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▶ The efficacy of disulfiram for the treatment of alcohol use disorder.

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Given effective supervision from family or clinicians to help ensure patients keep taking the tablets, this first systematic synthesis of research finds that on average the drug disulfiram, which produces an unpleasant physical reaction to drinking, does act as an aid to abstinence in the treatment of alcohol dependence.

Summary 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. It inhibits the liver enzyme aldehyde dehydrogenase, preventing acetaldehyde being converted to acetate. After drinking alcohol, acetaldehyde accumulates, causing flushing, throbbing headache, nausea, vomiting, and chest pain. Disulfiram is therefore indicated for patients who wish to remain abstinent. Generally administration of disulfiram is supervised and, like other medications, combined with behavioural therapy.

This review aimed to analyse trials to date which randomly allocated adults or older teenagers to different doses of disulfiram, or to disulfiram versus other (including a placebo) or no treatments. It was restricted to trials which reflected drinking outcomes for all the patients, regardless of whether they dropped out of treatment and/or the study. [Editor's note: an important safeguard against bias due to the more promising patients remaining in treatment.]

Published between 1979 and 2010, 11 trials totalling 1527 patients fulfilled these criteria, four from India, five Europe, and two the USA. Patients were mainly alcohol-dependent men, though four trials targeted non-dependent hazardous drinkers. In eight studies patients were required to have a close associate who could supervise them to make sure they took the medication. In all but one study, medication was supplemented by counselling or other psychosocial therapies. Typically patients complied well with the

treatment and took their medication as required.

Main findings

The proportion of patients who sustained abstinence was the most common measure of success. On this yardstick, in six of the 10 relevant studies disulfiram produced significantly better outcomes than placebo, none, or other treatments. Though not the case in the remaining four studies, in no case did other treatments significantly better disulfiram. Moreover, five of the seven studies to assess this found that on disulfiram patients on average lasted significantly longer before drinking or relapsing, though four of the five were from India and shared similar procedures and patients.

Across the seven studies in which tablet-taking was supervised, disulfiram significantly improved the overall abstinence rate, but the variation in the results of these studies was so large that that it was inappropriate to amalgamate them as if they were testing the same treatment in similar circumstances.

Most of the six studies comparing disulfiram with other medications intended to reduce drinking found disulfiram had a greater effect on abstinence and/or days until lapse or relapse, though again, four of these studies were from India and shared similar procedures and patients.

Medication was not supervised in all three studies where the comparator was an inactive placebo. One small Austrian study of 26 teenage patients (of whom only half could be followed up for three months) found a higher abstinence rate among disulfiram patients. The remaining two US studies found no such effect. In all three, many patients did not take their medication or complete treatment. Nevertheless, amalgamated results from these three studies cumulate to a significant improvement in abstinence.

The two (both Danish) studies which compared disulfiram with no treatment at all – not even a placebo – were inconclusive about its efficacy among the usual run of patients. One found a positive impact on abstinence, but the patients were all in the month leading up to major surgery and risked complications aggravated by drinking. Another found no such effect among patients discharged from hospital after having to be admitted for the treatment of alcohol withdrawal symptoms. [Editor's note: In both studies it seems medication was taken under medical supervision twice a week but patients had to choose to attend the clinic rather than being supervised by family at home.]

The authors' conclusions

Primarily among alcohol-dependent men whose consumption of the drug was supervised, disulfiram increased the proportion abstinent and the number of days before drinking. Among patients who took their medication more or less as required, it also led to fewer days of drinking. It is unclear whether beyond this type of caseload, non-treatment seeking patients and those drinking at hazardous but non-dependent levels also benefit from disulfiram, and whether the impacts extend beyond a year, the longest follow-up period in the studies.

FINDINGS Though overall encouraging, these findings fall short of a convincing endorsement in the circumstances of a trial in which patients are randomly allocated to disulfiram rather than it being a positive choice, especially in societies where effective

family supervision of severely dependent drinkers is less available. Additional evidence from non-randomised studies does however support the drug's efficacy among patients who choose (perhaps under pressure) to take the drug, and choose to be supervised to make sure they do.

