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Does Disulfiram Help to Prevent Relapse in Alcohol Abuse?

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Abstract

When taken in an adequate dose, disulfiram usually deters the drinking of alcohol by the threat or experience of an unpleasant reaction. However, unless its consumption is carefully supervised by a third party as part of the formal or im-plied therapeutic contract, it is usually discontinued and the deterrent effect is therefore lost. In most studies, disulfiram administration has not been supervised and most reviews fail to stress the crucial importance of supervision. Unsupervised disulfiram has little or no specific effect. We have therefore reviewed all published clinical studies in which there was evidence that attempts had been made to ensure that disulfiram administration was directly supervised at least once a week. We found 13 controlled and 5 uncontrolled studies. All but one study reported positive findings, which were usually both statistically and clinically significant in controlled evaluations. In the sole exception, involving 'skid-row alcoholics', it seems that adequate supervision was not achieved. In general, the better the supervision, the better the outcome.

Provided that attention is paid to the details of supervision and that supervisors are given appropriate training, supervised disulfiram is a simple and effective addition to psychosocial treatment programmes. Compared with unsupervised disulfiram or no disulfiram control groups, it reduces drinking, prolongs remissions, improves treatment retention and facilitates compliance with psychosocial interventions such as community reinforcement, marital and network therapies. The supervisor may be a health professional, workmate, probation officer or hostel worker but is usually a family member. Treatment should probably continue for a minimum of 12 months. Supervised disulfiram appears to be more effective than supervised naltrexone and may be more effective than unsupervised acamprosate. The crucial importance of supervising the consumption of disulfiram has been overlooked or minimised by many reviewers.

1. Disulfiram in Alcohol Abuse

It has been well known for over 50 years that most patients who take disulfiram at an adequate dosage will experience an unpleasant and occasionally dangerous reaction within a few minutes of drinking alcohol. As little as half a unit of alcohol (approximately 5g) may be sufficient to cause the disulfiram-alcohol reaction (DAR).[1] Thus, disulfiram deters such patients from drinking alcohol, or from repeating the experience if they have already had an unpleasant DAR. Obviously, disulfiram has no effect on drinking behaviour if patients for whom it is prescribed either discontinue it or do not take it in the first place.

Some patients need to take higher dosages of disulfiram than the usual range of 200 to 500 mg/day in order to obtain plasma concentrations of the active metabolite of disulfiram sufficient to inactivate liver aldehyde dehydrogenase (ALDH). Other patients are incapable of producing the active metabolite at concentrations high enough to inactivate the ALDH isoenzymes adequately. Thus, in some patients disulfiram treatment will not cause a reaction if alcohol is consumed.[2]

Since many individuals with alcoholism are very ambivalent about altering their drinking habits, it is understandable that many of them will also be ambivalent about taking disulfiram. This ambivalence is not, of course, unique to disulfiram. Compliance rates with many treatments are surprisingly low, but good compliance is obviously of particular importance in individuals with alcoholism. For them, as for patients with chronic schizophrenia, poor compliance with the medication which is prescribed specifically to treat their condition is not just a common problem but can actually be an inherent characteristic of the condition.

In the case of patients with chronic schizophrenia, compliance can be improved by using depot injections. Because there is no readily available pharmacologically effective depot preparation of disulfiram, other methods of improving compliance have to be used. These usually involve recruiting a third party, such as a family member or a probation officer, to supervise or monitor disulfiram intake. The importance of supervision was recognised by a few authors even in the early days of disulfiram treatment.[3,4] Numerous studies (discussed in section 3) show that such third party involvement greatly improves compliance and therefore greatly improves the effectiveness of disulfiram. In 1986, an influential publication by the Royal College of Psychiatrists[5] noted that 'it is becoming more frequent for the doctor to suggest that a third person supervises the [disulfiram] . . . a relative or someone at work'.

2. Early Reviews of Efficacy

Opinions have been divided over the effectiveness of disulfiram in treating alcohol abuse. Following a review of the literature, Soyka[6] concluded that 'Disulfiram . . . lithium and various other substances have been tested in an attempt to increase abstinence rates in alcoholic patients, all with little or no success'. The reference he gives for this statement, Fuller et al.,[7] is to a fairly classically designed randomised controlled trial. Disulfiram presents certain difficulties in experimental design which do not apply to most other drugs. Because the DAR can be dangerous, it would obviously be hazardous and unethical to inform the patients that half of them would be taking a placebo, since they might then be tempted to risk drinking with serious consequences. Fuller et al.[7] got round this problem ingeniously. A third of the patients were prescribed oral disulfiram 250 mg/day, even though this dosage would not have been enough to produce a sufficiently deterrent DAR in many patients.[1] A second group were told that they were receiving disulfiram but were only given 1 mg/day – a dosage certainly insufficient to produce a DAR. The remaining third received only riboflavine.

