DRUG & ALCOHOL FINDINGS

Disulfiram treatment

The landmark study which stimulated researchers to investigate how disulfiram can be made to work and pioneered research methods capable of delivering clinically useful answers. Expert commentary plus the hindsight reflections of the original researcher.

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What is disulfiram?

Disulfiram blocks the breakdown of alcohol at the acetaldehyde stage by inhibiting the hepatic enzyme aldehyde dehydrogenase. This leads to an accumulation of acetaldehyde in the body and to the disulfiram-ethanol reaction, characterised by flushing of the face and upper trunk, throbbing headache, palpitations, tachycardia, nausea, vomiting, and general distress. With large doses of alcohol, arrhythmias, hypotension and collapse may occur. The reaction usually starts within 10 to 30 minutes of drinking and can last several hours.

The rationale of this treatment is that a patient cannot drink while under protective cover of the drug and they will thus only have to make a daily decision to take the medication rather than have to resist the sudden temptation at any moment to drink ... It is [however] a drug which should only be used with discretion and its dangers should not be discounted. The disadvantages ... include the potential dangers of the drug-ethanol reaction, side-effects of the drug, and a covert message that more basic therapeutic work is not needed.

Best results with disulfiram are probably likely to be seen when one or both of the following conditions are fulfilled. Firstly, the use of the drug should be explained to, and negotiated with, the patient so that taking the tablets becomes not only acceptable but wanted; the patient is not being muzzled, or surrendering autonomy, but making a free decision to engage in this type of treatment. Secondly, an acceptable degree of supervision should be set up (the tablet taken in the doctor's office, for instance, or in the medical room at work, or under the eyes of the wife), or a contingency management plan or therapeutic contract established.

Extracts from: Edwards G., *et al.* *The treatment of drinking problems. A guide for helping professions*. 3rd edition. Cambridge University Press, 1997.

In September 1986 the *Journal of the American Medical Association* published an article by Richard Fuller and colleagues titled "Disulfiram treatment of alcoholism."[1] Before completion of this well-designed study at nine Veterans Administration Medical centres, disulfiram (Antabuse) was controversial in the treatment of alcoholism due to the lack of sophisticated scientific data on which to base judgment of its effectiveness. Fuller and colleagues used state-of-the-art clinical research methods to design and conduct a study which could answer the question of disulfiram's efficacy beyond reasonable doubt.

The study not only provided these answers, but also defined the methodology for this type of research. Since its publication it has served as a model for testing the usefulness of medication-based treatments for alcoholism. For instance, Dr Fuller and colleagues paid great attention to patient selection criteria, to the use of placebo pills for comparison, to validating patient self-reports of drinking with biological markers and reports from cohabiting friends or relatives ('collaborative sources'), and to urine tests indicating whether the medication had actually been taken. They also introduced into alcoholism treatment research new statistical methods used successfully in other branches of health care research. In particular, they introduced survival analysis, using the time it takes to relapse to alcohol use as their primary measure

In this year-long study, 605 ex-servicemen were assigned at random to three medication groups: active disulfiram (250mg dose); inactive disulfiram (1mg); and placebo (no dose). Patients were expected to attend for supportive counselling during the course of the study and were encouraged, but not mandated, to attend Alcoholics Anonymous meetings. Each patient and his collaborative source were questioned periodically during the study about the patient's alcohol consumption and social well-being. The interviewers were unaware of the patient's medication group assignment.

This information was used to calculate abstinence rates and the time elapsed prior to a return to drinking for the three groups. The main finding were summarised as follows: "Using a randomised, controlled, blinded study design, we did not find that disulfiram provided additional benefit to the treatment services provided at our nine clinics in aiding our patients to remain completely abstinent or in delaying the time to relapse."

A positive finding, however, was that among patients who completed all seven interviews, those who did drink did so less frequently (on fewer days) when they were given active disulfiram than patients given the other two medications. Compared to patients who did *not* complete the interview schedule, these patients were slightly older, had been alcohol abusers longer, and had lived at their current addresses longer. This finding led the researchers to suggest that disulfiram is not necessary for patients who are able to achieve total abstinence (about 20% of the total number of patients entering the study) but that it be reserved for older, more socially stable men who relapse to drinking.

