INVITED REVIEW

RECENT DEVELOPMENTS IN DISULFIRAM TREATMENT

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Abstract — This paper reviews the controlled studies which have led to the increasing recognition that supervised disulfiram is one of the few demonstrably effective interventions in alcoholism, both alone and as an adjunct to psychosocial methods. The specifically behavioural implications of disulfiram treatment are also noted. It examines techniques for maximising disulfiram’s therapeutic effectiveness and reviews recent research into its pharmacokinetics, mode of action, toxicology and bioavailability. Finally, the prospects for an effective depot preparation are discussed.

INTRODUCTION

Disulfiram is a much misunderstood drug. In the early days of disulfiram treatment, the frequent use of alcohol challenges to demonstrate the disulfiram-ethanol reaction (DER) distorted the perception of disulfiram by both doctors and patients (Billet, 1964) because deliberately inflicting an unpleasant experience on patients created the impression that disulfiram was a variety of aversion therapy. In reality, aversion therapy, whether chemical, electrical or psychological, involves the repeated association of alcohol and alcohol-related cues with an unpleasant experience or thought process with the aim of producing a lasting distaste for alcohol. However, alcohol misusers commonly alternate periods of relatively controlled drinking with repeated courses of disulfiram which are initiated at the first sign of a return to heavy drinking (Jensen, 1984; Duckert and Johnsen, 1986). Obviously, this is inconsistent with the concept of lasting aversion.

As psychologists such as Heather (1989) have recognised, disulfiram is in some respects a psychological treatment as well as a pharmacological one. The psychological mechanism underlying the use of disulfiram is deterrence and it is not necessary to experience the DER to be deterred. Disulfiram enables patients to expose themselves to alcohol-related cues and environments while the usual alcohol-drinking response is prevented, and it facilitates the practice and development of alternative, alcohol-free coping techniques. Exposure and response-prevention is the treatment of choice for other repetitive or compulsive patterns of damaging or unwanted behaviour (Brewer, 1990).

In addition to reinforcing psychological treatments aimed specifically at such behaviours, disulfiram benefits psychosocial interventions in a more general way, for no patient will profit much from such interventions if he (or she) continues to drink heavily or has frequent relapses. To the extent that supervised disulfiram improves the chances of abstinence or sobriety during a particular treatment programme, it increases the likelihood that the other effective components of the programme will make an impact. A particular virtue of disulfiram is that it helps patients to practise and perfect their new, alcohol-free coping techniques in real life as well as in the often rather artificial atmosphere of the clinic. This feature of treatment with disulfiram is similar to the ‘immersion’ concept of foreign language teaching in which students are encouraged or required to use the new
language not just during isolated lessons but also in the teaching of unrelated subjects such as history or physics. Immersion has been shown in controlled studies to be a more efficient method of teaching (Brewer, 1992b).

THE IMPORTANCE OF SUPERVISION

Disulfiram is often advised for ‘well-motivated’ alcoholics. In reality, well-motivated alcoholics tend to do well whatever treatment is recommended, even if it is minimal. Most patients who come for treatment are ambivalent. This means that on some days they may feel very much like complying with treatment, while on other days they may not. Numerous studies have shown that only a small proportion of those prescribed unsupervised disulfiram will take it regularly (Azrin et al., 1982; Brewer, 1986a) and many of these patients would probably do well without disulfiram. They would certainly do almost as well if given either a placebo or pharmacologically inactive doses of disulfiram (Fuller et al., 1986). Consequently, it is not surprising to find suggestions, even among some of the earlier papers on disulfiram, that a degree of supervision or family involvement may be useful (Fox, 1958; Billet, 1964).

STUDIES OF SUPERVISED DISULFIRAM

These are reviewed chronologically and include both controlled and uncontrolled trials.

Bourne et al. (1966) 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 had long histories of severe alcohol misuse resistant to other methods. The authors came to the modest conclusion that probation-linked supervised disulfiram seemed to be a useful idea and worth developing.

In a retrospective study, Haynes (1973) investigated the effectiveness of supervised disulfiram as one condition of a probation order. With the patients acting as their own controls, he found an almost 13-fold reduction in alcohol-related offences compared with their previous record.

The first published study which investigated objectively the relationship between supervision and outcome was done by Gerrein et al. (1973). They found significant improvements in outcome when disulfiram was supervised during daily out-patient attendance compared with unsupervised disulfiram.

