


# DRUG & ALCOHOL FINDINGS Research

## analysis

This entry is our analysis of a study considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original study was not published by Findings; click [Title](#) to order a copy. Free reprints may be available from the authors – click [prepared e-mail](#). [Links](#) to other documents. [Hover over](#) for notes. [Click to](#) highlight passage referred to. [Unfold extra text](#)  The Summary conveys the findings and views expressed in the study. Below is a commentary from Drug and Alcohol Findings.

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

**Rose A.K., Jones A.**

**Addiction: 2018, 113(8), p. 1396–1406.**

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*With patchy evidence of the effectiveness of baclofen, and serious concerns about the medication's safety, is it 'premature' for the muscle-relaxant to be prescribed as a treatment for alcohol use disorders?*

**SUMMARY** High relapse rates following treatment for problem drinking – [as high as](#) 70% within six months after leaving treatment – highlight the complexity of alcohol use disorders and the need for multiple treatment pathways to help improve patient outcomes.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) [recommends](#) a combination of psychosocial treatments and pharmacotherapies to be used where possible.

The three licensed pharmacotherapies for the treatment of alcohol use disorders in the UK are:

- Naltrexone [an opioid-blocking drug, which may help in the treatment of problem drinking by reducing the reward or pleasure of drinking and reducing craving induced by environmental stimuli].
- Acamprosate [the way this works is unclear].
- Disulfiram [medication which causes unpleasant physical reactions if alcohol is drunk].

However, among the most severely affected by problem drinking, these drugs are often unsuitable. Naltrexone and disulfiram cannot be used in those with alcohol-related liver disease, and acamprosate should be avoided in those with kidney damage.

An alternative, the muscle-relaxant baclofen, has attracted interest as a pharmacotherapy for alcohol use disorders. Baclofen stimulates receptors associated with regulating emotion, [which may in turn](#) (there is no certainty) be useful as a psychological lever on alcohol use disorders by mitigating anxiety, alcohol withdrawal, and the rewarding and/or pleasurable effects of alcohol.

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In France, 'off-label' prescribing of the drug for alcohol use disorders was three times the rate in 2011 as it was in 2007. This practice of prescribing for a reason other than what the drug has been licensed for is [associated](#) with health concerns, including a lack of (or delay in) reporting adverse



#### Key points From summary and commentary

There are a limited number of pharmacotherapies licensed for treating alcohol use disorders, and these are not always suitable for the most severely affected. An alternative, the muscle-relaxant baclofen, has attracted interest.

As a treatment for alcohol use disorders, baclofen has been associated with higher rates of abstinence than a placebo, but confers no benefit when it comes to increasing the number of days abstinent, or decreasing heavy drinking, craving, anxiety, and depression.

These results suggest that baclofen may have some potential, but its current use as a treatment for alcohol use disorders would be premature.

drug reactions, which may result in overestimating baclofen's safety and tolerability – increasing its use in a wider range of patients with alcohol use disorders without sufficient evidence.

The current paper involved a **meta-analysis** (a method of combining the results of studies) of randomised controlled trials, testing baclofen's effect on drinking behaviour, craving, and mood against the effect of a placebo. The primary outcomes were number of days abstinent, number of drinking days, and rate of abstinence after treatment, and the secondary outcomes were craving, anxiety, and depression.

A search for eligible studies yielded 12 papers with a high degree of difference in terms of dosage, treatment length, psychosocial treatment provided, follow-up periods, and patient characteristics. For instance, baclofen doses ranged between 30 and 270 mg per day, with some trials involving patients whose doses were continually adjusted based on their response to the medication. Treatment duration ranged between three and 20 weeks, follow-up periods between zero and 52 weeks, and the participants were a mix of inpatients and outpatients with varying degrees of severity and duration of alcohol use disorders.

## Main findings

Rates of abstinence were greater following treatment with baclofen compared with placebo. No other measure showed a superior baclofen effect relative to placebo – including the two other primary outcomes (number of days abstinent and number of drinking days).

