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▶ Medical treatment of alcohol dependence: a systematic review.

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With from 2011 naltrexone licensed for this purpose, Britain now has the full suite of major medications authorised for the treatment of alcohol dependence. Largely from a primary care perspective, this US review examines a half century of evidence for whether drugs aid recovery and which work best.

Summary Funded by the US government's alcohol institute, this review of drug-based treatment for alcohol dependence aimed to express the evidence base in such a way as to underpin the expansion of these treatments to medical settings including primary care and specialist clinics. It searched for research published in English in the half century from 1960 to 2010 which involved randomly allocating adult patients to medication versus either no treatment, a placebo, or some other treatment. The attempt was made to focus on studies which offered either no accompanying psychosocial therapy or only brief therapies of the kind which might be undertaken in general medicine as well as specialist clinics. Only drugs subject to at least two trials were included in the analysis.

The reviewers found 85 eligible trials involving nearly 19,000 patients. Of these, 11 studies concerned disulfiram, a drug which blocks the breakdown of alcohol in the body, producing unpleasant reactions in response to even low levels of drinking and acting as an aversive deterrent. Other pharmacotherapies for alcohol dependence are generally thought to work by blocking the rewards people experience from drinking or by stabilising body systems disrupted by chronic alcohol intake. Among these, most researched was naltrexone, tested in 33 trials. By blocking the body's own opiate-type chemicals, the drug is thought to reduce the rewarding feelings patients gain from drinking. Next most extensively researched with 24 trials was the anti-craving medication acamprosate. SSRI antidepressants were investigated by seven trials, while the anti-convulsant topiramate was the subject of four. Various other medications were less extensively researched.

Main findings

One study with the highest score for methodological rigour found no advantage for **disulfiram** over placebo when administration of the medication was not supervised. However, most other studies found supervised disulfiram reduces drinking more than a placebo, and there was some evidence that it may be more effective than naltrexone, acamprosate, and topiramate. Compliance is a problem with disulfiram; daily supervision of ingestion appears essential to clinical success.

Though based on few studies, **topiramate** seems effective in the treatment of alcohol dependence. There is, however, little evidence to support the use of **antidepressants** (either SSRIs or tricyclics), although one recent randomised trial found the combination of sertraline and naltrexone more effective with depressed alcoholics than naltrexone alone.

Acamprosate may promote abstinence, although studies have had mixed results, and some larger multi-site US studies found no advantage over placebo. European studies are more favourable, possibly due to differences in subject populations, including fewer patients still drinking when they entered the studies. Taken as a whole, this review suggests that on average the drug does have a modest impact among patients able to abstain for at least a few days beforehand.

Most relevant studies have found oral **naltrexone** is effective relative to a placebo, including 12 of the 15 most methodologically rigorous. Just two studies evaluated long-acting monthly injections of depot naltrexone, both finding it more effective than a placebo.

Whether brief psychosocial or supportive interventions enhance the impact of medications was investigated by 11 trials. Some found patients do better when medication is supplemented by extensive rather than no or minimal psychosocial support, others that brief support can be as effective as longer and/or more sophisticated therapies. The latter included three of the more methodologically rigorous studies which tested supplements appropriate in most medical settings: medical management, a supportive, compliance-focused intervention; low intensity support for primary care patients; and infrequent consultations with a doctor.

The authors' conclusions

This corpus of work shows that pharmacotherapy for alcohol dependence is feasible in primary as well as specialist medical settings, and that overall effects on drinking are on average positive, though modest. Though it is clear that some alcohol dependent patients benefit from pharmacotherapy, what type of patients do or do not is unclear.

In medical settings, current research suggests initially considering either oral naltrexone, topiramate, or (with abstinent patients) acamprosate for patients without contraindications to their use. If daily supervision of ingestion is feasible, disulfiram can be considered for motivated, abstinent patients. Medication should be accompanied by brief support aimed at making it more likely that patients will comply with treatment. Some patients may require more extensive psychosocial intervention, but it is unclear which categories this applies to. Even when intensive psychological help is unavailable, medication plus brief support from medical carers can lead to clinical improvements.

While these conclusions are based on a comprehensive search of the literature, it should be noted that non-English language articles and unpublished papers were excluded. Also,

drawing conclusions is hampered by differences between patients in the studies, which may influence their responses to treatment, and by the typically short-term follow-up of the studies, many of only three to six months duration. In particular, data is lacking on long-term effects on illness and death. Often accompanying psychosocial therapies and supports are inadequately described, and these have not been sufficiently researched.

FINDINGS These comments focus on the review's conclusions regarding the relative benefits of the major medications it reviewed. For discussion of the absolute efficacy of these substances relative to no treatment or to a placebo, see these Findings analyses of reviews of disulfiram, naltrexone and acamprosate, and this feely available 2009 review of topiramate.

The featured review comes at a time when naltrexone (in the form of a 50mg tablet marketed as Adepend) has recently been licensed in the UK for the treatment of alcohol dependence, supplementing acamprosate and disulfiram as the major medications licensed for that purpose. 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.

Which medication to choose?

The review seems to have interpreted findings that disulfiram may be superior to other major medications in the light of the nature of the studies and the patients concerned, ending with the reverse recommendation that these other medications be preferred to disulfiram as the default option, unless the taking of the tablets can effectively be supervised. While this seems an appropriate reading of the evidence, it perhaps understates the role disulfiram can play, especially in specialist centres and when clinicians are available to take on the supervisory role in the absence of suitable relatives or other associates of the patient. Details below.