At the time of the study by Fuller et al.,[7] unsupervised disulfiram treatment was standard practice for treatment of alcohol abuse in the US.[8] The study by Fuller et al.[7] was designed to rigorously test the effectiveness of unsupervised disulfiram. Therefore, as was subsequently pointed out,[9] although all patients were offered (and many received) follow-up counselling at weekly intervals

for several months, provision was not made to ensure that patients took at least 1 weekly dose of disulfiram under supervision. However, the number of abstinent days did increase slightly at 12 months in the group receiving disulfiram 250 mg/day. The work of Azrin et al.[10] showed that nearly all patients prescribed disulfiram without third party supervision had discontinued it within 3 months. The small proportion of patients who regularly take disulfiram even without supervision – about 20% in the study by Fuller et al.[7] – thus appear to be a very atypical and unusually compliant group of patients. They may be similar to the patients in a study by Edwards et al.[11] nearly 50% of whom had good outcomes at 12 months despite having no active treatment of any kind following an elaborate initial research-oriented assessment. In a letter published after the publication of the trial, Fuller[8] noted the importance of supervision and reported that he had attempted, unsuccessfully, to get funding for a further study in which the contribution of adequate disulfiram supervision would be separately assessed.

Unfortunately, as so often happens after the publication of influential papers, subsequent criticism, published as letters, is often ignored by later reviewers, even if it is accurate.[12] Although the study by Fuller et al.[7] is often discussed in reviews because of its thorough design, the limitations of a study of unsupervised disulfiram should be considered by reviewers. Reviewers need to distinguish between the mainly negative results of a larger number of trials of unsupervised disulfiram, which, in our view, often have poor designs, and the much smaller number of trials in which the consumption of disulfiram is more or less diligently supervised. Of these latter studies, the study by Azrin et al.,[10] which produced the most positive results of all such trials, was noted in a review by Saunders[13] as having a particularly convincing experimental design.

In a review by Miller and Hester[14] in 1986, treatments for alcoholism were classified into those for which sound evidence for effectiveness exists; those whose effectiveness or specific effectiveness has yet to be demonstrated; and those which are demonstrably lacking in any specific effect. In their review, disulfiram was placed firmly in the latter category.[14] However, in more recent reviews, Miller[15,16] has revised this view and now regards supervised (but not unsupervised) disulfiram as a treatment of proven effectiveness. In recent meta-analyses of the literature,[17-19] 2 of the treatment approaches for alcohol abuse which consistently perform well are Community Reinforcement Therapy (CRT) [see section 3] and Behavioural Marital Therapy, both of which lend themselves to (and often incorporate) supervised disulfiram therapy.[20]

It is interesting that in his review[16] of studies of treatment programmes including disulfiram, Miller includes studies of disulfiram implants. Studies involving disulfiram implants have generally produced better results than trials involving patients treated with unsupervised oral disulfiram.[21] However, any effectiveness cannot be attributed to a pharmacological process since Johnsen and Morland[21] have shown conclusively that for commercially available disulfiram implants, it is impossible to detect a blood concentration of disulfiram (or its presumed active metabolites) and that alcohol administered intravenously under blinded conditions, does not provoke a DAR. All pharmacological treatments have nonspecific or placebo effects as well as pharmacological effects. Disulfiram is no exception.

It may be noted at this point that disulfiram was generally preferred over the only alternative alcohol-sensitising drug, calcium cyanamide (now no longer available), because of the relatively short half-life of the latter – about 12 hours. This made the task of supervising oral medication much more demanding than with disulfiram, whose alcohol-sensitising effects will usually persist for at least 2 or 3 days after the last dose and may sometimes last for up to a week or even more. Liskow et al.[22] found that when patients drank after discontinuing disulfiram, the time between the last dose of disulfiram and drinking averaged 51 ± 50h on the first occasion, 60 ± 58h on the second, and 52 ± 52 h on the third.

3. A Review of Studies of Supervised Disulfiram

To assess whether disulfiram successfully prevents relapse in alcohol abuse, we reviewed the literature on disulfiram in alcoholism treatment. Because of evidence that unsupervised disulfiram is of little value, clinical studies were included only if there was evidence that attempts had been made to ensure that disulfiram administration was directly supervised at least once a week. A search of MEDLINE up to January 2000, previous reviews and any other papers known to the authors revealed 13 controlled and 5 uncontrolled studies. These are reviewed chronologically and are summarised in table I.

