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### ► [Naltrexone and combined behavioral intervention effects on trajectories of drinking in the COMBINE study.](#)

Gueorguieva R., Wu R. Donovan D. et al.  
**Drug and Alcohol Dependence: 2010, 107, p. 221–229.**

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*Reanalysis of the largest US study of medication-based alcoholism treatment confirms that either naltrexone or psychological therapy improved outcomes more than medical care and placebos, while the two in combination or acamprosate added little. It also revealed previously invisible benefits when certain types of patients received certain treatments.*

**Summary** The featured report used a more sophisticated and sensitive methodology to re-analyse outcomes from the US COMBINE trial which [reported its original outcomes](#) in 2006. This new analysis looked for patterns in drinking over the 16 weeks the study's treatments were offered to alcohol-dependent patients, and assessed the degree to which the trial's treatment combinations affected the chances that a patient would exhibit preferable patterns (such as consistent low drinking) rather than those which represent a poorer outcome (such as daily heavy drinking).

As described in an earlier [Findings analysis](#), 11 clinics screened nearly 5000 applicants who had answered trial ads or had been referred to the trial by their clinicians. Of these, 1383 were dependent on alcohol, achieved at least an initial four days without drinking, agreed to join the study, and were randomly allocated to one of nine combinations of abstinence-oriented pharmacological and psychosocial treatments. Though more socially integrated and less severely dependent than some UK alcohol treatment caseloads, they were heavy drinkers, averaging 21 UK units (each 8g alcohol) most days.

Over the 16 weeks of treatment the core psychosocial support was nine appointments intended to represent a medical management programme deliverable by non-specialist primary care staff given adequate training and supervision. Typically sessions lasted under 20 minutes and focused on assessing, monitoring and feeding back the medical consequences of the patient's drinking, and promoting adherence to pharmacotherapy. Most of the staff delivering this care were nurses.

For half the patients, this medical care was supplemented by typically 10 sessions of psychological therapy incorporating motivational interviewing and cognitive behavioural and 12-step elements.

All the patients were also randomly allocated to pharmacotherapy consisting of dummy placebo pills, acamprosate, naltrexone, or both active medications.

The key question was how far the extra therapies improved on the study's most basic intervention – medical management with inactive placebo pills. Adding psychological therapy improved drinking outcomes to the point where medication failed to create further improvements. But roughly the same gains resulted from adding naltrexone, even without psychological therapy. These were the only supplements which created significant gains. Combining them and even also adding acamprosate did not further improve outcomes, and acamprosate alone did not augment outcomes from the basic intervention. For example, across the 16 weeks of treatment, 58% of patients receiving basic care achieved a "good clinical outcome" – drinking at most moderately with few adverse consequences – compared to 71–78% when either naltrexone or psychological therapy were added. Abstinence and relapse outcomes followed the same pattern as did outcomes a year after treatment, though by this time the differences had faded to the point where none were statistically significant.

#### Main findings: drinking

The featured analysis broadly replicated these findings with some significant nuances. Based on drinking records assessed by researchers at nine points during the 16 weeks, the patients clearly fell in to six patterns; three (✓) were considered good outcomes and three (✗) poor:

- ✓ **Abstainers:** 37% of patients were very unlikely to drink on any of the days of the 16-weeks treatment period;
- ✓ **Infrequent drinkers:** 24% of patients were consistently unlikely (between about 1 in 10 and 1 in 5) to drink on any of the days;
- ✓ **Frequent to infrequent:** 12% of patients started the treatment period with around a 50% chance of drinking on any particular day but gradually drank less often, ending up drinking on around 30% of days;
- ✗ **Increasing to frequent drinkers:** 11% of patients started being unlikely to drink (around a 1 in 10 chance on any day) but gradually drank more frequently until they drank on average about every other day;
- ✗ **Increasing to near daily drinkers:** 8% of patients started the treatment period unlikely to drink but escalated until by the end they drank nearly every day;
- ✗ **Near daily drinkers:** apart from a small dip at the start of the treatment period, 7% of patients drank virtually every day and by the end remained the most frequent drinkers in the study.

