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▶ The state of pharmacotherapy for the treatment of alcohol dependence.

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Review finds some but inconsistent and often modest support for each of the four medications approved by the US administration for the treatment of alcohol dependence: disulfiram; acamprosate; oral naltrexone; and once-monthly, injectable, extended-release naltrexone.

Abstract This US review focuses first on the four preparations approved by the US Food and Drug Administration for the treatment of alcohol dependence: disulfiram; acamprosate; oral naltrexone; and once-monthly injectable, extended-release naltrexone. All four have demonstrated some ability to reduce drinking and/or increase time spent abstinent, but results have not always been consistent. Except disulfiram, which has an aversive mechanism of action, effective pharmacotherapies for alcohol dependence are thought to work by blocking the rewards people experience from drinking or by stabilising systems dysregulated by chronic alcohol intake. Topiramate and baclofen have also demonstrated some efficacy in treating alcohol dependence. The efficacies of many of these regimens are modest and are limited by patient non-adherence to treatment and differences in the manifestations and causes of alcohol dependence. Their effectiveness could be enhanced through increased knowledge of the pathophysiology of alcohol dependence, through the identification of predictors of response to specific medications, and by modalities which improve adherence to medication regimens. Further details below.

By blocking the breakdown of alcohol in the body, **disulfiram** produces unpleasant reactions in response to even low levels of drinking, so acts as an aversive deterrent. Specifically it inhibits the action of the liver enzyme aldehyde dehydrogenase, preventing the conversion of acetaldehyde to acetate. As a result, after drinking alcohol, acetaldehyde accumulates, causing flushing, throbbing headache, nausea, vomiting, and chest pain. Its potential role and its shortcomings were highlighted in an early randomised trial which suggested that it could work as long as patients took it, but that most would fail to do so. Later work has emphasised the need for patients to agree to a trained associate (such as a supportive family member or friend) supervising their

disulfiram consumption to help ensure the drug is taken.

Numerous trials mainly conducted in Europe have shown that **acamprosate** raises abstinence rates among recently detoxified patients. Some research also suggests it may be effective among patients who have not yet become abstinent. However, two major US trials were negative, possibly because patients had to sustain relatively short periods of abstinence before entering the studies. When naltrexone was already being prescribed, two studies found that adding acamprosate conferred no further benefit.

By blocking the body's own opiate-type chemicals, **oral naltrexone** is thought to reduce the rewarding feelings patients gain from drinking. Analyses of over 20 trials involving about 4000 patients have found convincing evidence that it reduces the likelihood of relapse to heavy drinking. There is also some evidence that it enhances abstinence rates. Overall the impacts are modest, though some patients do strongly benefit. These may include patients with a family history of alcoholism, relatively intense craving for alcohol, and certain genetic variants of cellular receptivity to opiate-type drugs, but the clinical utility of these indicators has yet to be demonstrated. Benefits are also more likely among patients who take medication as recommended.

Extended-release naltrexone helps overcome the problem of patients failing to take the oral form of the drug. As approved in the USA, it takes the form of a long-acting intramuscular injection which blocks the action of opiate-type drugs for a month or possibly longer. Two randomised controlled trials have confirmed that such preparations do reduce drinking. The most recent tested the approved product and found that over a six-month period repeated injections curbed heavy drinking, particularly among men and patients who had sustained several days abstinence before entering the study.

Of the **other agents** which have been tested, evidence is greatest for the anticonvulsant topiramate. In trials which randomised patients to the drug or to a placebo, topiramate reduced heavy drinking and increased abstinence rates, though side-effects were common. Three similar trials have been completed with baclofen. The two European trials found that it increased continuous abstinence rates, but a US trial found no effect on either heavy drinking or abstinence.

FINDINGS In Britain disulfiram and acamprosate have been approved for the treatment of alcohol dependence. No extended release naltrexone product has been licensed for any medical purpose. Non-licensed products or products licensed for another purpose can be used subject to the discretion and extra responsibility of the individual prescriber. A review published by England's National Treatment Agency for Substance Misuse concluded that naltrexone and acamprosate show minor positive effects when combined with psychosocial interventions, that naltrexone is most clearly indicated for patients who have lapsed or 'slipped', and acamprosate for supporting abstinence among patients who fear craving will lead to a lapse. Guidance partly based on this review stressed that drugs should be seen as an adjunct to psychosocial therapies, not as a treatment in their own right.

Without being conclusive either way, two major British studies have provided greater support for naltrexone than for acamprosate. Both studies were plagued by high drop-out rates and poor compliance with treatment, but in the naltrexone study, those patients who did complete the study and largely complied with treatment drank substantially less on naltrexone than on placebo pills. 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. Details in background notes.

Head-to-head trials of naltrexone versus acamprosate within the same study help to

eliminate the possibility that caseload or regimen differences account for their relative impacts. Like the UK studies, such studies conducted in Spain, Germany, the USA, and Australia, have consistently favoured naltrexone. The Australian study applied minimal filters to who could participate. Caseloads in the other studies (though often severely dependent) were relatively socially integrated. In all these studies the patients can be assumed to have been relatively highly motivated to tackle their drinking problems. Details in background notes.

The featured US review usefully complements clinical guidelines drawn up by a panel of experts convened by the US health department on how the four US-approved medications can be incorporated in to medical practice. All these medications are best seen as helping to create a relatively intoxication-free space during which patients can be helped to find other ways to cope and to construct lives incompatible with a return to heavy drinking. Each has its own strengths and limitations.

Patients committed to abstinence who have strong home-based or clinical support, especially in the form of someone to supervise consumption, can sustain disulfiram therapy and remain abstinent as a result, though some will not be suitable due to medical contraindications. The possibility of a severe reaction to drinking means that it would be unacceptable to use the drug in patients who have little chance of sustaining abstinence. In other circumstances, pharmacotherapies like naltrexone and acamprosate − which do not demand total abstinence − are more likely to be adhered to and can cut consumption. Even with these drugs, 'compliance' − the degree to which patients take the pills as intended − is a key issue. It can be improved by counselling designed to motivate compliance and to minimise side effects such as fatigue and nausea, and by engaging family members or other associates to monitor consumption of the pills. Naltrexone may 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 only rarely such that 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. This is a greater problem with the irreversible long-acting naltrexone injection.

Though there are these pointers to which *types* of patients might benefit most from which medication, the review points out that there is no secure way of deciding which is preferable at the level of the individual patient. Fortunately, all the US-approved medications have a good safety profile and (in their oral forms) are easily terminated without problems, allowing patients and doctors to take a trial and error approach to finding a medication which works. Greater risks due to administration by injection and its irreversibility, higher costs, and especially its non-approved status in the UK, mean that injectable long-acting naltrexone 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 pills, they have responded well to the medication.

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