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▶ A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence.

Pettinati H.M., Oslin D.W., Kampman K.M. et al.

American Journal of Psychiatry: 2010, 167(6), p. 668–675.

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First evidence that combining sertraline for depression with naltrexone for drinking is more effective than either medication alone when dependent drinking is complicated by clinical depression.

SUMMARY Alcohol dependence prolongs depression, and persisting depression during abstinence is associated with relapse to heavy drinking. The implication is that both disorders should be identified and managed. However, depression in alcohol-dependent patients does not consistently react well to antidepressants, and on their own, antidepressants do not appear to affect drinking. It seems possible that antidepressants are best supplemented by a medication which directly targets drinking. Over a 14-week period, the featured study at a single US clinic tested that expectation by prescribing the antidepressant sertraline together with naltrexone – approved in the USA and the UK for the treatment of dependent drinking – to patients suffering both alcohol dependence and major depression.

Patients were 170 adults who responded to newspaper ads or heard of the study from local professionals, friends or family, and who research staff diagnosed as suffering major depression (persisting after three days of abstinence) and alcohol dependence. Extra questions were asked to try to establish whether their depression was independent of the patient's drinking, the aim being to focus on cases of depression not itself caused by heavy drinking, and therefore less likely to remit on attainment of abstinence. Among the requirements were that patients who joined the study should not already regularly be taking an antidepressant. Patients averaged 43 years old and were typically single men who had completed their high school education, and who reported a family history of alcohol or drug problems. Over the month before starting treatment, according to their own accounts they had drunk heavily on over two-thirds of days, on each of those days averaging about 174g alcohol or 22 UK units, and they averaged severe to very severe depression at the time they joined the study.

Key points

Alcohol dependence prolongs depression, and persisting depression during abstinence is associated with relapse to heavy drinking, suggesting both need to be treated.

However, depression in alcohol-dependent patients does not consistently react well to antidepressants and on their own, these drugs do not appear to affect drinking.

The featured study tried combining treatment for major depression and alcohol dependence using high-dose sertraline and naltrexone. It found the combination reduced drinking more than each drug alone, and also seemed to more effectively alleviate depression.

All patients were offered weekly individual cognitive-behavioural therapy targeting drinking and also depression. Additionally, they were randomly allocated to be prescribed:
- only inactive placebo medications which mimicked sertraline and naltrexone;
- sertraline (plus a naltrexone placebo);
- naltrexone (plus a sertraline placebo);
- both sertraline and naltrexone.

The aim was that neither patients nor the research staff assessing them would know which (if any) drugs they had actually been prescribed, an attempt to eliminate the influence of expectations leaving only their pharmacological effects to account for any differences in outcomes. Though 4 in 10 patients left treatment before the end of the 14 weeks, nearly three-quarters received at least 80% of their intended treatments, a figure which did not significantly differ depending on the prescribed medication.

To maximise the chances of a beneficial impact, target doses of both drugs were relatively high: 200mg per day of sertraline (recommended daily doses start at 50mg) and 100mg a day of naltrexone (rather than the recommended 50mg). It was at 100mg that the largest trial of naltrexone to date found it improved drinking outcomes.

Main findings

Generally the combined medications substantially and significantly promoted abstinence compared to the either alone or to placebos, and also helped more with depression, though not to a statistically significant degree.

Apparently due to fewer patients relapsing to the point where they were admitted for inpatient alcohol detoxification, serious adverse events were fewer among patients prescribed both sertraline and naltrexone; 1 in 8 experienced these incidents compared to over 1 in 4 among each of the other sets of patients, including those prescribed only placebos. However, 7 of the 42 joint-medication patients left treatment due to other adverse effects compared to just 2 of 49 naltrexone patients, 4 of 40 prescribed sertraline, and 1 of the 39 prescribed no active drugs.

Nearly 85% of patients completed weekly assessments of their drinking over the 14 weeks of the trial.