As in the original report, adding acamprosate to the care package made no difference to the chances that a patient would fall in to one or other category, but adding either naltrexone, psychological therapy, or both, increased the chances of a good outcome. However, they did so in different ways. Psychological therapy particularly helped prevent patients who started well escalating to near daily drinkers. In the absence of psychological therapy, naltrexone helped more patients sustain near abstinence. The two together (ie, psychological therapy plus naltrexone) particularly helped more patients decrease the frequency of their drinking over the 16-week period. Compared to medical care and placebo, it also reduced the numbers who escalated to near daily drinking but also the numbers who consistently abstained.

#### Main findings: heavy drinking

"Heavy" drinking was defined as any day on which a man drank five or more US standard drinks (nearly 9 UK units) or a woman four or more drinks (7 UK units). The featured analysis focused on a three-way classification:

- ✓ **Abstainers from heavy drinking:** 60% of patients consistently almost never drank heavily;
- ✗ **Sporadic heavy drinkers:** 30% of patients were consistently unlikely (about a 1 in 4 chance) to drink heavily;
- ✗ **Consistent heavy drinkers:** another 10–11% of patients started treatment **unlikely** to drink heavily but then deteriorated until from the middle of the treatment period they had about an 8 in 10 chance of drinking heavily on any given day.

As in the original report, adding acamprosate to the care package made no difference to the chances that a patient would fall in to one or other category, but adding either naltrexone, psychological therapy, or both, increased the chances that a patient would almost never drink heavily. Though preferable to doing without both, combining naltrexone and psychological therapy was in one respect worse than doing either one or the other, slightly raising the chances of a patient being a sporadic heavy drinker.

## The authors' conclusions

Compared to medical care and placebo tablets, this re-analysis of data from the COMBINE trial confirmed that naltrexone and the study's psychological therapy increased the probability of lower risk drinking trajectories during the 16-week treatment period, and also that acamprosate had no impact either alone or in combination with other treatments. The analysis also threw up some new findings, suggesting that there are subgroups of patients who derive greater benefit from specific treatment combinations.

In the absence of psychological therapy, naltrexone particularly reduced the probability of consistent near daily drinking and of escalating to frequent drinking. With or without naltrexone, psychological therapy reduced the numbers who escalated yet more sharply to near daily drinking, but did not increase the chances that a patient would consistently abstain.

Conceivably these findings reflect naltrexone's ability to blunt the rewarding effects of alcohol and the role psychological therapy played in preventing relapse in the face of high-risk situations. But this relapse-prevention effect is undermined if relapse occurs early before these skills have been learnt and practised. Such patients then potentially discontinue therapy, meaning they never benefit from its skills-acquisition phases.

The puzzle remains of why adding psychological therapy to naltrexone weakened the drug's ability to prevent consistent near daily drinking. Set against this however, it also decreased the numbers in the next worst category who escalated to near daily drinking, meaning that overall the combination did as well as naltrexone alone in preventing resumption of near daily drinking. The same combination also led to the greatest chance that patients drinking on about half the days at the start of treatment would decrease the number of days on which they drank, perhaps consistent with gradually learning that drinking is (due to naltrexone) less rewarding and developing the skills to act on this by cutting back. Such an effect was invisible to the original analysis, which found the combination effectively equivalent to either of its components on its own.

It should be remembered that strict inclusion/exclusion criteria in the COMBINE study resulted in a relatively homogeneous sample of potentially more capable and compliant patients, who were able to achieve four days of abstinence before treatment started. In a more severe population, the drinking patterns identified by the featured analysis and the impact of the treatments on these might differ.

**FINDINGS** For these relatively stable and compliant patients, well structured but straightforward medical care plus naltrexone (in this case, 100mg a day) seemed at least as likely to achieve good outcomes as specialist psychological therapy. A similar message emerged from [another US study](#) which used the more typical 50mg a day dose: with naltrexone, primary care-style consultations were as effective as specialist cognitive-behavioural therapy; without the drug, cognitive-behavioural therapy was the more effective option.

Seemingly contradicting the featured study, several studies have found that naltrexone improves outcomes from cognitive-behavioural therapy. However, none compared this combination against naltrexone plus a systematic, compliance-promoting medical management programme.

Other studies have also found naltrexone effective in caseloads of the kind who might be treated in primary care, [including one](#) in which non-specialist nurses (who also formed the majority of the medical care staff in the featured study) delivered both medication and counselling. The featured study also confirms findings that acamprosate plus naltrexone at best only marginally better than naltrexone alone, which is generally more effective than acamprosate alone.

