

Original Contributions

Disulfiram Treatment of Alcoholism

A Veterans Administration Cooperative Study

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We conducted a controlled, blinded, multicenter study of disulfiram treatment of alcoholism in 605 men randomly assigned to 250 mg of disulfiram (202 men); 1 mg of disulfiram (204 men), a control for the threat of the disulfiram-ethanol reaction; or no disulfiram (199 men), a control for the counseling that all received. Bimonthly treatment assessments were done for one year. Relative/friend interviews and blood and urine ethanol analyses were used to corroborate patients' reports. There were no significant differences among the groups in total abstinence, time to first drink, employment, or social stability. Among the patients who drank and had a complete set of assessment interviews, those in the 250-mg disulfiram group reported significantly fewer drinking days (49.0 ± 8.4) than those in the 1-mg (75.4 ± 11.9) or the no-disulfiram (86.5 ± 13.6) groups. There was a significant relationship between adherence to drug regimen and complete abstinence in all groups. We conclude that disulfiram may help reduce drinking frequency after relapse, but does not enhance counseling in aiding alcoholic patients to sustain continuous abstinence or delay the resumption of drinking.

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ALCOHOLISM is a problem of immense magnitude in the United States.¹ Disulfiram is, to our knowledge, the only pharmacologic agent used specifically for the treatment of alcoholism in this country. The ingestion of alcohol by a person who has been taking

See also p 1489.

disulfiram results in an unpleasant reaction manifested by nausea, vomiting, flushing, light-headedness, abdominal pain, and tachycardia. The rationale underlying the use of disulfiram is that an alcoholic taking disulfiram will not drink because he or she will not want to suffer the consequences of the

disulfiram-ethanol reaction. Disulfiram has been available for use since 1948, and many studies have claimed it to be an effective treatment for alcoholism. However, its efficacy has not been established because of flaws in the design of most studies evaluating the drug.²⁻⁴ Of the nearly 100 studies reporting on the efficacy of orally administered disulfiram, most were not controlled, and only one⁵ was "blinded." Other methodological problems included nonrandom assignment, short duration of follow-up, success or failure of treatment based only on the patient's self-report, ill-defined criteria for successful treatment, inadequate sample size, and, except in one study, failure to assess adherence to the disulfiram regimen.

The purpose of the present randomized, controlled study was to evaluate disulfiram as it is usually used in clinical practice, ie, in combination

with alcoholism counseling and given to patients to take at home. This study was a multicenter, blinded study using a sample size large enough to detect a clinically relevant effect (a 12% greater abstinence rate in the disulfiram group than in the control groups). This report gives the results of our evaluation of disulfiram therapy in 605 alcoholic men.

METHODS

Patient Recruitment

Nine Veterans Administration (VA) medical centers participated in this study. Participating investigators supervised the conduct of the study at each of the centers. Research assistants recruited patients, conducted follow-up interviews, and obtained urine and blood specimens that were analyzed in central laboratories.

Patients presenting for treatment at each participating alcoholism treatment unit were screened for eligibility by the research assistant after a physical examination and liver function tests were done. At seven hospitals patients were screened while they were still inpatients. Two hospitals had exclusively outpatient programs and patients were screened on an outpatient basis. Only men younger than 60 years old were included if they met the National Council on Alcoholism diagnostic criteria for alcoholism.⁶ Patients were excluded if they lived alone (because we wanted a corroborative report about the patient's drinking and social behavior); had a condition that contraindicated the use of disulfiram (heart disease, organic brain syndrome, schizophrenia, major affective illness, idiopathic seizure disorder or current use of anticonvulsive medications, de-

used state-of-the-art clinical research methods to design and conduct a study that could answer the question of disulfiram's efficacy beyond a reasonable doubt.