Azrin (1976) published the first of two studies in which he investigated the effects of both supervised and unsupervised disulfiram combined with a package of essentially behavioural (as opposed to psychodynamic) out-patient interventions which he called community reinforcement therapy (CRT). CRT had already been shown by Hunt and Azrin (1973) to be significantly more effective than conventional out-patient treatment, and both CRT and the methodology employed by Azrin have often been mentioned as examples of good practice in treatment and research (Saunders, 1985). Interestingly, these same commentators have generally failed to mention Azrin’s finding that supervised disulfiram significantly increased the effectiveness of the CRT programme.

Robichaud et al. (1979) also found a significant improvement when supervised disulfiram was used as virtually the sole treatment in an employee alcoholism programme (EAP). The patients were required to take disulfiram 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.

Azrin and colleagues followed up their earlier studies with another (Azrin et al., 1982) which confirmed the effectiveness of properly supervised disulfiram. However, they 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 subjects, involving the non-alcoholic partners and giving them simple training to improve the quality of supervision was the most
important component of treatment and made it unnecessary, in most cases, to offer more than basic levels of counselling and support.

Brewer and Smith (1983) published a pilot study of 16 habitual drunken offenders attending London courts with an average of 6.3 alcohol-related convictions and an average maximum period of abstinence outside prison of only six weeks. Patients were offered regular counselling and supervised disulfiram 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 of them had exceeded their longest abstinence in the previous 2 years.

A prospective study by Sereny et al. (1986), though not controlled in the classic fashion, gave rather impressive results. 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 three 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 supervision during their out-patient attendance. Sixty-eight of 73 patients agreed to this arrangement (See Table 1).

By these criteria, 27 patients (40%) were totally and 12 patients (18%) partially successful; 20 (29%) were failures and 9 (13%) undetermined. These are good results in a group of patients who would normally be regarded as having a poor prognosis. In other respects, their treatment appears to have been much the same as on previous occasions so that the good outcome, compared with both their own previous performance and that of the general run of patients treated in the same centre without supervised disulfiram, seems likely to have been due to the addition of supervised disulfiram to the programme.

Finally, a multi-centre British study by Chick et al. (1992) confirmed the effectiveness of supervised disulfiram but was also designed to discover whether the effectiveness was due to the psychological and symbolic impact of supervision or to the deterrent and pharmacological effects of disulfiram. The subjects were patients receiving standard out-patient alcoholism treatment who were randomly assigned to supervised disulfiram or supervised 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 gamma glutamyl transpeptidase, very clearly favoured the disulfiram group.

While research even into such well-established treatments as antidepressant drugs has sometimes required meta-analysis to accommodate both the numerous negative reports and the positive majority, there is no need for such statistical legerdemain in the case of supervised disulfiram. There are no negative reports.

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**Table 1. Definition of treatment outcomes with mandatory disulfiram therapy**

1. **Total success**
   - (a) Sober for at least 6 months and remains in the mandatory disulfiram program at the time of the study, or
   - (b) Discharged from mandatory disulfiram after 12 months of sobriety

2. **Partial success**
   - (a) Patient had 3–6 months of sobriety on mandatory disulfiram by the end of the study, or
   - (b) Patient remained sober on mandatory disulfiram for more than 6 months, then drank

3. **Failure**
   - Drank or missed two appointments within 3 months of joining the mandatory disulfiram program

4. **Undetermined**
   - Continuously sober but on mandatory disulfiram for less than 3 months by the end of the study

From Sereny et al. (1986).
Authoritative reviews and statements

Since 1988, Miller, an internationally recognised authority on the clinical trials literature, has accepted that the evidence for the effectiveness of supervised disulfiram is convincing (Miller, 1989, 1992), and Heather (1989) has expressed similar views. Personal communications from H. Fingarette and A. Marlatt indicate that they also accept the evidence.

PHARMACOLOGY AND PHARMACOKINETICS

As Hart and Faiman (1992) admit; 'Although disulfiram has been studied for over 40 years, it is still not clear whether disulfiram or a metabolite is the active chemical species responsible for ALDH [aldehyde dehydrogenase] inhibition in vivo'. Disulfiram appears to be a pro-drug which has to be metabolised to another compound (possibly 5-methyl N,N-diethylthiocarbamate sulfoxide among other contenders) before the enzyme inhibition which causes the reaction with alcohol can take place (Johansson et al., 1991; Kitson, 1977; Hart and Faiman, 1992; Petersen, 1992). This oxidative biotransformation, which has only recently been explored, may well involve the liver. Severe liver disease or individual metabolic idiosyncracies may sometimes reduce or prevent the formation of the active metabolite of disulfiram (Lenz, 1957; Johansson and Stankiewicz, 1989; Johansson, 1992).