Particularly when disulfiram was compared to other treatments, the findings should be interpreted in the light of the abstinence outcomes which (instead of the intended outcome of drinking at or below safe levels) the review was forced to adopt. Disulfiram targets absolute non-drinking, while other medications such as naltrexone are strongest at preventing heavy drinking. For example, the verdict that disulfiram is superior to other medications rests largely on the Indian trials. Of these, the comparison with acamprosate found no difference in the typical intensity of drinking on drinking days and no significant difference in the number of days on which patients drank. The corresponding comparison with naltrexone was decisive in its finding that fewer patients relapsed at some time to heavy drinking on disulfiram, but less so in respect of typical drinking intensity (a difference of one UK unit or 8g alcohol) or the number of days patients altogether avoided drinking over the follow-up year (306 on disulfiram v. 243 naltrexone). In India, virtually complete compliance with medication and with the studies suggests that the family influences (wives and parents supervised consumption) and motivations of these typically employed married men detoxified at a private hospital were greater than some UK treatment populations. Nevertheless, for their longer term sobriety, it was perhaps worrying that in both studies, on average disulfiram patients ended with more intense craving for drink than patients on other medications.

Another questionable implication of the review is that disulfiram has been shown to be more effective than a placebo. Across three studies it found a significant advantage in terms of abstinence which was overwhelmingly due to the large numbers in a 1986 US trial. But the review amalgamated findings from patients prescribed an active dose of disulfiram with those prescribed an inactive dose intended as a placebo, but which patients could honestly be told was a drug which caused adverse effects on drinking. Though not a statistically significant difference, it so happened that it was in this group that the greatest proportion sustained abstinence. To attribute this to an effect of disulfiram, as the review implicitly does, is an unusual interpretation. It is better seen as a classic placebo effect, reflecting the patients' expectations rather than the reality of the drug's impact.

Results from the first major randomised trial of disulfiram were taken to mean that the medication will only work among the sometimes minority of patients prepared to keep taking it – the most 'compliant' patients and research subjects. This was also read as one of the messages of a UK trial, which 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.

In this which is still the major British study, the impact of the treatment appeared to have waned by the end of the six-month follow-up period. Whether impacts are indeed short-lived was the prime concern of a commentary on the featured study. Its main source was a German study of the intensive treatment of severe alcoholics using disulfiram and a similarly aversive medication for two years, which resulted in high rates of long-term abstinence, outlasting the treatment period by seven years. In this study, joined by under half the patients who were asked and were eligible, administration was supervised by clinic staff, and few patients dropped out of treatment, perhaps spurred on by what were usually serious medical consequences of highly excessive drinking.

Disulfiram is one of the three main medications licensed in the UK for the treatment of

alcohol dependence and endorsed in national guidance for Scotland and England and Wales. The other medications are acamprosate and naltrexone (licensed in 2011), for which the guidance envisages a more routine and/or first-line post-detoxification role than for disulfiram. The latter comes with the caution that total abstinence is required to avoid unpleasant and potentially dangerous reactions, and that the positive evidence derives only from situations where consumption has been supervised. Compared to the main alternative medications, the experts behind the English/Welsh guidance found the evidence for disulfiram "much weaker and the potential for harm was greater [so] did not consider disulfiram as a suitable first-line pharmacological treatment for relapse prevention in individuals with alcohol dependence". It has its greatest role they thought among patients who are relatively older, socially stable, impulsive, highly motivated, and enjoy strong home-based or clinical support, especially in the form of someone to supervise consumption.

However, given strong clinical support from a specialist multidisciplinary team, it seems that disulfiram can successfully be prescribed to most patients who qualify for outpatient detoxification. As well as or instead of supervision, an associate can take on a less onerous monitoring role, feeding back to the doctor whether the patient is taking the tablets while the doctor does the persuading, opening up effective treatment to a wider range of patients and medical settings. Arguably GPs with their family and local ties are in a better position to engineer these regimens than specialist centres. Allied with intensive support, disulfiram has also successfully been used as a fallback option for patients who have not done well in less radical and risky therapies such as acamprosate.

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.

Thanks for their comments on this entry in draft to Colin Brewer. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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