Now licensed for this purpose in the UK, the implications of these studies are that naltrexone can be a valuable supplement to medical counselling (by GPs or nurses) of dependent drinkers of the kind who might be treated in primary care, especially when specialist alcohol therapy is refused or unavailable. It is likely to be more effective than acamprosate, though more limited in its application due to contraindications and side-effects. However the featured study's medical counselling was possibly more structured and extensive in content (motivational support, compliance management, and education) and in time commitment than typical primary care approaches. In terms of which patients are suitable, level of consumption seems less important than whether they have retained sufficient stability to comply with treatment and are not so multiply problematic that more intensive care is required.

More comment and citations in the [Findings analysis](#) of the original results of the trial.

## More on the featured study

Though an advanced study and a sophisticated analysis, the featured report's findings were often based on tests which the researchers decided to do *after* they had seen the results emerging from their new methodology. 'Post-hoc' analyses of this kind are best seen as generating hypotheses for testing in a study specially designed for this purpose. The main problem is that they can produce 'statistically significant' results by capitalising on what may in fact be chance variations in the effectiveness of the intervention between different subsamples or on different measures.

Other reanalyses of the COMBINE data have also used the methodology of the featured study. [One applied it](#) to drinking patterns in the [three months before](#) the patients entered the study to explore whether some types of drinkers may have responded better to the different treatments. Most notably this analysis suggested that acamprosate *did* have an impact, but a negative one, making some of most heavily dependent near daily drinkers (in particular, the ones able to stop drinking for the longest time – about 12 days – prior to starting treatment) *more* likely to drink heavily at the end of treatment than if they had been prescribed a dummy placebo tablet. An extended period of abstinence before treatment was also thought one of the reasons why the British acamprosate trial found no beneficial impacts [below](#).

In the featured study this negative impact of acamprosate on some patients was counterbalanced by positive impacts on other types of patients, especially intermediate severity patients who had drunk frequently before treatment but not nearly every day. These same intermediate patients also particularly benefited from naltrexone, being nearly twice as likely to sustain abstinence than if they had been prescribed a placebo. Another kind of analysis also spotlighted intermediate severity patients who before preparing for treatment had been drinking on 25% to 55% of days as particularly benefiting on the same yardsticks from acamprosate and naltrexone.

In contrast to the drugs, there was no sign that the study's psychological therapy was differentially effective for different types of pre-treatment drinkers. Like the featured analysis, these findings too were often based on 'post-hoc' analyses, so are best seen as generating hypotheses for testing in a study specially designed for this purpose.

A [further analysis](#) was similar to the one above, but divided patients up on the basis of their *heavy* drinking patterns before treatment. This time there was no indication that different types of patient benefited more or less from different treatments. However, it *did* confirm the previous report's finding that the very dependent near daily drinkers and heavy drinkers who stopped drinking on average 12 days before treatment started – several days longer than other patients – had very good drinking outcomes, almost as good as the low severity patients who were drinking or drinking heavily *relatively* infrequently before treatment started. These were also [the patients](#) for whom acamprosate seemed counterproductive. Despite their very frequent heavy drinking before treatment and other indicators of severity of dependence, these patients were also the ones most likely to say they were committed to abstinence and demonstrated this by abstaining in the fortnight leading up to treatment entry.

Lastly the same methodology [has been used](#) to divide patients up on the basis of trends in how many of their prescribed tablets they took and how many therapy sessions they attended. Unsurprisingly, the most diligent patients also cut down their drinking and heavy drinking most, while those who early on started missing pills or sessions did worst. More interesting was that patients who missed sessions early (often due to dissatisfaction with their therapist) could substantially be 'rescued' from very poor heavy drinking outcomes if they had been prescribed one of the active medications rather than a placebo. Likewise patients who early on started to skip their prescribed acamprosate tablets could partially be 'rescued' in the same way by psychological therapy. It seemed that patients who effectively rejected either therapy or acamprosate could nevertheless be helped if they received a different kind of treatment.