Whichever metabolite or metabolites of disulfiram are responsible, they cause irreversible inhibition of at least some of the ALDH systems which are the major pathway of alcohol metabolism following its initial conversion to acetaldehyde. The duration of the inhibition thus depends partly on how quickly new ALDH is synthesised after disulfiram is discontinued (Kitson, 1977) and partly on the biological half-life of the active metabolite. Individual variability in these processes may explain why some patients can resume drinking 2 or 3 days after discontinuing disulfiram while others report severe reactions a week or even 10 days later.

Gessner (1989) notes that as well as inhibiting ALDH leading to high acetaldehyde levels, which cause vasodilatation, disulfiram inhibits dopamine beta-hydroxylase, which transforms dopamine to noradrenaline. The normal response to vasodilatation includes the release of noradrenaline but since this process is partly inhibited by disulfiram, the fall in systolic pressure is greater than would be accounted for by acetaldehyde alone.

Peachey et al. (1981a) found that when subjects were given approximately 3.5 g of alcohol at hourly intervals after 48 hr treatment with disulfiram at approximately 250 mg daily, acetaldehyde levels and DER ratings became progressively lower with each drink. Similar results were observed with calcium carbimide (Peachey et al., 1981b). The relevance of such small doses of alcohol to clinical practice is uncertain, but the possibility that some patients may be able to 'burn off' the DER, at least on standard doses of disulfiram, should be kept in mind.

A further variable is that different formulations of disulfiram may have very different bioavailabilities, and as with many other drugs, absorption may be modified by food. In particular, the effervescent tablets widely used in Scandinavia may have more than twice the bioavailability of the standard British tablets (Andersen, 1992).

DOSAGE

The studies reviewed above have all produced positive and, in most cases, clinically useful as well as statistically significant improvements, with no negative findings to set against them. However, for a significant proportion of patients, the dose of disulfiram used in the studies will have been too low. Disulfiram is an effective drug, but as with many drugs the same dose does not suit all patients. Even with drugs like antibiotics, the dose needs to take account of variations in weight. Given the pharmacological complexities just mentioned, it is to be expected that significant individual variations in dosage requirements will occur.

This is not always important. Of 84 patients in one study who agreed to take disulfiram under family supervision, only 24% risked
drinking while still taking disulfiram or within 2 or 3 days of discontinuing it (Brewer, 1986a). This suggests that the majority of patients will not take the risk if they believe that they are likely to get an unpleasant reaction, and that for many patients a pharmacologically adequate dose is therefore not crucial. However, it is impossible to predict which patients will take the risk, and for the significant minority who will do so, dosage then becomes very important. If it is adequate, they will get an unpleasant reaction and will probably not repeat the experience. If it is not adequate, they will get little or no reaction and may lose faith in both therapy and therapist.

A retrospective study (Brewer, 1984) found that about 50% of patients did not get much of a reaction with alcohol on doses of between 200 and 300 mg of disulfiram daily. This proportion decreased sharply as the dose of disulfiram was increased but one patient failed to react even on a dose of 1.2 g daily. In a prospective study using volunteers (Christensen et al., 1991), only a minority of those taking up to 300 mg daily experienced a reaction after 10 g of alcohol which was thought to be unpleasant enough to make them refuse a second drink. Furthermore, the disulfiram used in this study probably had a relatively high bioavailability. Whatever the cause, an inadequate or absent reaction is no reason for therapeutic despair. It is a reason for increasing the dose of disulfiram until either a reaction does occur or unacceptable side-effects appear.