### Drinking outcomes

The most popular drinking outcomes in the trials were number of heavy drinking days and number of days abstinent.

**Heavy drinking days:** Six papers examined the effects of baclofen versus placebo on the number or percentage of heavy drinking days. There were no significant differences.

**Abstinent days:** Six papers examined the effects of baclofen on the number or percentage of cumulative days abstinent. There were no significant differences.

While baclofen did not show a significant benefit on these two primary outcomes measures, abstinent rates at the end of treatment indicated there was a positive effect of baclofen.

**Abstinence rate:** Six papers 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, based on an 'intention to treat' analysis (incorporating all those randomised, whether or not they proceeded to receive the treatment or placebo). However, these findings were based on a small number of trials and likely driven by large positive effects in two trials led by the same researcher (1 2).

To assess the clinical significance of the findings, a 'number needed to treat' analysis showed that for every eight people treated with baclofen, one would achieve abstinence due to the treatment.

### Potential psychological mechanisms of therapeutic effect

**Craving:** Eleven papers examined the effects of baclofen on alcohol craving. There were no significant differences between baclofen and placebo.

**Depression:** Eight papers examined the effects of baclofen on depression. There were no significant differences between baclofen and placebo.

**Anxiety:** Eight papers examined the effects of baclofen on anxiety following treatment. There were no significant differences between baclofen and placebo.

## The authors' conclusions

As a treatment for alcohol use disorders, baclofen has been associated with higher rates of abstinence than a placebo. However, there has been no evidence of a superior effect on measures of number of days abstinent, heavy drinking, craving, anxiety, or depression. These results suggest that the observed increasing use of baclofen as a treatment for alcohol use disorders is premature.

The analysis showed that for every eight people treated with baclofen, one would achieve abstinence. This was similar to estimates for acamprosate (one for every 11 people treated) but better than effects of naltrexone (one for every 36 people treated) (3 4). This evidence, which

should be addressed with caution, could inform future randomised controlled trials testing the effectiveness of baclofen; if baclofen is able to increase abstinence rates it may be a more useful treatment for those seeking (or requiring) total abstinence rather than moderating how much they drink.

Several important issues limit the strength of existing trials. Questions remain around how the body processes baclofen, responses to varying doses, treatment duration effects, and individual patient factors (eg, severity of dependence, and type of craving). It is possible that larger, well-designed randomised controlled trials may highlight ways in which baclofen can be used as an effective pharmacotherapy for alcohol use disorders, at least in specific patient subpopulations.

**FINDINGS COMMENTARY** While the meta-analysis revealed that baclofen was associated with significantly higher rates of abstinence compared to placebo, this was based on the small number of trials that reported abstinence outcomes (six out of 12), and represented success against only one of three primary outcomes selected for the research.

**SMMGP**, a membership organisation supporting good practice in drug and alcohol treatment – and representing keyworkers, therapists, doctors, psychiatrists, psychologists, nurses, non-medical prescribers, peer mentors, and expert patients – **said** of the featured review:

*"Baclofen still holds some promise of being a useful pharmacological tool for [alcohol use disorders], particularly in specific patient subpopulations. Current evidence-based treatments (naltrexone, disulfiram, acamprosate) are contraindicated in those with severe hepatic and renal impairment, and as baclofen is extensively excreted by the kidneys it may be a candidate for use in those most high-need patients with alcohol-related liver disease. But until we have a robust evidence base comprising of adequately powered [randomised controlled trials], its use remains somewhat premature."*

Though there may be some hope for baclofen, **safety concerns** mean it is not currently recommended for treating alcohol dependence in the UK. To understand the context for why baclofen has been considered too risky, consult two Effectiveness Bank commentaries, the **first** written to accompany one of the 12 randomised controlled trials from the featured review, and the **second** considering extending the use of baclofen (along with nalmefene, naltrexone, acamprosate, and topiramate) to non-detoxified, less severely dependent or non-dependent drinkers.

