insert Figure 2*

Drinking Outcomes

*Abstinent days*: Six articles examined the effects of baclofen on (cumulative) abstinent days as a number or percentage, versus placebo. There were no significant differences between baclofen and placebo (k = 6; SMD=0.03 [95% -0.10, 0.15]; Z=0.42, p= .67, I2=23%).

*Heavy Drinking Days*: Six articles examined the effects of baclofen on the number or percentage of heavy drinking days, versus placebo. There were no significant differences between baclofen and placebo (SMD= -.26 [95% CI -0.68, 0.15]; Z= 1.24, p= .21, I2= 95%). Note that one study [43] had an outlying effect size in which confidence intervals did not overlap any of the other effect sizes or the pooled estimate. Removal of this effect size reduced the pooled estimate (k= 5; SMD= .05 [95% CI -0.04, 0.14]).

*Abstinence rate (Figure 3)*: Six articles examined abstinence rates at the end of treatment. Treatment with baclofen was 2.67 times more likely to lead to abstinence following treatment than placebo using ITT analysis (OR= 2.67 [95% CI 1.03, 6.93]; Z= 2.01, p = .04, I2= 76%). The NNT demonstrated that 8 [95% CI 5, 16] individuals would need to be treated with baclofen for one to remain abstinent due to the treatment. For complete cases only, treatment with baclofen was 2.77 times more likely to lead to abstinence than placebo (OR = 2.77 [95% CI 1.07, 5.38]; Z = 2.10, p = .04, I2 = 71%, NNT = 6 [95% CI 4, 13 (see supplementary Figure 2)].

*Insert Figure 3*

Potential psychological mechanisms of therapeutic effect

*Craving*: Eleven articles examined the effects of baclofen on alcohol craving. There were no significant differences between baclofen and placebo (k = 11, SMD= -0.13 [95% CI = -0.36, 0.09]; Z= 1.18, p= .24, I2= 87%).

*Depression*: Eight articles examined the effects of baclofen on depression. There were no significant differences between baclofen and placebo (k = 8, SMD= 0.06 [95% -0.22, 0.34]; Z= 0.43, p= .67, I2= 87%).

*Anxiety*: Eight articles examined the effects of baclofen on anxiety following treatment. There were no significant differences between baclofen and placebo (SMD = -0.03 [95% CI -0.24, 0.18]; Z= 0.29, p= .77, I2= 75%).

Publication bias and statistical power

Due to the small number of effect sizes for each outcome (ks<12) we did not conduct statistical examinations of publication bias/asymmetry[36]. Visual inspections of the funnel plots for each outcome (see supplementary materials) demonstrate considerable asymmetry and a lack of studies with high precision (low power). For example, to find effect sizes similar to another pharmacotherapy, such as disulfiram (g= .58) [7], studies would need a total N of 96 at 80% power and α= .05. As seen by table 1, the majority of studies would be underpowered and the average statistical power to find this effect size across all studies is 66% (with dropouts this reduces to 56%).

**Discussion**

This paper brings together all published RCTs to date which have investigated the efficacy of baclofen, relative to placebo, in terms of reducing harmful drinking, craving, anxiety, and/or depression (the latter 3 being potential psychological mechanisms of action). Twelve double-blind RCTs were analysed. Rates of abstinence at the end of treatment were greater following baclofen compared with placebo. However, no other measure showed a superior baclofen effect relative to placebo. This discussion will focus on each outcome measure before highlighting specific issues which limit the existing evidence base, and outlining what is needed for future research.

*Drinking outcomes*: The most often used drinking outcomes were number of HDD and AD. Overall, baclofen did not show a significant benefit on these measures. However, when examining abstinent rates at the end of treatment, there was a positive effect of baclofen; participants on baclofen were 2.67 times more likely to be abstinent at the end of treatment than those on placebo. It should be cautioned that this outcome is based on a small number of trials and likely driven by large positive effects in Addolorato et al’s[22, 23] trials. For clinical significance, NNT analysis showed that for every 8 people treated with baclofen, one would achieve abstinence due to the treatment. Referring to Cochrane reviews, this is similar to estimates for acamprosate (NNT = 11) but better than effects of naltrexone (NNT = 36), for any return to drinking[5, 6]. Although caution should be taken when interpreting these findings, it indicates that any future RCTs should be careful when choosing key outcome measures. If baclofen is able to increase abstinence rates it may be a more useful treatment for those seeking (or requiring) total abstinence rather than controlled intake. Given the high cost and needs of those with AUDs and the lack of safe pharmacotherapy alternatives for those with liver cirrhosis, baclofen may offer a viable alternative.