These indicated that more combined-medication patients had remained abstinent throughout than

These indicated that more combined-medication patients had remained abstinent throughout than patients in the other three groups – 54% versus 21% to 28%, or on average 24% across the three sets of patients not prescribed both drugs. More joint-medication patients had also avoided heavy drinking – 63% compared to 34% across the other three groups, and they 'survived' longer without relapsing to heavy drinking – typically 98 days compared to 26.

Among the 67% of patients for whom this assessment could be made, in the last three weeks of the trial more joint-medication patients no longer met the study's criterion for depression – 83% versus 48% to 69%, or on average 58% across the three sets of patients not prescribed both drugs. The latter difference just missed meeting the study's criterion for statistical significance, a stringent one adjusted for the many chances of finding a significant result purely by chance. Also not statistically significant, but favouring joint-medication patients, were differences in average severity of depression towards the end of the trial.

The authors' conclusions

Findings suggest that the commonly found combination of depression and dependent drinking responds relatively well to treatment with both an antidepressant and a medication for alcohol dependence – or at least, to the specific combination of sertraline and naltrexone at the doses prescribed. Joint-medication patients were significantly less likely to be drinking or drinking heavily and more tended to experience remission of their depression. However, these findings require replication before they can justify changing current clinical practices.

Another implication of the findings was that there may be relatively little advantage in prescribing an antidepressant alone for depressed patients who are also alcohol dependent, an implication in line with a large multi-clinic trial.

It should be borne in mind that the patients in this study agreed to participate in a research study rather than seeking treatment in the normal way, and their treatment took place at a substance dependence treatment facility, perhaps attracting a different type of patient than mental health services. Also it is unclear whether the short-term effects of the treatments over the 14 weeks they were being prescribed will persist.

FINDINGS COMMENTARY British guidelines which took account of the featured study recommended considering naltrexone for at least moderately severely dependent drinkers, but specifically recommended against using antidepressants routinely for treating alcohol misuse with no accompanying depression. When depression has been shown to be independent of drinking (eg, when it persists despite a week or more of abstinence), some non-SSRI antidepressants may, the guidelines suggested, be more effective than the SSRI type trialled in the featured study. The featured study confirms that on its own, an SSRI antidepressant is no better than a placebo at reducing drinking and that it can also be no better at alleviating depression. But when prescribed alongside high-dose naltrexone, it seems from the study that the SSRI sertraline *can* reduce drinking and perhaps too depression. However, the authors' caution that their finding requires replication seems well founded. Earlier studies (described below) of the same drug combination found neither added to the impact of the other, but in one depressed patients were excluded, and both used half the doses used in the featured study. Another later study of adding a similar SSRI antidepressant to naltrexone found no significant overall effects on depression or drinking among dependent drinkers suffering what for most was judged to be major depression independent of their drinking.

If medications are to be prescribed, this leaves the evidence in favour of high-dose treatment with both sertraline and naltrexone in alcohol-dependent patients with independent clinical depression, though with just the featured study to support this, neither its authors nor the experts who produced the British guidelines consider this sufficient to justify wholesale revision of practice. Additionally, adverse effects seen in this study (and another) may limit use of this combination, as may concerns about aggravation of drinking or of its intoxicating effects sometimes seen when antidepressants are prescribed to dependent drinkers or when normal drinking occurs while antidepressants are being taken.

Other features of the trial limit it as a guide to practice. Though follow-ups six and nine months after treatment entry were envisaged, the only results so far seem to be for the three-month treatment period itself. With just three days of abstinence to go on, it is also unclear how well the research team were able to distinguish between depression which would remit anyway after a period without heavy drinking, and free-standing depression which would need additional treatment – perhaps why the antidepressant alone had no beneficial effects on depression relative to placebos. The authors' caution that patients had not entered treatment either for depression or drinking in the normal way is potentially important. About 72% were assessed as middle or upper class, 9 in 10 had completed high school, and in a city where just 42% of the population are white, in this study 72% were, all indicative of relatively high socioeconomic status. In Britain and probably too in the United States, this is not the typical caseload of a publicly funded alcohol treatment service.