Bourne et al.[23] published the first study in which disulfiram was routinely supervised, generally as one component of a probation order. Although the study was uncontrolled, the results were very encouraging given that virtually all these patients were offenders with recurrent alcoholism with long histories of severe alcohol abuse resistant to other treatment methods. About 60% of the 196 study participants were compliant with disulfiram treatment and were supervised by probation officers, during the 30 to 60 days of a suspended prison sentence. Most took it for longer than was legally required. The authors came to the conclusion that probation-linked supervised disulfiram seemed to be a useful idea and worth developing.

Gallant et al.[24] undertook a randomised, controlled study of compulsory versus voluntary treatment of 84 offenders with chronic alcoholism which theoretically included disulfiram administered under supervision. Unfortunately, it seems that patients very rarely turned up for treatment and there were no immediate sanctions for noncompliance. Accordingly, very few patients seem to have actually received disulfiram. We question if this study should be regarded as a valid assessment of supervised disulfiram treatment, but we have included it for the sake of completeness. It is the only study to have found no benefit.

Liebson and Faillace[25] described an ingenious method of improving compliance in a group of 10 poor prognosis 'skid-row alcoholics'. In this study, disulfiram was combined in a capsule with chlordiazepoxide at a dosage of 75 to 125 mg/day. The idea was that chlordiazepoxide would act as a positive reinforcer which would be an incentive for patients to continue taking disulfiram, rather as in a later study (Liebson et al.[29]) combining disulfiram with methadone maintenance therapy. Depending on the time of administration, the chlordiazepoxide would act as either a tranquilliser or a hypnotic – effects which would be attractive to many patients with alcoholism and much less damaging than using alcohol for these purposes. Weekly supervision is implied, though not entirely clear, but improving compliance was clearly central to the study. This was a pilot study but 6 patients had remained in treatment for a mean of 6 months at the time of the report.

In a retrospective study conducted in Colorado Springs, US, Haynes[26] investigated the effectiveness of supervised disulfiram for 12 months as one condition of a probation order in 138 offenders with recurrent alcoholism. Some patients left town, often for legitimate reasons, and 12% were jailed for noncompliance. In the remainder, acting as their own controls, after 12 months there was an almost 13-fold reduction in alcohol-related offenses compared with the participants' previous record.

The first published study which investigated objectively the relationship between supervision and outcome was done by Gerrein et al.[27] in 49 patients. There was a significantly better outcome when disulfiram treatment was supervised for 8 weeks during daily outpatient attendance compared with unsupervised disulfiram treatment.

Azrin[28] published the first of 2 studies in which he investigated the effects of both supervised and unsupervised disulfiram combined with CRT, a package of essentially behavioural (as opposed to psychodynamic) outpatient interventions. CRT had already been shown in a study by Hunt and Azrin[40] to be significantly more effective than conventional outpatient treatment, and both CRT and the methodology employed by Azrin[28] have often been mentioned as examples of good practice in