The study reported in this article not only provided answers to important questions regarding the use of disulfiram in alcoholism treatment but also defined the methodology for conducting this type of research. It has served as a model for testing the usefulness of medication treatment of alcoholism for the past 10 years. For instance, Fuller and colleagues gave much attention to patient selection criteria; the use of placebo (i.e., inactive) pills for comparison; validation of patient self-reports of drinking, both with the use of reports from cohabiting friends or relatives (collaborative sources) and biological measurements; and medication compliance markers in the urine. In addition, Fuller and colleagues also emphasized new statistical methods (i.e., survival analysis, which utilizes the time it takes to relapse to alcohol use as the primary unit of analysis), which have been used successfully in other branches of health care research, into the alcoholism treatment research arena.

In this year-long study, 605 male veterans were assigned at random to three medication treatment groups: active disulfiram (i.e., 250-milligram dose), inactive disulfiram (i.e., 1-milligram dose), and placebo (i.e., no dose). Patients were expected to attend supportive counseling sessions during the course of the study and were encouraged, but not mandated, to attend Alcoholics Anonymous meetings as well. 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. Fuller and colleagues used this information to calculate abstinence rates and the time elapsed prior to a return to drinking for subjects in the three medication treatment groups.

Fuller and colleagues sum up their main finding as follows:

Using a randomized, 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 (p. 1454).

A positive finding, however, was that patients who were given disulfiram had fewer drinking days during the study when compared with the patients in the other medication groups.

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DISULFIRAM TREATMENT OF ALCOHOLISM

Commentary by Raymond F. Anton, M.D.

KEY WORDS: disulfiram; drug therapy; AOD dependence; drug efficacy; veteran

Previous to the completion of this well-designed scientific study, which was conducted at nine Veterans Administration Medical Centers, the medication disulfiram (Antabuse[®]) was controversial in the treatment of alcoholism. The controversy over its efficacy was rooted in the lack of sophisticated scientific data on which to base its effectiveness. Fuller and colleagues

These patients were slightly older, had been alcohol abusers longer, and had lived at their current addresses longer than had those who relapsed. Fuller and colleagues go on to say,

Thus, the results of this study indicate that disulfiram is not necessary for those patients able to achieve total abstinence [about 20 percent of the total number of patients entering the study] but suggest that disulfiram be reserved for those older, more socially stable men who relapse (p. 1454).

As the authors suggest in their concluding remarks, the generalizability of the results may be limited because the population under study did not include subjects of higher socioeconomic employment or women. However, this landmark study indicated that well-founded scientific inquiry could be applied to alcoholism treatment to achieve clinically useful results.

Despite the rather straightforward and clear results of this investigation, some clinicians and researchers could not completely accept the overall findings because they could point to patients who successfully used disulfiram to achieve long-lasting sobriety. This led investigators to inquire about the conditions under which disulfiram could be used with a greater expectation of success. For example, Chick and colleagues (1992) studied patients whose disulfiram intake was monitored and found that patients who took disulfiram under controlled circumstances did better than those who did not.

Since the publication of this seminal article by Fuller and colleagues, other studies of disulfiram as well as related aversive treatment medications all seem to point to motivation and compliance as crucial variables that may predict who will respond best to this type of treatment approach (e.g., Allen and Litten 1992).

In many ways, this seminal study proved to be a watershed for future investigation of pharmacologic agents for the treatment of alcoholism. It paved a methodologic pathway for other treatment outcome studies to follow. For example, a large Veterans Administration cooperative study on the efficacy of

lithium carbonate in alcoholics borrowed heavily from the methodologies developed in Fuller and colleagues' disulfiram trial (Dorus et al. 1989). Defined patient-selection criteria, compliance monitoring, validation of patient drinking reports, and survival analyses all continue to be mainstays of modern alcoholism treatment research.

The technological "spinoffs" from this thoughtful scientific endeavor are beginning to pay off as the discovery of new medications for the treatment of alcoholism are coming to fruition. For this seminal alcoholism research study, the future then, is now. ■

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