Despite the featured study, there seems no reason to alter the conclusions reached in 2006 by Findings in an analysis of three relevant reviews and other studies. The conclusion was that when depression is relatively severe, clinically diagnosed, and not simply related to drug use or withdrawal, antidepressants are an effective intervention for depression but not sufficient to address substance dependence. The best way to identify patients who will benefit is to delay diagnosis of depression until detoxification is completed and withdrawal symptoms have abated, but this not always possible or desirable. The key issue is not whether dependence was a consequence of substance dependence but whether it is or has become a condition which will remain serious even when dependence has remitted. Making such a diagnosis is not easy and in cases of doubt, both conditions should be treated without undue delay. Cognitive-behavioural therapies can be effective to the point where medication creates little or no further benefit, and where available could be tried first. Further details below.

The medications as sole alcohol therapies

Naltrexone has an established if modest record of curbing heavy drinking (and to a lesser extent, drinking as such) among alcohol-dependent patients.

Antidepressants do not help curb drinking in non-depressed alcohol-dependent patients and can aggravate drinking among the type of patient characterised by early onset of problem drinking, a family history of drink problems, and an impulsive/antisocial personality (1 2). Among non-dependent patients cases of increased drinking and of pathological intoxication apparently due to drinking while taking SSRI

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antidepressants have led to a call for prescribers and patients to be more clearly warned about the risks.

Among depressed alcohol-dependent patients, drinking reductions have been noted, but not consistently enough for antidepressants to be seen as a treatment for these patients' drinking problems (1 2 3). When depression is effectively treated with antidepressants, drinking may consequentially subside, but still few patients sustain abstinence.

Antidepressants can, however, help alleviate depression among depressed dependent drinkers, particularly when steps have been taken (such as a period of abstinence) to establish that the depression will not quickly remit when drinking stops. Some trials have indicated that these benefits are no greater than those which can be achieved by well structured cognitive-behavioural therapies, and the greatest and most consistent benefits have been seen among patients not offered psychosocial therapy. Complicating the issue are questions of dose and the type of antidepressant. The type trialled in the featured study (an SSRI) has been less effective in alleviating depression than other types with a wider spectrum of effects, though some of the main alternatives are also contraindicated due to risks of lethal interactions with alcohol and other drugs.

The combination therapy

The findings outlined above have prompted reviewers to call for ways to effectively supplement antidepressants with alcohol treatments among depressed alcohol-dependent patients. Two earlier randomised trials of the combination trialled in the featured study found neither drug added to the impact of the other when prescribed at the more standard doses of 50mg of naltrexone daily and 100mg of sertraline. However, one of the trials excluded depressed patients. It found no benefit in terms of drinking outcomes from adding sertraline to naltrexone among dependent drinkers, and some indication that even at these doses, the combination led to more adverse effects and to more patients leaving treatment early.

Another trial did recruit patients (aged 55 or older) who were both clinically depressed and alcohol-dependent. It tried supplementing sertraline with naltrexone, finding no added benefit either in terms of drinking or depression. In this study, two-thirds of the patients were judged to have alcohol-induced depression, though they remained depressed after detoxifying from alcohol and three days of abstinence.

Prompted by the featured trial, researchers in New Zealand tried adding a the similar SSRI antidepressant citalopram to naltrexone in the treatment of dependent drinkers suffering what for three-quarters was judged to be major depression independent of their drinking. At what were generally around the usual recommended doses of the two medications (40mg daily citalopram and 50mg naltrexone) it found no significant overall effects on depression or drinking. With or without the antidepressant – and perhaps aided by what appears to have been comprehensive and well structured and supervised counselling/case management – patients substantially improved over the 12 weeks of the trial. Unlike the featured trial, there was no requirement in this trial for patients to have stopped drinking before the start of treatment.

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