Table I. Clinical trials of supervised disulfiram

Reference	Design	No. of patients	Frequency of disulfiram supervision	Control group[a]	Dosage (mg/day)	Setting	p Value[b]	Comment
Bourne et al.[23]	U	196	Daily	NA	500	Skid-row alcoholics	NA	Compliance approximately 60%
Gallant et al.[24]	RCT	84	Thrice weekly	No disulfiram ± group therapy	500	Recurrent skid-row alcoholic offenders	NA	Few patients in any group attended
Liebson and Faillace[25]	U	10	?weekly	NA	250	Skid-row alcoholics	NA	Disulfiram combined in capsule with chlordiazepoxide
Haynes[26]	U	138	Twice weekly	NA	Not stated	Recurrent alcoholic offenders	NA	13-fold reduction in arrests
Gerrein et al.[27]	RCT	49	Twice weekly	Unsupervised	250	Outpatients	<0.05	Improved longer term retention
Azrin[28]	RCT	20	Daily	Unsupervised	?250	Outpatients	<0.005	Better results with less counselling. 2 year follow-up
Liebson et al.[29]	RCT	6	Daily	Unsupervised	250-500	Patients with alcoholism receiving methadone maintenance therapy	<0.001	1 *vs* 17% drinking days
Robichaud et al.[30]	RCT	21	Daily/alternate days	A-B-A design	250-500	Employees with alcoholism	<0.01	5-fold reduction in absenteeism
Azrin et al.[10]	RCT	43	Daily supervisor with special training	Unsupervised	250	Rural outpatients	<0.01	Nearly 100% abstinence at 6 months in treatment group
Brewer and Smith[31]	U	16	Twice weekly	NA	200-800	Offenders with recurrent alcoholism	NA	Average abstinence 30 weeks, *vs* 6 weeks in previous 2 years. 9/16 totally successful
Keane et al.[32]	RCT	25	Daily	± Spouse contracting	Not stated (?250)	Outpatients	NS	Contracting improved compliance and outcome
Sereny et al.[33]	Before and after	68	Thrice weekly	Patients acted as own controls	250-500	Outpatients where treatment had failed on 3 previous occasions	NA	40% total success; 18% partial success
Chick et al.[34]	RCT	126	Daily	Supervised ascorbic acid (vitamin C)	200	Outpatients	<0.05	$p \leq 0.01$ on some measures
Gerber et al.[35]	Non-random ised	20	?Daily	Healthy volunteers	Not stated	Outpatients with liver disease	NA	Quality of life and liver function normalised at 6 months
Besson et al.[36]	U[c]	46	Daily	Acamprosate or placebo	Not stated	Outpatients	NA	Disulfiram improved acamprosate effects
Carroll et al.[37]	RCT	18	Weekly	Naltrexone 50 mg/day	250	Patients who abused alcohol and cocaine	<0.01	Reduced drinking associated with reduced cocaine use
Carroll et al.[38]	RCT	122	Twice weekly/weekly	No disulfiram	250-500	Patients who abused alcohol and cocaine	<0.01	Longer retention in treatment ($p < 0.05$)
Tønnesen et al.[39]	RCT	42	Twice weekly	No treatment	800 twice weekly	Outpatients with alcoholism awaiting surgery	<0.02	Complete preoperative abstinence in treatment group

a In most cases, the control group received at least standard levels of psychosocial treatment.

b Main outcome measures.

c Disulfiram patients unrandomised in a RCT of acamprosate.

NA = not applicable; **NS** = not significant; **RCT** = randomised controlled trial; **U** = uncontrolled.

treatment and research (e.g. Saunders[13]). Disulfiram treatment was supervised in the disulfiram group (i.e. 50% of patients) both by family members and by counsellors at each counselling session. Apart from the highly significant differences in favour of supervised disulfiram, this study is noteworthy for the unusually long follow-up period (2 years) during which the improvements were maintained.

Liebson et al.[29] studied supervised disulfiram in 6 patients receiving methadone maintenance therapy who also abused alcohol. In the experimental group, dispensing of the daily methadone dose was made contingent on taking disulfiram under professional supervision, and alcohol consumption was considerably and significantly lower than in the unsupervised control group.

Robichaud et al.[30] also found a significant improvement when supervised disulfiram was used as virtually the sole treatment in an employee alcoholism programme. The 21 patients in the study were required to take disulfiram at work under nursing supervision for an average of 10 months as a condition of remaining in employment. The absenteeism rate before treatment was 9.8%. During disulfiram treatment, it fell to 1.78% and rose again to 6.7% when the disulfiram was discontinued. Counselling was also offered to these patients, most of whom had previously had alcoholism treatment, but few of them took up the offer.

To follow up his earlier study, Azrin and his co-workers conducted another study in 43 patients which confirmed the effectiveness of properly supervised disulfiram.[10] The study also made the very important (and unexpected) discovery that for patients with reasonably intact relationships, who constitute, in many studies, a majority or at least a large minority of participants, involving the partners who do not have alcoholism and giving them simple training to improve the quality of supervision was the most important component of treatment. In such cases, adding more intensive counselling conferred no additional benefit. Disulfiram effects were maintained throughout the 6 months study period. As in the previous study by Azrin[28] supervision involved both associates and counsellors. One of us (also one of Azrin's co-authors) has recently tried to replicate this study with William Miller. The work is not yet complete but it proved almost impossible to randomise patients to the disulfiram group because of the inability of the project to obtain immediate evaluation for disulfiram prescribing. Many patients had to wait up to 4 weeks to actually receive disulfiram. Consequently, the Azrin protocol could not be truly replicated.