In the absence of a simple blood test to establish whether the dose is adequate, I suggest the following approach. For those patients in whom an early relapse, though undesirable, would not be particularly disastrous, an initial dose of 200 to 300 mg daily for an average-sized person is appropriate. If the patient risks drinking and there is little or no reaction, the daily dose should be increased to 400 or 500 mg and more if necessary. Some patients who risked drinking on a lower dose will not take the risk on a higher dose, particularly if they had at least some reaction on the smaller dose. In one case, the patient did not react sufficiently until the dose was increased to 600 mg daily (Brewer, 1993b) and I have treated patients who needed as much as 1.5 g daily. Several standard textbooks note that the dose may need to be increased, but there is no agreement about an upper limit (Brewer, 1993a). In my view, the upper limit will depend largely on how well the drug is tolerated. Some of the early disulfiram studies employed doses of up to 2 g daily but the risk of neuropathy, in particular, is dose-related.

For patients in whom an early relapse would be particularly undesirable, and potentially disastrous in terms of employment or marriage, the choice may sometimes lie between starting at a higher dose, perhaps 500 mg daily, or doing an alcohol challenge.

THE ALCOHOL CHALLENGE

The traditional technique for giving an alcohol challenge was described in earlier versions of the manufacturer’s data sheet. Four tablets (800 mg) of disulfiram are given on the first day, reducing by one tablet each subsequent day to a maintenance dose of 200 mg daily. On the 5th day, the patient is given a challenge dose containing 15–30 g of pure ethanol. However, disulfiram and some of its metabolites are slowly excreted at a variable rate, and it seems unlikely that levels of ALDH inhibition will have stabilised so soon after a succession of changing daily doses. The result of this test may therefore be misleading. Furthermore, 15 g of ethanol may be more than enough in some patients to produce a very unpleasant DER. The usual object of the challenge dose is not to make the patient feel very ill, but merely to convince him that something highly unpleasant will indeed happen if he drinks significant amounts of alcohol and that the whole procedure is not, as some patients appear to suspect, a rather ingenious bluff.

A kinder and less hazardous challenge can be done when patients have been on a consistent dose of disulfiram (typically, as indicated above, 200–300 mg daily) for at least 5 days. This should be long enough for blood and tissue levels of the relevant metabolites and
enzymes to stabilise in most cases. The initial dose of alcohol consists of only 12 ml of 40% spirits (approx. 5 g ethanol) on an empty stomach. A few patients produce a definite flush on that dosage, in which case they need no further alcohol, but most do not and if there is no reaction after 20 min they receive a further 25 ml of spirits (approx. 10 g ethanol) or a little more if they are heavier than average. At this dosage of alcohol, a positive DER rarely consists of anything more than a noticeable flushing with tachycardia and, sometimes, a slight fall in blood pressure. If there is no reaction, the dosage of disulfiram is increased and the test repeated after a few days until a positive result is obtained. This version of the alcohol challenge can readily be done as an out-patient procedure (Brewer, 1984), although basic resuscitation drugs and equipment should be available and some textbooks recommend in-patient treatment. This seems unnecessary in view of the short duration of the procedure.

There are still a few cases where it may be necessary to carry out the challenge in the traditional way with enough alcohol to make the patient manifestly ill. However, it is important to remember that deaths do occasionally occur, especially if the patient is in poor health. Even patients not having a planned alcohol challenge should be routinely warned that drinking while taking disulfiram can be fatal, but the patient, not the physician, is the person who is supposed to be frightened by the DER.

Treatment of severe disulfiram–ethanol reactions

In most cases, even those few which come to medical attention, no specific treatment is required. Hypotension usually responds to lying down but standard pressor agents may be used if necessary and serious cardiac complications such as ischaemia or arrhythmias should receive appropriate treatment. The effectiveness of intravenous ascorbic acid, a traditional remedy, is not objectively established but it is probably fairly harmless. Diphenhydramine reduces the severity of the reaction between calcium carbimide and alcohol (Stowell et al., 1986) and is probably helpful in a severe DER. However, the most effective and specific treatment is the intravenous infusion of 4-methylpyrazole which inhibits alcohol dehydrogenase and thus prevents the formation of further acetaldehyde (Lindros et al., 1981).

How long should treatment last?

This is a topic which is as important as debates about the optimum length of treatment with anti-depressants or neuroleptics, or with chemotherapy in tuberculosis. Unfortunately there is little research to guide us, and practice varies widely. At one end of the spectrum, some patients use supervised or unsupervised disulfiram intermittently for short periods either to protect themselves in high risk situations or to terminate a pattern of initially moderate drinking that looks as if it is getting out of hand (Duckert and Johnsen, 1986). However, Azrin (personal communication, 1989) feels that many patients need disulfiram indefinitely, although his longest follow-up was 2 years. My own record is a patient who has taken disulfiram on and off for 11 years and continuously for the past 6 years, it having proved impossible to keep him sober with any other treatment (Brewer, 1993b).

