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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▶ High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebo-controlled trial.

Müller C.A, Geisel O., Pelz P. et al.

European Neuropsychopharmacology: 2015, 25, p. 1167–1177.

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From Germany the first trial to rigorously test high doses of the muscle relaxant baclofen for the treatment of dependent drinking found post-detoxification drinking reductions of a magnitude rarely seen; serious safety issues remain of concern in routine practice.

SUMMARY In the USA and Europe few medications have been approved for the treatment of dependent drinking: disulfiram, acamprosate, nalmefene, and naltrexone oral and injectable. Some have repeatedly been found effective in rigorous clinical trials, but effects have been modest – there is room for improvement through additions to this range.

One possible addition is baclofen, a medication taken by mouth as tablets. The drug relaxes muscles and is approved for preventing muscle spasms resulting from neurological conditions. The few trials which have randomly allocated alcohol-dependent patients to baclofen versus placebo have found patients can take the drug without experiencing deterrent side effects (ie, they 'tolerated ' the drug well), but also found inconsistent impacts on drinking. Given its low ability to cross the blood-brain barrier, these might be related to the low doses of baclofen (30mg to 80mg per day) used in the trials.

Key points
From summary and commentary

From Germany the first trial to rigorously test high-dose baclofen for the treatment of dependent drinking 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.

Against this background, researchers decided to test high-dose baclofen (up to 270mg a day in three daily doses) for the treatment of alcohol dependence by randomly allocating 56 patients seen at a psychiatric centre in Berlin to the medication or to an inactive placebo. Patients and research assessors were not told which patients were taking baclofen, an attempt to eliminate expectation effects and leave only the effects of the medication. To join the trial, patients had to be adults dependent on alcohol who had just completed a medically managed withdrawal from alcohol (detoxification) and who were not legally required to attend for treatment nor suffering serious psychiatric problems. Averaging in their late 40s, about 70% were men. Most were employed and had close family who had been dependent on alcohol. Before treatment they were very heavy drinkers, averaging 199g alcohol per day, nearly 25 UK units.

The 24-week trial consisted of four phases. For up to the first four weeks, doses of baclofen and placebo were increased to a maximum 270mg a day depending on how well the patient tolerated the dose. Then the dose was maintained for 12 weeks before being tapered to zero over the next four weeks, after which patients were followed up for another four weeks. Tapering was instigated prematurely if patients started drinking. Patients were scheduled to visit the clinic from 13 to 17 times, where they were offered nine sessions of structured, supportive clinical care intended to influence them to take the medication as intended.

Abstinence from drinking was the main outcome assessed, based not just on the patients' accounts but also breathalyser and blood tests. At the end of the trial just five patients could not be followed up. On the assumption that patients who left the study had relapsed to drinking, all 56 were included in the analysis of outcomes.

Main findings

Of the 28 patients prescribed each of the preparations, during the initial dose-setting phase about the same number allocated to baclofen or placebo (6 or 7) dropped out of treatment or started drinking and had to leave. After that, lapse to drinking became more common among placebo patients, meaning that in all 24 left treatment early (18 due to resumed drinking) compared to 16 prescribed baclofen (10 due to resumed drinking). After medication ended and during the four-week follow-up, a further two baclofen patients and one prescribed placebo started drinking. Across the entire study period 19 placebo patients were known to have started drinking versus 12 prescribed baclofen, and 3 versus 10 were known to have remained abstinent.

Focusing on the period when medication was prescribed, 12 of the 28 baclofen patients remained abstinent compared to four allocated to a placebo, a statistically significant advantage for baclofen, so unlikely to have been a chance finding. Baclofen patients also lasted longer before starting drinking – 83 out of the 141 scheduled medication days versus 67 – but this difference fell short of statistical significance. The picture was similar when the analysis was confined to the 12 high-dose weeks, except that the difference in time to resumed drinking (favouring baclofen) became statistically significant.

Baclofen had no statistically significant effects on craving for alcohol, or symptoms of anxiety or depression. No baclofen patients said the drug had produced alcohol-like effects (euphoria or stimulation), and none reported craving for the drug after dosing ended. Though the drug was not associated with any serious adverse events, two baclofen patients ended treatment due to fatigue, a complaint reported by seven placebo patients but nearly twice as many (13) allocated to baclofen. Among the other most common complaints, seven placebo and four baclofen patients reported headaches, while four placebo versus nine baclofen patients reported disturbed sleep.