As the authors acknowledged, the generalisability of their results may be limited because the study groups did not include women and few were in professional or executive employment. However, this landmark study indicated that well-founded scientific inquiry could be applied to alcoholism treatment to achieve clinically useful results.

Though they were rather straightforward and clear, some clinicians and researchers could not completely accept the findings because they could point to patients who *had* successfully used disulfiram to achieve long-lasting sobriety. This

# of alcoholism

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led investigators to explore the conditions under which disulfiram could be used with a greater expectation of success. For example, Jonathan Chick and colleagues studied patients whose disulfiram intake was monitored and found that those who took disulfiram under controlled circumstances did better than those who did not.[2] Other studies of disulfiram and related aversive medications all seem to point to motivation and compliance as crucial variables predictive of who will respond best.[3]

In many ways, this seminal study proved a watershed for investigations of pharmacological agents for alcoholism treatment, paving a methodological pathway for other treatment outcome studies to follow. For example, a large Veterans Administration study on the efficacy of lithium carbonate in alcoholics borrowed heavily from the methodologies developed by Dr Fuller and colleagues.[4] Defined patient-selection criteria, compliance monitoring, validation of patient drinking reports, and survival analyses, continue to be mainstays of modern alcoholism treatment research. These technological 'spin-offs' from this thoughtful scientific endeavour are now beginning to bear fruit in the discovery of new medications for the treatment of alcoholism. For this seminal alcoholism research study, the future then, is now.

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1 Fuller R.K., *et al*. "Disulfiram treatment of alcoholism: A Veterans Administration cooperative study." *Journal of the American Medical Association*: 1986, 256(11), p. 1449–1455.
2 Chick J., *et al*. "Disulfiram treatment of alcoholism." *British Journal of Psychiatry*: 1992, 161, p. 84–89.
3 Allen J.P., *et al*. "Techniques to enhance compliance with disulfiram." *Alcohol Clinical and Experimental Research:* 1992, 166, p. 1035–1041.
4 Dorus W., *et al*. "Lithium treatment of depressed and non-depressed alcoholics." *Journal of the American Medical Association*: 1989, 262(12), p. 1646–1652.

HINDSIGHT

Negative findings, positive results

by **Richard K. Fuller**
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In the late 1960s I began treating alcoholics. Being a physician, I prescribed disulfiram for my patients. Because it was an approved drug in the United States, I thought disulfiram had been proven to be efficacious – until this notion was challenged by my mentor, Harold Roth. A review of the literature showed that most clinical studies of disulfiram had been uncontrolled, and most of the controlled trials had other methodological flaws. To be fair, many of these studies had been done when disulfiram was introduced, and the appropriate design of randomised clinical trials was not yet fully developed.

Our initial study of 126 men using modern clinical trial methods found a trend towards more sustained abstinence in men who received disulfiram, but this was not statistically significant. However, the study's design meant there was a high probability that even if the drug *had* been effective, this would not have been picked up, so we were unable to conclude that disulfiram was *in*effective. To resolve this issue, we needed a larger sample. This led us to the Veterans Administration Cooperative Studies Program, which supported a study of disulfiram treatment taking subjects from several centres.

Designing a study of disulfiram is more complicated than of almost any other drug because the *expectation* of becoming sick if one drinks accounts for its effect, rather than a direct pharmacological action. To control for this, while the experimental group received 250mg disulfiram, one control group received 1mg, an ineffective dose. Both were told they were receiving disulfiram. A second control group received a vitamin and were told this. The first control group had the expectation of a disulfiram-ethanol reaction, the second did not.

We did not find any benefit from disulfiram treatment except in a subset of men who were not continuously abstinent. I thought these generally negative findings would result in a reduction of disulfiram use in clinical practice, but it is my understanding that sales of disulfiram have been relatively stable in the United States. We also found a positive relationship between compliance with disulfiram and abstinence. However, the compliance rate was low. Others have used staff or relatives to observe the ingestion of disulfiram to improve compliance and reported better results.

Dr Fuller cleverly constructed a study in which the controls could be given an inactive pill yet honestly be told they were getting the drug.

While it did give a reasonably definitive verdict on the efficacy of disulfiram given to patients to take at their discretion, the study's importance lies as much in its methodological implications as in its results. It used techniques featured in other medical clinical trials but uncommon at the time in alcoholism treatment studies and was a methodological pioneer for future clinical trials of alcoholism treatment.