There is a fairly urgent need for a study comparing different lengths of treatment to try to establish a reasonable minimal period. I usually advise patients, and their families, that it should be taken for at least 6 months before they try abstaining without it, on the understanding that they should resume supervised disulfiram immediately if there is even a slight relapse.

Disulfiram and controlled drinking

In those cases where controlled drinking might be a reasonable treatment goal, I tell patients that it should not be discussed until
they have abstained for 6 months while taking disulfiram and a further 6 months without it. By that time, some patients will have got so used to not drinking that they do not want to make the experiment, but in any case I suggest that controlled drinking is more likely to succeed if it is preceded by a period of abstinence rather than attempted immediately after many years of heavy drinking. This hypothesis should not be very difficult to test.

Low dose disulfiram

The severity of the DER depends partly on the dose of disulfiram. By adjusting the dose, it is possible in some patients to provide a kind of 'biochemical ceiling' which enables patients to drink one or two units of alcohol in the space of an hour or two without any reaction but which causes increasing discomfort if they exceed that rate. Only Japanese authors have published anything on this concept (Mukasa et al., 1964; Mukasa and Arikawa, 1968), and they used calcium carbimide rather than disulfiram, but the technique can work with disulfiram. Indeed, the long action of disulfiram means that it can be used to control drinking on a temporal as well as a quantitative basis. No complications of treatment are mentioned in either of the reports but there may be some risk of toxicity from elevated acetaldehyde levels. However, many Japanese have a hereditary deficiency of ALDH which causes a response to drinking similar to the DER and is associated with reduced per capita alcohol consumption in areas with a high incidence of the deficiency (Harada et al., 1982). There is no suggestion that ALDH-deficient individuals experience any long-term acetaldehyde toxicity.

Disulfiram in methadone programmes

Patients who misuse both alcohol and opiates are not rare, and alcohol misuse can make it difficult to stabilise patients on methadone maintenance. Rather than expelling alcohol misusers from methadone programmes, as often happens. Liebson et al. (1973) found it more constructive to offer to continue methadone provided that patients swallowed some disulfiram before swallowing their methadone. This approach was highly effective, perhaps because most patients value their methadone more than they value their alcohol and will therefore generally accept disulfiram in order to remain in treatment.

TOXICITY, SIDE-EFFECTS AND DRUG INTERACTIONS

A recent review analyses spontaneous reports of adverse drug reactions (ADR) to disulfiram to the Danish Committee on ADRs from 1968 to 1991, and also includes reports to the WHO Centre for International Drug Monitoring. The authors conclude that disulfiram has an 'intermediate' incidence of ADRs (1/200–1/2000 per treatment year) and that the risk of death from the only potentially lethal side-effect, disulfiram hepatitis, is one in 25,000 patients per year. The hepatitis is clearly idiosyncratic and not dose-related (Poulson et al., 1992). A disproportionate number of cases involved patients treated not for alcoholism but for nickel or cobalt allergy. The time from starting disulfiram treatment to onset ranged from 16 to 120 days, with a peak around 60 days.

Despite the rarity of disulfiram hepatitis and the occasional occurrence of serious hepatotoxic reactions to many other commonly prescribed drugs, such as chlorpromazine, it has become common advice and practice in the U.S. not to start disulfiram treatment until the results of liver function tests are available (Wright et al., 1988), and there is a tendency to regard liver function tests which are more than moderately abnormal as a contraindication to disulfiram. However, this attitude is far from universal (Black and Richardson, 1985; Phillips, 1990) and it certainly seems illogical given that for more patients than most clinicians will see in a lifetime, continued heavy drinking
constitutes a much greater hepatotoxic risk-factor than does disulfiram.

Indeed, Meyers (1993), a psychologist who feels that disulfiram should be much more widely offered, complains that this excessively cautious attitude often leads to delays in starting disulfiram treatment, during which some patients suffer further alcohol-related harm. In contrast, some physicians regard the use of disulfiram in alcoholic cirrhosis as both unremarkable and potentially life-saving (Gitlow, 1980; Jensen, 1984).