Brewer and Smith[31] published a pilot study of 16 offenders with chronic alcoholism who were attending London courts with an average of 6.3 alcohol-related convictions and an average maximum period of abstinence outside prison of only 6 weeks. Patients were offered regular counselling and supervised disulfiram treatment at the probation office as conditions of probation. At the end of the study, the average maximum period of abstinence for the whole group was 30 weeks and all but one participant had exceeded their longest abstinence in the previous 2 years.

Keane et al.[32] used 'spouse contracting' in a study of 25 patients to try to improve disulfiram compliance. The control group were simply encouraged to use disulfiram. The contract group did somewhat (but not significantly) better during the 3 month study but unlike the studies by Azrin[28] and Azrin et al.[10] there was no professional supervision of disulfiram consumption during counselling sessions.

A prospective study by Sereny et al.,[33] though not controlled in the classic fashion, gave rather impressive results (see below). Noting that a significant number of patients relapsed repeatedly despite compliance with a conventional treatment programme, they devised a radical but constructive response to patients who had relapsed at least 3 times. Instead of declining to offer further treatment, they told them that they would be accepted for further treatment but only if they agreed to take disulfiram under professional supervision during their outpatient attendance. 68 of 73 patients agreed to this arrangement. In this study 'total success' was defined as being sober for at least 6 months and remain-

ing in the mandatory disulfiram programme at the time of assessment, or having been discharged from mandatory disulfiram after 12 months of sobriety. By these criteria, 27 patients (40%) were totally successful. 12 patients (18%) were partially successful, treatment failed in 20 (29%) and treatment outcome was undetermined in 9 (13%). These are good results in a group of patients who by definition would normally be regarded as having a poor prognosis. In other respects, the management of these patients appears to have been similar to that provided on previous occasions. The good outcome, compared with both the previous outcomes in these patients and that of other patients typically treated in the same centre without supervised disulfiram, thus seems likely to have been attributable to the addition of supervised disulfiram to the programme.

A multicentre study of 6 months' duration conducted in the UK by Chick et al.[34] confirmed the effectiveness of supervised disulfiram. This study was also designed to discover whether the effectiveness was attributable to the psychological and symbolic impact of supervision or to the deterrent and pharmacological effects of disulfiram. The 126 participants were patients receiving standard outpatient treatment for alcoholism who were randomly assigned to supervised disulfiram or supervised treatment with ascorbic acid (vitamin C). Where possible, supervision was delegated to family members who were given appropriate instruction but in other cases, medication was supervised by clinic staff or community nurses. The results, which included a significant reduction in γ-glutamyl transpeptidase levels, very clearly favoured the disulfiram group.

Gerber et al.[35] studied quality of life (QoL) and liver function in a group of 20 patients with alcoholism receiving supervised disulfiram. QoL and liver function were assessed at baseline and after 6 months. QoL was also assessed in 20 volunteers matched for gender, age, education and social status. At baseline, but not after 6 months, patient QoL was significantly lower than that of volunteers (ANOVA $p < 0.01$). Bilirubin levels, γ-glutamyl transpeptidase levels, and mean corpuscular volume all returned to normal in this period.

Some studies have included new pharmacotherapies such as acamprosate and naltrexone. An example is the controlled study involving 46 patients of disulfiram and acamprosate by Besson et al.[36] which produced interesting results. An important conclusion of the study is that the effectiveness of acamprosate is increased by combining it with disulfiram given under professional supervision. Patients were randomised to acamprosate but not to disulfiram. However, a breakdown of the results shows that the patients who took disulfiram alone had a better outcome and higher retention than those who took acamprosate alone.

The effectiveness of disulfiram can also be seen in a comparison of disulfiram with naltrexone in individuals who abused both alcohol and cocaine.[37] In a 12 week study, 18 patients were randomised to disulfiram or naltrexone, supervised weekly by a nurse. Attrition was high in both groups but lower with disulfiram. On all measures of both cocaine and alcohol use, the disulfiram group did significantly better than the naltrexone group.

A recent randomised controlled trial conducted by Carroll[38] of 122 patients who abused both alcohol and cocaine compared various types of psychotherapy – cognitive-behavioural therapy (CBT) and twelve-step facilitation (TSF) – with ordinary clinical management (CM) with and without disulfiram. Disulfiram ingestion was monitored by a nurse twice weekly for the first month of treatment and weekly thereafter. According to the study authors,[38] 'The CBT/disulfiram group had the highest rate of retention (mean 8.8 weeks), followed by CM/disulfiram (8.4 weeks), TSF/disulfiram (8.0 weeks). Subjects assigned to disulfiram treatment were retained significantly longer than those assigned to no medication [8.4 versus 5.8 weeks ($p < 0.05$)]. No significant differences in retention by psychotherapy were found'. It has recently been suggested that disulfiram has significant effects in reducing cocaine use even in patients who do not have comorbid alcohol abuse.[41]