For France – mentioned in the review as a country seeing increasing 'off-label' prescribing for alcohol dependence – an **important development** came on 24 April 2018 with the **release of their verdict** on the balance between safety and benefit from a special scientific committee set up by the country's National Agency for the Safety of Medicines and Health Products. Two major French trials had, said the committee, produced modest and patchy findings in favour of baclofen "the clinical relevance of [which] appears to be questionable", while on the other side there was "a potentially increased risk of developing serious adverse events (including death) especially at high doses". For the committee it meant that "the benefit risk balance is negative" – in other words, that the risks outweigh the benefits. The assessment was made as part of the process for considering an application for the marketing authorisation of baclofen in the treatment of alcohol-dependent patients, a process continuing with hearings taking place in July 2018. The committee's **conclusion** in July – they supported the use of baclofen in the treatment of alcohol-dependent patients, despite independent experts earlier claiming that the benefit-risk ratio was negative, but rejected the marketing authorisation proposed by a pharmaceutical company.

Flaws in the evidence base have been **identified**, raising concerns not only about the safety of baclofen, but confidence in its potential benefits. This includes two of the trials cited in the featured paper which reported success on the grounds of increasing abstinence:

- A small **Dutch trial** published in 2016 included patients who had been detoxified before treatment. It tested both high- and low-dose baclofen against a placebo. Since patients had to leave the study after the first relapse, the time it took to reach this point was the main outcome measure. On this and other measures baclofen made no significant difference. For example, over the entire medication period 50% of high-dose baclofen patients relapsed to heavy drinking compared to 48% low-dose patients and 47% allocated to a placebo. Few baclofen patients were able to tolerate dose increases up to the intended levels. More baclofen than placebo patients reported feeling fatigued, sleepy or drowsy, and also dizziness. Furthermore, patients at risk of suicide had been excluded and no suicide attempts were reported.

- A German trial, the first trial to rigorously test high-dose baclofen for the treatment of dependent drinking and [analysed](#) for the Effectiveness Bank, found substantial increases in abstinence after detoxification. However, the trial lasted just 16 weeks in total and any patient who drank had to leave treatment. It is unclear whether high doses are generally more effective than typical doses or only for a few patients, and whether they can sustain abstinence longer term. In high doses baclofen can dangerously augment alcohol's sedative effects, though in trials risks have proved manageable and few patients have left treatment due to side effects.

The [BACLOVILLE](#) clinical trial ([registered here](#)) purportedly found that over half of patients (57%) either became abstinent or significantly decreased their consumption to normal levels, compared with 37% of patients who were given placebos ([5 6](#)). However, these results, and more broadly [baclofen's safety](#) for patients in the study, have been difficult to scrutinise; while the findings of the trial have been reported at conferences, they have yet to be published in a peer-reviewed academic journal. The study was [completed](#) in 2015.

Among the [adverse drug reactions](#) associated with the muscle-relaxant baclofen, the most frequent are drowsiness, dizziness, and confusion. The level of sedation is linked to the dose of baclofen. However, the exact role of baclofen in cases of severe sedation or coma is uncertain, and may be the result of a complex equation of baclofen dosing and recent dose increases, as well as concomitant drinking, and the ingestion of other drugs or medications. The main risk factor for severe sedation is heavy drinking, which is not unlikely in patients with alcohol use disorders.

The authors of the featured study concluded that although baclofen may have some potential, its current use as a treatment for alcohol use disorders is premature. Adding to this appraisal evidence of the safety of baclofen, and it could be argued that the use of baclofen without further study is less premature, and more an unjustified risk to safety.

*Thanks for their comments on this entry in draft to research author Dr. Abi Rose of the University of Liverpool (United Kingdom), and Dr. Florian Naudet of the University of Rennes (France). Commentators bear no responsibility for the text including the interpretations and any remaining errors.*

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