Developed in the late 1940's(1, 2), disulfiram (Antabuse®) is the oldest of the three agents currently approved by the US Food and Drug Administration (FDA) for the treatment of alcoholism. In the presence of ethyl alcohol (ethanol), it occasions an immediate and profoundly uncomfortable physical sickness known as the disulfiram-alcohol reaction(D-AR). This includes facial flushing, a significant drop in blood pressure, severe headache, and markedly severe nausea and vomiting. First confirmed when early investigators tested it on themselves(3), the D-AR lasts from 30 minutes to several hours depending on the amounts of both ethanol and disulfiram in the body. Disulfiram inhibits aldehyde dehydrogenase, the enzyme that changes acetaldehyde--ethyl alcohol's first breakdown product-- into carbon dioxide and water; it raises the acetaldehyde level in the blood resulting in the D-AR. Early clinicians saw this as a conditioning tool and would provoke the D-AR in active drinkers to demonstrate the drug's aversive qualities. In present day practice, an FDA black box warning prohibits giving disulfiram to a person with alcohol in the body. For some, the D-AR can become dangerous, for example those in whom a sudden drop in blood pressure increases in the pulse rate in an already failing heart.

Clinical Safety

Disulfiram itself can cause three rare but harmful reactions. The first is disulfiram psychosis(4) in which patients may develop hallucinations--especially visual hallucinations, delusions and mental confusion while taking the drug, usually for periods of a few months to a year, although it can occur more immediately. The psychosis clears with discontinuing the drug and may be relieved promptly by adding a very low dose of a dopamine blocking agent, such as haloperidol at 0.5mg daily. The principal danger is the risk to harm of self or others while in a psychosis. The second is a disorder of the peripheral nerves that lose both sensation and muscle strength, especially in the feet, lower legs, and hands. (5, 6) This is not known to occur at daily doses of 250mg or less and most often returns to normal when the drug is stopped.

The third is much more ominous: Disulfiram Induced Hepatitis (DIH). This occurs very rarely but can be catastrophic. The medical literature suggest that acute liver failure from disulfiram results either in death or liver transplant, from 16% of affected patients in one study (7) to about 30% of published case reports. DIH does not occur without warning, however, and our group has filed what we believe is the first case report of averted DIH liver failure. (8) A monitoring protocol applied in the first three months after starting disulfiram brought to light the dramatic rise in the liver's transaminase enzymes that signaled stopping the drug before failure could ensue. The monitoring procedure includes determining aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations shortly before initiation of disulfiram and again at 2 and 6 weeks, at 3 months, 6 months and every 6 months after while on disulfiram. Those cases complicated with hepatitis B or C or other potentially hepatotoxic medications require AST and ALT testing at baseline, two weeks after initiation, at one month and then monthly thereafter. With proper monitoring disulfiram is safe in complicated cases and far more gentle to the liver than ethanol. The practice of starting disulfiram with no AST or ALT monitoring for the first several months risks missing the indicators of incipient DIH.

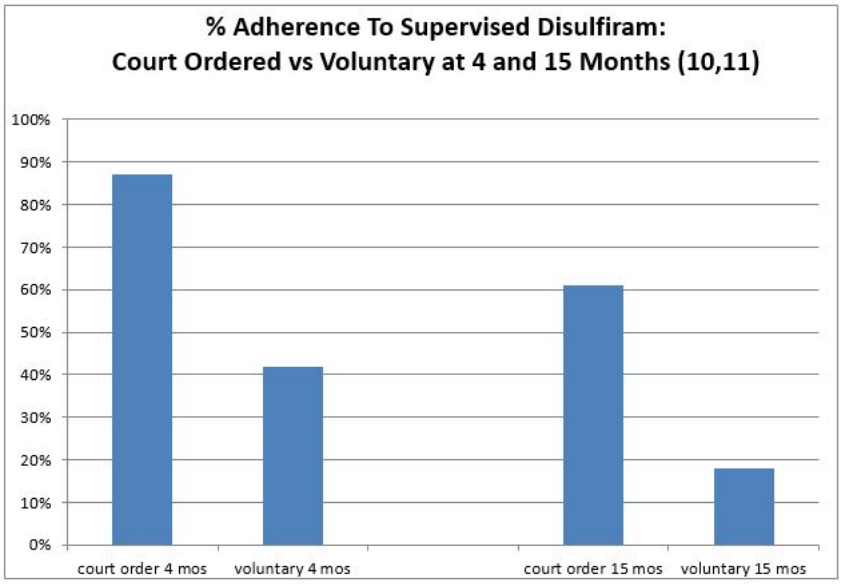
Clinical Adherence: Court and Clinic Cooperation

The compliance of patients in taking disulfiram is its main drawback in treatment settings. A large multicenter trial conducted in the US VA healthcare system pronounced voluntary disulfiram treatment as ineffective due to patient non-compliance in taking the medicine. (9) For many this remains the perception of disulfiram's usefulness today.

However, this considers disulfiram only in a disease model of alcoholism in which one takes a medicine to treat an illness. See our series "Models of Alcoholism." An alternative view combines both the disease model and the model of social/governmental intervention for public safety in a way that offers striking improvements in disulfiram treatment adherence. The Figure below shows the results of combining court order with monitored disulfiram administration in a clinic. The court/clinic combination boosts adherence to high levels at 4 months (10) (87%) that remained high at 15 months (61%) in the sample (11), both significantly higher than voluntary compliance alone (The statistical error rate is less than one chance in a thousand, $p < 0.001$.). These data suggest that court order can double the rates of voluntary disulfiram use in a supervised administration setting at

4 months and triple it at 15 months.

By implication, monitored disulfiram adherence means no alcohol use. In this setting, therefore, court ordered – clinic supervised disulfiram administration can potentially result in many months of alcohol free living for sizable numbers of alcoholic people. While this helps the court to assure public safety in the short term, a truly important question for further research asks: To what extent do those engaged in court ordered alcohol free living make the additional life changes necessary for stable, long-term abstinence? Further evaluation of the court-clinic combination appears well warranted and likely to provide both courts and clinics with improved clinical practice methods.



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The NCADD Research Update welcomes constructive comments on current installments and suggestions for further topics.

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