During the high-dose phase baclofen doses averaged 180mg a day and peaked at an average 192mg, significantly lower than corresponding 'doses' of placebo and below the potential maximum of 270mg a day. The dose of baclofen reached did not predict who would remain abstinent.

The authors' conclusions

Individually adjusted, high-dose baclofen supported alcohol-dependent patients in maintaining abstinence and was well tolerated, even when patients resumed drinking, results which might extend pharmacological treatment options. Compared to previous studies, baclofen doses were relatively high, possibly why it was more effective than placebo in this study but not in a larger US trial which prescribed 30mg a day. The drug's impacts do not seem to depend on reaching a set dose, so dose can probably be individually adjusted without jeopardising effects on drinking.

Findings suggest baclofen does not work primarily by reducing craving or anxiety. Another suggested mechanism is substituting for alcohol by producing similar effects, yet in this study no patient reported alcohol-like effects, or craving or withdrawal symptoms after the drug was withdrawn.

Results confirm the good safety profile of baclofen found in previous trials, though lack of data on safety at high doses demands care and close monitoring; in this study about two-thirds of the baclofen patients (but just a third prescribed a placebo) did not reach the maximum 270mg per day dose. Alcohol-dependent patients with psychiatric conditions have been known to take dangerously high doses of baclofen to induce intoxication, suggesting extra care before prescribing it to alcohol-dependent patients with psychiatric conditions and/or who have previously attempted suicide.

Despite clear-cut results favouring baclofen, the study's sample was too small to be definite about the drug's future role in the treatment of alcohol dependence, and the study was conducted at a single site; elsewhere results might differ. Only abstinence was assessed, not whether baclofen curbs drinking in patients who continue to drink.

FINDINGS COMMENTARY In this trial, and even at just 30mg a day in trials in Italy, baclofen has greatly reduced drinking among alcohol-dependent patients, though not in a US trial among less heavily dependent drinkers recruited through ads rather than at treatment clinics; details ▸ below. It is rare for any medication or psychosocial therapy to register such large impacts. But while the abstinence gap between baclofen and placebo patients was large, it seems this reflected poor outcomes among the placebo patients as much or more than the good performance of baclofen. In a US trial patients prescribed a placebo and supported using the same psychosocial programme as in the featured study were during treatment abstinent on nearly three-quarters of days. Possibly at such high doses, patients and their clinicians in the featured trial guessed who was and was not being prescribed baclofen, and those who missed out on the medication reacted badly, and/or by chance this small single-site study produced results which would not be replicated in a larger and more diverse sample.

As an anti-relapse medication, baclofen seems so far to have been tested only against an inactive

placebo, not against established medications like disulfiram, acamprosate or naltrexone, and not against structured psychosocial therapies. Such therapies have been shown to have impacts as great as those of some medications. Trials have mostly been at a single centre in Italy and involved just 12 weeks of medication with little or no post-treatment follow-up period.

Recent findings leave the evidence on baclofen's effectiveness in reducing drinking patchy, including no significant impacts overall in the largest published trial to date. At the same time, safety concerns raise doubts about whether on balance health is improved by baclofen treatment of dependent drinking, especially in the relatively uncontrolled, widespread implementation seen in France and among suicide-prone patients (1 2).

Limitations of trials to date and safety concerns in respect of high doses (▸ below) mean it would be premature to prefer baclofen to the established medications, though it may offer an alternative when these have proved insufficiently effective or are contraindicated. It remains unclear whether high doses of baclofen are generally more effective in suppressing drinking than usual doses, or only among patients who do not respond to lower doses, and if the latter, what proportion these are of all patients who might be prescribed the drug. Greater risk with higher doses may limit the application of these findings.

Safety is an issue

The authors' caution that more needs to be known about the safety of high doses of baclofen – and especially so among heavy drinkers – is an important consideration. Baclofen is not licensed in the UK for the treatment of alcohol dependence, though it has been used by some clinicians. In its mainstream use to prevent muscle spasms, the drug is recommended to be taken in doses no greater than 100mg a day; most of the data on safety will have been gathered at doses below this level.

UK guidelines reconsidered in 2013 do not recommend it as a relapse prevention medication in moderate or severe alcohol dependence, because it has not been shown be have a clear effectiveness advantage over safer medications licensed for these purposes.