Carroll et al.[38] also found significant effects of disulfiram on consecutive weeks of cocaine abstinence, alcohol abstinence and abstinence from both cocaine and alcohol: 'Effect sizes (d) for disulfiram compared with no medication on duration of abstinence from cocaine, alcohol and both were, respectively, 0.42, 0.68 and 0.46'. In contrast, the specific effect of the psychotherapies was rather modest: 'Effect sizes for the active psychotherapies compared with CM on duration of abstinence were 0.16 for cocaine, 0.11 for alcohol and 0.18 for both cocaine and alcohol'.

This is an important study, not only because it is further evidence for the effectiveness of supervised disulfiram, but also because retention in therapy is desirable in many cases, though probably not in all. Clinicians working in relapse prevention obviously need to spend enough therapeutic time with patients to help them to make positive cognitive and behavioural changes. In our view, supervised disulfiram is clearly one of the most effective techniques for maximising treatment retention but the sobriety that it usually imposes also gives patients a better chance of dealing with ambivalence and denial and of learning and consolidating new coping skills and strategies.

Finally, Tønnesen et al.[39] used twice-weekly supervised disulfiram as the sole treatment in a controlled study of intervention versus no intervention in 42 patients who were drinking more than 60g of alcohol daily to measure the benefits of abstinence for a month before major surgery. All patients receiving disulfiram apparently abstained completely and had significantly fewer postoperative complications (31 *vs* 74%, $p < 0.02$) than the non-intervention group.

4. Components of Effectiveness in Disulfiram Treatment

The powerful deterrent effect that has been seen in some studies of disulfiram implants (e.g. Johnsen and Morland[21]) which actually have no measurable pharmacological activity underlines the importance of 3 separate but mutually reinforcing factors which are a unique feature of treatment with disulfiram or other alcohol-sensitising drugs.

First, there is the real and unpleasant DAR. Patients taking disulfiram may know in various ways about this reaction. All of them will have been warned about it and many will believe what they have been told without the need to directly experience it themselves. Some know of it vicariously from observing or hearing about the reaction in other individuals. A variable proportion of patients make the discovery for themselves by actual experiment.[1] According to Liskow et al.[22] over 75% of those who drank while receiving disulfiram reported experiencing a DAR, with more than one-third of those experiencing the DAR reporting it to be severe (85% of patients were taking 250 mg/day, the rest 500 mg/day). It is only because disulfiram has, and is known to have, this very real potential for an aversive effect that it deters many patients from drinking by the mere fact of taking it. Further evidence for a specific deterrent effect of the DAR comes from Japanese studies showing that per capita alcohol consumption is reduced in those parts of Japan where there is a high incidence of inactive forms of ALDH. Other studies show that Asians in whom 1 parent (one allele) has the inactive ALDH are protected from 75 to 90% against alcoholism and in these individuals, heavy drinking is reduced by 66% even if they were born and raised in the US or Canada.[42,43] Furthermore, individuals who inherit an inactive ALDH from both parents are complete abstainers.[43]

Secondly, taking disulfiram regularly (or having an implant inserted with a supposed active life of 3 or 6 months) surely has certain symbolic connotations. It indicates that here is a patient who is willing, however uncertainly or ambivalently, to surrender some control over his or her freedom or urge to drink. Such patients announce both to themselves and to the wider world that they are not merely talking about changing their drinking habits, or making often unconvincing promises to do so, but are actually doing something about it. These patients are at the 'action' stage in the well known Prochaska and DiClemente model of changing addictive behaviour. Furthermore, the patient is in-

volving some third party (the family member or probation officer in the case of oral medication; the surgeon in the case of the implant) for the specific purpose of strengthening a resolve which he or she knows is often tenuous, varies from one day to another, or not infrequently fails altogether.