Evidence for disulfiram's superiority rested largely on three Indian trials comparing the drug with acamprosate, naltrexone, and topiramate. Though each found significant differences, some were small, and other measures did not significantly differ. Nevertheless, the cumulative impression is that in this context disulfiram was on average preferable to medications which permit drinking, but are intended to moderate it. However, the context was both uniform and, in UK and European terms, atypical. Virtually complete compliance with medication and with the studies suggests that the family influences (wives and parents supervised consumption), resources and motivations of these typically employed married men detoxified at a private hospital were stronger than in typical UK and European treatment populations. Nevertheless, for their longer term sobriety, it was perhaps worrying that in all three Indian studies, on average disulfiram patients ended with more intense craving for drink than patients on other medications. The remaining study from Finland was able to complete the follow up of just 17 of 81 patients allocated to disulfiram and even fewer allocated to naltrexone or acamprosate. More did return postal surveys, but still just 42% of all the randomised patients, and by the end about half the patients were considered to have dropped out of the study.

The choice between acamprosate and naltrexone is complicated by contrary considerations. Head-to-head trials (1 2) have found naltrexone somewhat more effective 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.

British studies

Disulfiram

British experience and studies suggests disulfiram can have a broader and more frontline role than the featured review envisages. A major UK trial at seven specialist clinics found the drug effective at least in the first months of treatment when its daily consumption was supervised mainly at home by the patient's female partner, and both knew the consequences of drinking while taking it. Over the six months they were followed up, disulfiram patients reduced their drinking days and amounts drunk by significantly more than patients prescribed a vitamin, though by the end the extra reduction had evened out, as had the time they had lasted without drinking.

Nearly half the patients (but no more so on disulfiram) effectively rejected or dropped out of treatment, but this was less than in studies of other medications, perhaps because many patients had active intervention at home on a daily basis centred on ensuring the tablets were taken, and others were in regular clinical contact for medication supervision. Follow-up interviews were completed with 8 in 10 of all the patients, an acceptably high rate, lending confidence that the findings do reflect the impact of the medication, and were not an artefact of selective drop-out.

Findings of an audit of a service in Leeds show that given strong clinical support from a specialist multidisciplinary team, disulfiram can successfully be prescribed to most patients who qualify for outpatient detoxification. As for many patients in the trial described above, in this service clinicians took on the supervision role which might otherwise to be shouldered by families, presumably extending effective treatment to patients without someone in their lives willing and able to make sure they took the tablets and acceptable to the patient.

Naltrexone and acamprosate

Without being conclusive either way, in line with the international literature, another two major British studies provided greater support for naltrexone than for acamprosate. Both suffered 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. As with the disulfiram trial, one lesson from both 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.

Across six centres, the naltrexone trial found that compared to a placebo, the drug did not delay a return to drinking or to heavy drinking, but did (non-significantly) tend to reduce the amount drunk in the last month of the study, a trend partially reflected in

biochemical markers of heavy drinking. Patients on naltrexone also experienced significantly less craving for alcohol and by the end of the study nearly two-thirds were judged by their doctors to have improved, about 20% more than in the placebo group. Possible side-effects seen more often in the naltrexone group included nausea and pain, but adverse effects did not result in noticeably more naltrexone patients having to terminate treatment. However, the study excluded patients with serious physical illness, medicated psychiatric conditions, or who also abused other drugs.

These results assumed that the nearly 60% of patients who were lost to the study had resumed heavy drinking. When the analysis was confined to the 70 who completed the study and had largely complied with the treatment, the reduction in the amount subsequently drunk (on average half that in the placebo group) was statistically significant and corroborated by biochemical markers.

A different treatment regimen might have further improved outcomes. Naltrexone was introduced only after patients had been abstinent for on average 10–11 days, yet the drug seems to work mainly by reducing the experienced rewards of drinking, a mechanism which can only be activated if drinking occurs. Consistent with this theory, the study found that drinking was not delayed but (presumably because they 'got less out of it') patients on naltrexone went on to drink less than those receiving a placebo.

In contrast, a similar study of acamprosate found no impact on drinking, even among patients who took the drug. At least a week after detoxification at one of 20 British alcohol treatment units, the study randomised 581 alcohol dependent outpatients either to acamprosate three times a day or to placebo tablets, each supplied for six months. High drop-out and non-compliance rates meant that just a third of the sample completed the study, and by the end fewer than 30% were taking at least 90% of their tablets. Subjects lost to follow-up were assumed to have relapsed.

Acamprosate did not improve abstinence rates among the patients as a whole, nor among certain types of patients thought to respond well to the drug. Even among those who at least took the tablets for the first two weeks, there was no added benefit. Whether taking acamprosate or placebo, both groups drank on most days. Neither did acamprosate prevent relapse to heavy regular or binge drinking by over 80% of each group, though there was evidence of reduced craving and anxiety. About a month after medication ended, researchers interviewed 385 of the 581 patients. Abstinence rates had remained similar to those seen at the end of the medication period.

In contrast to some earlier research which provided high quality care characteristic of academic centres, apart from the tablets, patients received 'treatment as usual'. For many this seems to have been insufficient to prevent a high rate of pre-medication relapse and subsequent drop-out, making it much harder for acamprosate to demonstrate its worth. Nearly a third of patients did not remain abstinent for the week before being randomised into the study, 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 its effectiveness should be at its height.

UK policy and practice

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 option 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 2011 show that doctors in general have forefronted acamprosate, prescribed 107,389 times compared to 60,375 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.

This draft entry is currently subject to consultation and correction by the study authors and other experts.

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