French committee says risks outweigh benefits

For France 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 France's National Agency for the Safety of Medicines and Health Products (ANSM). 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 risks outweigh 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 scheduled for July 2018.

Arising primarily from its widespread prescribing for alcohol dependence in France, among the concerns are that it contributes to overdose deaths, particularly from suicide attempts. It has been calculated that prescribed at high doses, in France 1 in 100 more patients die per year than would have done if conventional medications had been prescribed instead. In alcohol treatment patients the drug has caused severe but recoverable medical problems. Less severe adverse side-effects are frequent, of which the most common are forms of tiredness and sedation.

In the featured study, two-thirds of baclofen patients did not reach maximum doses, presumably because many were starting to feel too unwell to further increase these dose. Despite the care the study exercised to adjust doses, nearly half the baclofen patients complained of fatigue, leading two of the 28 to terminate treatment. At lower doses too, fatigue can be a problem among a minority of alcohol-dependent patients (1 2) and is a recognised side-effect among patients prescribed the drug to prevent spasms.

The UK's prescribing guide warns that taking baclofen while drinking can magnify alcohol's effects. An account of baclofen-induced intoxication among alcohol-dependent emergency department patients in France indicates that fatal overdose is a risk when high doses of baclofen are taken in the presence of other drugs which depress the nervous system, including alcohol and benzodiazepine tranquilisers.

A recognised advantage of baclofen that it is only minimally metabolised by the liver, meaning it can and has been recommended for the prevention of relapse to drinking among patients with alcoholic liver disease. There has however been an apparently isolated case of baclofen-induced

hepatitis in an alcohol-dependent patient in France at doses of just 30mg a day. Cases of reversible psychiatric disturbance have also been reported with higher (120mg or 275mg per day) doses.

Despite these risks, in alcohol treatment trials with typically rigorous monitoring, and which like the featured trial have usually excluded seriously medically or mentally ill patients, baclofen's safety and side effects have not been a major issue and patients have not experienced psychoactive effects, become dependent on the drug, or developed a desire to continue taking it. A review conducted for the British Association for Psychopharmacology concluded that baclofen has generally been well tolerated by patients.

At usual doses, these findings from treatment trials have generally been confirmed by studies which have closely monitored how heavy or dependent drinkers respond to baclofen while drinking in laboratory conditions. However, these studies have also confirmed that even when tolerance has developed to alcohol, there can be additive effects of the kind which at higher doses escalated central nervous system depression to the dangerous levels seen in France (▸ above) and which magnify alcohol's detrimental effects on performance in manual or intellectual tasks (1 2).

Experience with high dose baclofen in alcohol dependence is not confined to the featured trial, though it does seem the first rigorous assessment. In 2008–2009 in Scotland, a hospital unit treating liver disease started prescribing individualised doses of the drug to 53 patients with alcoholic liver disease who had not done well on other treatments for their drinking or for whom these were contraindicated. Daily doses ranged up to 400mg but usually only for a few days. The typical maximum dose was 60mg a day and the treatment lasted for up to 18 months or longer after transfer to general practice, though typically only for about three months. Among patients who responded to a survey in 2010, drinking was substantially lower than before baclofen treatment, and for all patients hospital records suggested the treatment had helped prevent rehospitalisation by helping arrest disease progression. Side effects were typically tolerable and transient, and more common at higher doses, remitting when the dose was lowered. Most commonly reported was sleepiness. Initially some patients also felt a 'high' when taking baclofen which lasted a few hours. Successful treatment has also been reported in Australia of patients who had been failed by other treatments and who did not respond well to baclofen until doses were raised to 72mg to 125mg a day.

The featured study notes that in 2014 baclofen received temporary approval in France for the treatment of alcohol-dependent patients in doses up to 300mg a day. Approval was pending French trials, and stipulated baclofen be tried only after the failure of other treatments, and that doses over 120mg a day be subject to specialist advice. The move followed popularisation of the drug instigated by the account of a French alcohol-dependent cardiologist who treated himself with a maximum of 270mg a day of baclofen. Despite soaring sales and patient demand, the French authorities at first refused to sanction such usage due to insufficient evidence.