## Other studies of naltrexone and acamprosate

European studies of acamprosate [have on average](#) been more favourable than the featured analysis. Head-to-head trials [\(1 2\)](#) have found naltrexone somewhat more effective than acamprosate in reducing drinking. Naltrexone may also be the better option for people who are not aiming for or find it hard to stop drinking altogether, and for those with a strong desire to drink in order to achieve what they experience as a pleasurable state of intoxication. However, side effects are more common and more severe (though usually few patients have to stop taking

the drug) than with acamprosate, and the drug is contraindicated in patients with certain liver problems or who are also dependent on opiates. There is also the complication that in a medical emergency, patients who have recently taken naltrexone will find that opiates fail to control pain, one reason why some prefer not to take the drug.

Without being conclusive either way, in line with the international literature, [two major British studies](#) provided greater support for naltrexone than for acamprosate. The negative UK findings on acamprosate may have been related to the fact that nearly a third of the patients in the study did not remain abstinent for the week before starting the treatment, a requirement in some other studies. Outcomes in the British study may also have suffered from [not starting](#) the drug in the immediate post-withdrawal period, when theory suggests the drug's effectiveness should be at its height. This too may have been the reason why acamprosate appeared to worsen outcomes in the featured study for those heavily dependent patients who had been able to stop drinking on average 12 days before starting treatment.

Both UK studies suffered from high drop-out rates and poor compliance with treatment, but in the naltrexone study, patients who did complete the study and largely comply with treatment drank substantially less on naltrexone than on placebo tablets. One lesson from both studies seems to be that among typical British alcohol clinic caseloads, the support available from the staff and/or from families and friends is often insufficient to enable patients to sustain their commitment to treatment.

Given no overriding effectiveness differences, the decision between the two drugs can largely be a matter of individual choice and contraindications, licensing authorisation, and familiarity of the prescriber with the respective treatments.

For more details see these Findings analyses of an [omnibus review](#) of medical treatments for alcohol dependence, and of reviews focused on [naltrexone](#) and [acamprosate](#). Another review has focused on the main alternative to these types of medications, [disulfiram](#), which aims to enforce abstinence due to the aversive effects of drinking while the drug is active in the body.

### UK policy and practice

In the last few years naltrexone has been licensed in the UK for the treatment of alcohol dependence, supplementing acamprosate and disulfiram. The delay seems merely to have been due to no company seeking a licence rather than any misgivings on the part of the authorities.

With the field now opened up, naltrexone may in this guise (as opposed to its established role in the treatment of opiate dependence) gain a greater UK profile, commensurate with the more positive UK and to a degree international findings compared to the main alternative, acamprosate. Whatever the balance between these two medications, disulfiram continues to have different role as an enforcer of abstinence rather than to promote reduced drinking, playing a major part in the pharmacotherapy offered by specialist centres in particular.

On the basis of the evidence, acamprosate, disulfiram and naltrexone are all endorsed in national guidance for [Scotland](#) and [England and Wales](#). The guidance envisages a more routine and/or first-line post-detoxification role for acamprosate than for disulfiram, the latter coming with the caution that total abstinence is required to avoid unpleasant and potentially dangerous reactions, and that the positive evidence derives from situations where consumption has been supervised. Naltrexone is seen as fulfilling a similar role to acamprosate, but at the time the guidance was drafted it had no UK licence for the treatment of alcohol dependence, so the Scottish advisers felt they could not commend it for use in the NHS.

Though the positive US trials are acknowledged in the guidance for England and Wales, and despite its authorisation in the USA, injectable long-acting naltrexone is not recommended in either that or in the Scottish guidance. Greater risks due to administration by injection and its irreversibility, higher costs, and especially its non-approved status in the UK, mean this option will for the time being [best be seen](#) as a possible reserve for patients who have not done well with other therapies and who cannot be supported to consistently comply with oral naltrexone, especially if when they *have* taken the tablets, they have responded well to the medication.

[Statistics for England in 2012](#) show that doctors in general have fronted acamprosate, prescribed 117,405 times compared to 60,842 for disulfiram, figures dominated by GP prescribing. However, in hospitals disulfiram is prescribed slightly more often. In these settings patients are likely to be so severely dependent that at least initial abstinence is the [preferred objective](#), and there is the support for patients and the expertise to handle the risks of prescribing disulfiram.

*Thanks for their comments on this entry in draft to David Harding-Price, Council Member of the Royal College of Nursing of the United Kingdom. Commentators bear no responsibility for the text including the interpretations and any remaining errors.*

Last revised 26 July 2013. First uploaded 15 July 2013

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