Finally, the involvement of a third party in supervising oral disulfiram provides additional opportunities for involving family members in the broader therapeutic and monitoring enterprise. Any failure of compliance is thus more likely to be detected and reported promptly enough for professionals to intervene, either before drinking resumes or before a mere lapse turns into a full-blown relapse. A large proportion of disulfiram users (33% on the first occasion, 43% on the second, and 48% on the third occasion of disulfiram use) gave 'desire to drink' as their reason for stopping disulfiram.[22] According to Liskow et al.,[22]'This suggests that when patients and treatment personnel discuss whether disulfiram should be discontinued, this reason should be explored vigorously'. An awareness of this potent combination of pharmacology, symbolism and external control and monitoring is crucial to maximising the benefits of supervised disulfiram. There is evidence from studies of anxiety disorders that psychological treatments may improve medication compliance.[44] Support, encouragement and explanations can imbue confidence in patients concerning the efficacy of the prescribed medication.[44]

4.1 The Technique of Supervision

Having presented the case for the importance of supervising the consumption of disulfiram rather than simply leaving it up to the patient, let us now examine the process of supervision. It sounds, and is, a simple enough concept but as with many simple procedures, such as giving an intramuscular injection, measuring the blood pressure, or taking the temperature with an oral thermometer, there are right and wrong ways of doing it and therefore attention to detail is important. Even in those studies where the importance of supervision is recognised, few spell out the process in detail. Azrin[45] and Chick et al.[34] are exceptions. Table II summarises

Table II. Recommended approach to the supervision of disulfiram treatment (reproduced from Azrin,[45] with permission)

Identify a disulfiram monitor who would be substantially and negatively affected by resumption of drinking, e.g. spouse, family member, employer, partner, landlord
The monitor should normally have regular, ideally daily, contact with the patient
Specify precisely the time and place where the disulfiram could be taken conveniently, with both persons present
Have disulfiram taken at a time when other forms of medication are normally taken, i.e. the 'response-chaining' principle
Grind up the disulfiram tablet and dissolve it in a drink (coffee, tea, juice) to avoid any suspicion of later expulsion
If the monitor is not present when the patient has taken the disulfiram, the patient should take another tablet the same day, when the monitor is present, to provide absolute assurance to the monitor
The patient should thank the monitor for taking the time to observe
The monitor should comment on some positive attribute of the patient, that is associated with sobriety, i.e. job status, love by children, doing jobs around the house, financial security
At each therapeutic session, the monitor attends with the patient, if possible, so that the therapist can instruct, supervise, and provide feedback to both
At each therapeutic session, the disulfiram is taken in the presence of the therapist
The monitor is to telephone the therapist if the patient omits taking disulfiram for 3 days; the therapist then telephones the patient to arrange a session
When the usual 30-day supply of tablets is nearly depleted, the monitor prompts and assists the patient to renew the prescription; failure to do so has been one of the most apparent major causes of discontinuing disulfiram
The therapist asks the patient and monitor to rehearse probable situations which cause the reluctance to take the disulfiram, and teaches them how to overcome such interferences
The patient is taught to view the use and ritual of taking disulfiram as a means of providing assurance to themselves and their loved ones that they will not succumb to temptations that are otherwise beyond their control. It is emphasised that the central feature is the patient's desire, not coercion

detailed but fundamentally simple and sensible advice based on the study by Azrin.[45]

The involvement of families and other individuals or institutions in the treatment process is central to the concept of CRT and of the Network Therapy described by Galanter.[46] Both these models recognise that many patients with alcoholism appear to need and benefit from psychosocial interventions but also that any benefit is likely to be minimised or lost altogether if patients do not remain sober for most of the time. Patients who are intoxicated will not easily learn the new cognitive and behavioural skills that the psychosocial interventions are largely designed to teach them. Supervised disulfiram therefore seems likely to facilitate psychosocial interventions because of increased compliance with psychological therapy. It should also reinforce their effect because if supervised disulfiram deters a patient from having recourse to alcohol when he or she would normally (for whatever reason) feel tempted to use it, then that patient is obliged to practice helpful alternatives to drinking, the inculcation of which is one of the main aims of psychological components of treatment.[47,48] As the work of Azrin[28] demonstrated very clearly, taking supervised disulfiram makes it much less likely that treatment will be adversely affected because the patient has lost his or her job, has no where to live or has finally destroyed his or her marriage, because of yet another episode of intoxication. Galanter[46] stresses that the role of the supervisor is usually to encourage regular disulfiram consumption and to report noncompliance promptly, rather than to be actively coercive. Fortunately, patients will often do things for their therapist (whether physician or psychologist) that they would not do for themselves or for their partners.