Though high-dose patients in France have been recorded as generally achieving abstinence or low-risk drinking, a study which specifically probed for adverse effects by interviewing one GP's patients at least a year after treatment started found these were very common and sometimes severe and dangerous. The 116 interviewees had been drinking on average 179g of alcohol each day, nearly 22 UK units, and most had tried other medications before being prescribed what was typically 150mg of baclofen day but ranged up to 400mg. During their first year of treatment, two patients were hospitalised after experiencing hallucinations while misusing baclofen at very high doses and another had to be admitted with withdrawal symptoms after abruptly stopping a dosage of 180mg a day. Eight patients had adverse effects that contributed to ending the treatment most commonly due to sleepiness and depression, and ten had to cease increasing doses due to side effects. Of 146 patients, 10 experienced a "hypomanic" episode characterised by overexcitement. Half these patients had a history of bipolar disorders. Some patients reported sudden and potentially dangerous bouts of sleepiness of almost narcoleptic proportions. These and other less severe apparent side effects were extremely common, being recalled by nearly 80% of the 116 interviewees, most of whom had experienced sleepiness or less commonly inability to sleep. These recollections on the part of the patients may or may not have reflected the side effects of baclofen, but do suggest that the incidence of side effects may be underestimated when simply recorded rather than being specifically looked for.

Other trials

In Italy the first rigorous trial of baclofen in the treatment of alcohol dependence found that at 30mg a day the drug substantially promoted abstinence over a 30-day trial and dramatically reduced drinking to on average practically zero drinks per day.

Also in Italy the same lead researcher has trialled the drug at doses of 30mg a day among alcohol-dependent patients with cirrhosis as a means of sustaining abstinence after detoxification. In this relatively large 12-week trial involving 84 patients, baclofen substantially promoted abstinence and prevented relapse to heavy drinking; 60 days after treatment started 6 of 42 baclofen patients had relapsed compared to 19 of 42 prescribed a placebo. In the four weeks after the 12 weeks of medication, one baclofen patient relapsed and two prescribed a placebo. No baclofen-induced aggravation of medical problems was reported.

In the USA, records of the treatment of 35 alcohol-dependent patients with liver disease showed all but one sustained abstinence while being prescribed up to 30mg a day of baclofen for on average nearly six months, a long-term course which did not lead to a serious adverse effects and was tolerated well by the patients.

Not all the trials at the Italian unit have proved convincing. It hosted the Italian arm of a multi-national trial, for which it recruited 42 patients. For 12 weeks they were randomly allocated to placebo, the 30mg a day dose the unit had previously trialled, or to twice this dose, 60mg a day. Possibly because numbers were so few, no statistically significant effects were noted on the number of heavy drinking days, days not drinking, time to first lapse and relapse, or on craving. Later an unplanned analysis of the average number of drinks per day across the trial period found a significantly greater reduction among baclofen patients, which peaked at the highest dose. However, even the placebo patients averaged only about half a drink per day, and this analysis could have capitalised on prior knowledge of the outcomes to select one which perhaps by chance registered a statistically significant difference.

The Australian arm of the same trial also recruited 42 patients but was able to follow-up just 28. There were no overall statistically significant benefits of baclofen, but it did further reduce drinking among the 4 in 10 patients who had ever suffered or were suffering a diagnosable anxiety disorder, thought to indicate a particular role for baclofen among morbidly anxious patients. As well as the small follow-up number, this was another unplanned analysis which could have capitalised on what were really chance variations in outcomes.

Unlike the Italian trials, a US trial recruited participants not at alcohol treatment clinics but through advertisements. At about 98g a day most days, their drinking was relatively modest. Prescribed for 12 weeks at up to 30mg a day, compared to a placebo baclofen did not further reduce drinking or heavy drinking or reduce craving for alcohol.

Trials have generally tried the drug as a way of sustaining rather than achieving abstinence, but the Italian research team has also compared 30mg a day baclofen for 10 days to the 'gold-standard' diazepam treatment for mitigating withdrawal symptoms from alcohol, and found it about equally effective. The results seem to promise an unbroken pharmacological route from withdrawal through to maintaining abstinence, but whether baclofen can match the benzodiazepines in preventing or mitigating severe symptoms including seizures and delirium tremens remains unclear.

Recent French and Dutch trials have not confirmed the drinking reductions found in earlier studies. For these and other recent reports and research on baclofen see our analysis of a review published in 2017.

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