*Craving*: Baclofen did not have an effect on craving compared to placebo. Craving is a complex issue, with some suggesting different types including reward (involving opioid and dopamine dysregulation), relief (GABA-glutamate dysregulation), and obsessive craving (serotonergic dysregulation)[44]. Given baclofen’s GABAergic effects, baclofen may target relief craving, perhaps explaining the lack of results when using general urge measures. However, given the complex relationship GABA has with other neurotransmitter systems, e.g. dopamine/serotonin, baclofen could also affect other types of craving [45]. These possibilities have not been tested within an RCT.

Importantly, craving reflects an underlying appetitive emotional state which will fluctuate depending on the situation[46]. Possibly the real measure of an effective treatment will be its ability to reduce craving during high-risk situations. Leggio and colleagues[43] conducted a cue reactivity test on a subset of their trial’s patients. Although they found a marginal effect of baclofen in reducing craving in response to cues, this was not cue-specific (i.e. reduced craving was observed in response to water and alcohol cues). Future trials could look at craving in more detail, for example, determining prior to medication whether participants are more vulnerable to specific craving styles, whether baclofen reduces craving in certain high-risk situations, and whether any baclofen effect is associated with treatment outcomes.

*Negative Affect*: Baclofen showed no significantly superior effect on reducing ratings of anxiety or depression. Interestingly, although measures of anxiety did not change in Morley et al’s[41] trial, when they split participants by presence/absence of anxiety, they found a baclofen effect. Krupitsky and colleagues[42] also found a reduction in anxiety and depression during baclofen treatment, similar to that of diazepam and amitriptyline. However, this study did not measure drinking-related outcomes. Mood is regulated within the limbic regions and is likely to be involved in anxiety. GABA is prolific in these areas and so it remains a possibility that baclofen may somehow benefit certain populations, e.g. those with co-morbid mood disorders or susceptibility to stress-related alcohol reactivity. Although appropriate for our meta-analysis to focus on main effects, future clinical work may want to compare specific at risk populations.

*Heterogeneity*: The published RCT data has a high degree of heterogeneity in terms of dosage tested, treatment length, psychosocial treatment provided, follow-up periods, and patient characteristics. For instance, baclofen doses ranged between 30-270 mg/d, with some trials using individually titrated doses. Treatment duration ranged between 3-20 weeks, follow-up periods between 0-52 weeks (with variability in the measures taken at follow-up), and the participants were a mix of inpatients/outpatients with varying severity/duration of AUDs.

Similar to previous reports [9], the most common adverse events (AEs) were sedation-related. However, the way in which AEs were reported differed significantly across RCTs (see Supplemental document, Table 1). Therefore, although these studies do not highlight any major concern over the safety of baclofen, consistency in how AE data are reported would benefit the growing debate on baclofen safety and tolerability in AUD populations[32].

Given the range in dose and small sample sizes we were unable to identify a relationship between dose and effect size. However, looking at the individual studies there is some suggestion that baclofen effectiveness is dose-dependent. Beraha and colleagues (N=151), compared a high dose (≤150mg/d [mean: 93.6mg/d]) with a low dose (≤30mg/d) of baclofen and placebo[40]. No difference in drinking-related measures were found. However, post hoc analysis found that abstainers in the high dose group achieved a higher administration dose (102.4mg/d) of baclofen than those who relapsed (84.8mg/d). Several papers suggest that negative baclofen findings may be due to insufficient dosing[e.g. 47]. Case reports have claimed that doses of 270-180mg/d can supress craving and AUD symptoms[20]. Given that the majority of studies tested doses of ≤50mg/day, existing RCTs may not have tested doses sufficiently high enough to find an effect. However, Beraha et al’s[40] non-significant RCT involved a mean dose of 94mg/d, and Muller et al[48] did not find a significant difference in individually titrated dose across those who did/did not maintain abstinence. In addition, some studies have found significant effects with doses as low as 30mg/d[27].