4.2 Duration of Treatment

Long term outcome studies are notoriously difficult and expensive to do and are often vitiated by high withdrawal rates. This is true of all treatment modalities. Azrin[28] followed up a small cohort for 2 years but, in our view, the undeserved unpopularity of supervised disulfiram has generally excluded it from large trials such as Project Match.[49] Galanter,[46] whose 'network therapy' makes extensive use of disulfiram, supervised by a network of family members, friends or colleagues, stated that that 12 months was a reasonable minimum duration of treatment. According to Galanter,[46] abstinence is often 'well established' by then but he also states that some patients wish (or should be advised) to take it for longer. There are several case reports of patients who evidently felt they needed the protection of disulfiram for 10 or 15 years. At least 2 of these involved supervised disulfiram.[50,51] Conversely, one certainly comes across patients who seem to remain abstinent or achieve controlled drinking for many years after only a few months of supervised disulfiram. However, we feel that courses of less than 6 months are likely to be too short for most patients.

5. Discussion

Reviews even of such well established treatments as antidepressant drugs sometimes require meta-analysis to accommodate both the numerous negative reports and the positive majority. In our view, no such statistical ingenuity is needed to reach a conclusion about the effectiveness of supervised disulfiram. With only one exception, all the controlled studies reviewed in this article demonstrate an improvement over a variety of differently treated control groups which is not just statistically significant but often large, obvious and clinically important. In the one study of supervised disulfiram that did not show a positive effect,[24] the patients were a group of skid-row alcoholics who, it seems, simply failed to turn up regularly for treatment.

However, in our view the importance of supervision has not been given the recognition it deserves by some reviewers. On the subject of supervised disulfiram use, Gatch and Lal[52] say that 'more recent reviews have recommended that disulfiram works best when used as part of a treatment plan that includes careful monitoring, psychological therapy and social support . . .'; this is the only mention in their review of the importance of supervision. In a recent review, Hughes and Cook[53]

conclude that 'supervised oral disulfiram in a comprehensive treatment programme seems to have some efficacy in certain individuals'. We find it disappointing that they did not incorporate this important conclusion into their abstract. Discussing the highly positive results of the study by Liebson et al.,[54] Hughes and Cook[53] say that the study demonstrated 'the benefits of supervising disulfiram treatment, rather than the efficacy of disulfiram *per se*'. However, as we have already noted, if swallowing disulfiram did not make an unpleasant reaction with alcohol highly probable, then supervising it would surely have little effect. Disappointingly, in nearly half the controlled studies reviewed in their paper, disulfiram was either unsupervised or rather badly supervised and the technique of supervision is not discussed. Like several other reviews, there is quite a lot of discussion about the unsupervised study by Fuller et al.[7] in this review and there is no mention of the subsequent correspondence. In the discussion of the positive results of the study by Azrin et al.,[10] in which the study authors themselves stress the important role of supervised disulfiram, Hughes and Cook[53] put more emphasis on the potential improvement in outcome if unmarried individuals in the study had got married. In contrast, Litten et al.[55] stress the potential of disulfiram if attention is paid to compliance.

Although we do not suggest that supervised disulfiram is needed for all patients, there are several situations in which it seems particularly helpful. For example, patients with a history of repeated treatment failure (especially after nonpharmacological treatments), patients who have many drinking triggers and those facing serious consequences if they relapse. As well as sobriety, the benefits commonly include reduction in family worry, increase in family trust and involvement in treatment, a reduction in demoralising 'slips', improvements in self-confidence and self-image, and more opportunities to receive positive feedback from family members and friends.[56] These benefits far outweigh the relatively small risks of treatment.[57,58] In Britain, the National Poisons Centre knows of hardly any deaths from the DAR.[59] The only other potentially lethal complication of disulfiram treatment – fulminant hepatitis – is probably related to nickel sensitivity, which may explain why, although very rare, the majority of cases have been reported in women.[60] Even severe alcoholic liver disease is not a contraindication to disulfiram treatment[60] and major psychiatric illness is not an absolute contraindication.[61] In all instances, the risks of disulfiram use must be weighed against the high mortality and morbidity of unchecked alcohol abuse.

While we welcome a wider range of pharmacological interventions for alcoholism, 1 of the 2 most recent additions – naltrexone – seems to be less effective than supervised disulfiram.[37] The same may be true of acamprosate, though there has been no truly comparative study. However, both may sometimes be usefully combined with disulfiram.

A recent report[59] notes a 10-fold variation in disulfiram prescribing between the highest and lowest prescribing of 13 countries. Three Anglo-Saxon countries – the US, New Zealand and Britain – have the lowest figures. Gunne[62] has noted the prevalence of anti-medical (and often anti-science) attitudes among some controllers and providers of addiction treatment. If, as we believe, these attitudes are particularly evident in the US, this may partly explain the neglect of an old but still useful treatment.

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