*Psychosocial treatment*: Relapse rates in the baclofen-treated patients across Beraha et al’s [40](largely negative) and Muller et al’s [48](positive) studies were very similar (~25%), but placebo relapse rates were much higher in Muller et al’s. This may be because Muller et al. recruited outpatients, receiving minimal psychosocial treatment, whereas Beraha et al. tested predominantly inpatients receiving intensive psychosocial treatment. Therefore, baclofen may not provide much additional benefit from appropriate and more intensive psychosocial treatment. In some RCTs [e.g. 41, 49], all participants received coping skills and/or counselling treatments, and drinking-related outcomes decreased in all conditions. The current data does not allow for stratified analysis, however future research should isolate any unique effectiveness of baclofen.

*Pharmacokinetics*: Overall, the pharmacokinetics of baclofen appears to be linear. However, significant interindividual variability in baclofen clearance (56%) and estimated volume distribution (68.3) has been reported[50]. Marsot and colleagues[50] measured a number of covariates, none of which explained this variability in baclofen’s pharmacokinetics. Such variability across patients may help explain the inconsistency in results across studies. This is also likely to be an important factor in determining tolerability and safety issues, with some research finding a dose-dependent relationship between baclofen and AEs[31]. Given the increasing use of baclofen at higher doses, we would argue that some of the most important future research in determining baclofen’s efficacy and tolerability will be to clarify its pharmacokinetics, and identify factors which effect this process.

*Power*: It is likely that many of the published RCTs are underpowered. RCTs should be adequately powered to find effect sizes similar to those of currently licensed AUD pharmacotherapies, therefore the importance of the existing RCT evidence is limited. Given the wide range of responses to pharmacotherapies and safety issues surrounding drug treatments, it has been suggested that small-moderate effect sizes would indicate a beneficial treatment for AUDs[51]. To find a moderate effect (d = 0.5) size on continuous outcomes, baclofen RCTs must have at least 102 participants (80% power). A realistic provision for dropout rate should also be included; from the 12 studies identified, dropout rates ranged from 23%[23] to 71%[48] (mean: 38%). Importantly, two recent RCTs fulfilled this criteria and still found no effect of baclofen relative to placebo[34, 35].

*Summary*: Approximately 3.5% of drinkers in Europe would be classified as having an AUD. This relatively small proportion account for the majority of alcohol-related disease burden. It is important to identify efficacious AUD pharmacotherapies. Baclofen has produced positive results in a number of non-RCT studies. The current meta-analysis of published RCTs shows that baclofen may increase abstinent rates compared with placebo. Although this maybe a crucial treatment outcome, other drinking-related outcomes (often used to determine treatment efficacy) show no benefit from baclofen. Additionally, there was no significant reduction in craving or negative mood in baclofen, compared with placebo, groups. We highlight several important issues which limit the strength of existing trials, and provide speculative thoughts for future research which should provide more definitive answers concerning baclofen’s effectiveness. There are still important questions surrounding baclofen’s pharmacokinetics, dose-response effects, treatment duration effects, individual patient factors (e.g., dependence severity, craving type) and psychosocial treatments. It is possible that larger, well-designed RCTs may highlight ways in which baclofen can be utilised as an effective pharmacotherapy for AUDs, at least in specific patient sub-populations.

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**Figure 1. Meta-analysis search results and flow chart**

2199 articles identified from initial database searches (PubMed, Scopus, Psycinfo).

Search terms: “alcohol” AND “baclofen”

943 excluded as not being relevant to the current analysis

Not peer-reviewed articles. Non-human samples. Not a randomised control trial

1256 titles and abstracts screened

1229 excluded as not being relevant to the current analysis

Duplicate. Did not include appropriate outcome measures.

27 articles eligible for full text review screened

15 excluded as not being relevant to the current analysis

Did not include appropriate outcome measures. Re-analyses of data.

12 articles identified for meta-analysis

**Figure 2: Authors’ judgements of bias across each criterion, presented as a percentage of all included studies**



**Figure 3: Forrest plot of effect sizes comparing baclofen to placebo on abstinence rates following treatment completion.**



|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (date)** | **Single or Multi site** | **Participant population** | **Mean age (yrs)** | **Mean years of alcohol abuse or dependence** | **Recruited (n)** | **Completed (n)** | **Treatment length (weeks)** | **Dosage**  | **Psychosocial treatment** |
| Hauser et al., 2017 | Multi (4 centres) | Meeting criteria for alcohol use disorderChronic Hepatitis CVeteranCurrently drinkingOutpatient | 57 | - | 180 | 134 | 12 weeks | 1. Baclofen: 30 mg/d
2. Placebo
 | BBCET  |
| Reynaud et al., 2017 | Multi (39 centres) | Alcohol dependent.Outpatient | 49.4 | 13.5 | 320 | 190 | 26 weeks | 1. Baclofen: M = 153.5 mg (max. 180 mg)
2. Placebo
 | BRENDA |
| Krupitsky et al., 2017 | Single | Alcohol dependent  | 45.0 | 11.78 | 32 | ~12 | 12 weeks | i. Baclofen: 50 mg/dii. Placebo | Psychotherapy |
| Beraha et al., 2016 | Multi (5 centres) | Alcohol dependent. Inpatient and outpatient | 44.8 | 19.50 | 151 | 78 | 10 weeks, high dose phase16 weeks, total dose phase | 1. High dose: M = 93.6 mg/d (max. 150 mg/d)
2. Low dose: 30 mg/d
3. Placebo
 | Mix of group and individual therapy sessions. CBT, CRA, MinM |
| Leggio et al., 2015 | Multi (2 sites) | General population and clinic referrals. Meeting criteria for alcohol and nicotine dependence | 46.3 | - | 30 | 24 | 1. weeks
 | i. Baclofen: 80 mg/dii. Placebo | MM |
| Muller et al., 2015 | Single | Alcohol dependent. Inpatient and outpatient | 46.5 | 12.7 | 56 | 43 | 20 weeks (inc. 12 week high dose phase) | 1. Baclofen: M = 180 mg/d (max. 270 mg/d)
2. Placebo
 | MM |
| Ponizovsky et al., 2015 | Multi (15 centres) | Alcohol dependent. Outpatient | 43.65 | 14.6 | 64 | 40 | 12 weeks | 1. Baclofen: 50 mg/d
2. Placebo
 | Mix of group and individual therapy sessions, inc. principles of CBT, BRENDA, MI |
| Morley et al., 2014 | Single | Alcohol dependent. Outpatient | 46.83 | -  | 42 | 28 | 12 weeks | 1. Baclofen: 30 mg/d
2. Baclofen: 60 mg/d
3. Placebo
 | BRENDA |
| Garbutt et al., 2010 | - | General population meeting criteria for alcohol dependence | 48.9 | 14.45 | 80 | 61 | 12 weeks | 1. Baclofen: 30 mg/d
2. Placebo
 | BRENDA. Encouraged attendance to support groups. |
| Addolorato et al., 2007 | Single | Alcohol dependent, with liver cirrhosis. Outpatient | 49.25 | Median: 22.00 | 84 | 65 | 1. weeks
 | 1. Baclofen: 30 mg/d
2. Placebo
 | Individual counselling sessions. Encouraged attendance to support groups. |
| Addolorato et al., 2002 | Single | Alcohol dependent. Outpatient | 47.30 | 11.8 | 39 | 28 | 4 weeks | 1. Baclofen: 30 mg/d
2. Placebo
 | Routine psychological counselling |
| Krupitsky et al., 1993 | - | Alcohol dependent, with secondary affective disorders. Inpatients | 37.13 | 9.95 | 90 (52 in baclofen and placebo) | - | 3 weeks | 1. Baclofen: 37.5 mg/d
2. Diazepam: 15mg/d
3. Amitriptyline: 75 mg/day
4. Placebo
 | - |

**Table 1**. Key characteristics of included RCTs. Psychosocial treatments: BBCET = Brief behavioural compliance enhancement treatment, CBT = Cognitive Behavioural Treatment, CRA = Community Reinforcement Approach, MinM = Minnesota Model, MI = Motivational Interviewing, MM = Medical Management (see COMBINE study)