Disulfiram hepatitis nearly always causes obvious clinical signs and symptoms, and fever often precedes visible jaundice by 3–7 days (Iber et al., 1987). Such events should lead to early examination, investigation and diagnosis if patients are being seen at least every 2 or 3 weeks, as will usually be the case at the start of treatment, especially if they are encouraged to report any deterioration in their health. Iber et al. found 27 cases in their literature review. There were nine deaths but no patient died when disulfiram was discontinued as soon as jaundice was apparent. Five cases were confirmed by a further disulfiram challenge, without lasting harm.

Disulfiram neuropathy is rare during the first month of treatment, though one case was reported after only 10 days (Van Rossum et al., 1984). Onset after about 3 months of treatment is more typical, and it is important to note that most reported cases were receiving daily doses of 500 mg or more, although it can occur with as little as 200 mg daily. In one unusual case (Dandelot and Dupuis, 1979) there were no problems during 13 years of treatment at 500 mg daily, but neuropathy developed gradually over the next 2 years after the dose was increased for no particular reason (‘sans motif particulier’) to 1 g daily.

Most cases improve or recover (Van Rossum et al., 1984). In my experience, complete recovery is likely if disulfiram is discontinued as soon as such typical neuropathic symptoms as persistent numbness or paraesthesiae affecting the feet are noticed. I always warn patients about the small risk of neuropathy and describe the early manifestations, but because it is usually a late side-effect (Poulsen et al., 1992) I do not usually mention it until they have been taking disulfiram for at least a week or two.

Drowsiness is the most common minor side-effect reported in most studies. It usually diminishes after a few days and may be associated with the higher loading doses traditionally recommended. Patients who need a deterrent drug but do not tolerate disulfiram well may be treated with calcium carbimide (which is still available in Britain or a ‘named patient’ basis from the makers, Lederle), but disulfiram is to be preferred because its much longer duration of action makes supervision of administration much easier.

Larson et al. (1992) conclude that, ‘At the usual dosage, about 250 mg/day, disulfiram does not appear to increase significantly the risk of psychiatric complications or of psychiatric drug interactions [and] can be considered a treatment option for patients with alcohol dependence and other psychiatric disorders’. Branchey et al. (1987) are similarly reassuring about psychiatric side-effects but, as with several other drugs, psychotic reactions may very occasionally occur (Rossiter, 1992). However, disulfiram can increase the blood levels of some drugs and this is occasionally of clinical importance, notably with phenytoin and warfarin, which may require more frequent monitoring. It does not affect the metabolism of methadone or carbamazepine. Disulfiram has a protective effect against acetaminophen-induced hepatotoxicity (Poulsen et al., 1992).

The risk of death following deliberate overdose is low, especially in comparison with drugs such as tricyclic antidepressants. Lasting neurological damage can occur after attempted suicide if the dose is very high but this is rare and it is not always possible to exclude the effects of alcohol consumed at the same time (Krauss et al., 1991). Even if disulfiram had a much higher incidence of serious side-effects, this would have to be set against the much
greater toxicity of alcohol and the mortality rates of 10–20% reported in many long-term follow-up studies of alcohol misuse (Vaillant, 1973, 1982; Edwards et al., 1983). Apart from pregnancy, florid psychosis and established hypersensitivity, there are, in my view, no absolute contraindications to disulfiram which are not also contraindications to heavy drinking (Brewer, 1986b).

Alcohol in food and other non-beverage forms

In general, alcohol used to flavour cooked food — in sauces, for example — will have largely evaporated by the time it reaches the table. If there is already food in the stomach, absorption will be slowed and the risk of a significant or even noticeable DER is slight. Zuska and Pursch (1980) think the dangers of alcohol in food ‘have been anecdotally exaggerated’. Naturally, alcohol in uncooked food should be treated with more caution but its presence in significant quantities is usually obvious. In some patients, enough alcohol can be absorbed through the skin from aftershave or surgical swabbing to cause a very mild DER (Mercurio, 1952).

Stimulants for disulfiram-induced drowsiness

Despite the relatively low incidence of serious side-effects, drowsiness is a real problem for some patients, especially if doses higher than the normal range are needed to produce an adequate DER. Patients may sometimes use drowsiness, or any other side-effect, as an excuse to evade medication but most are willing to persevere if it can be prevented. Taking disulfiram at night sometimes solves the problem, but if drowsiness persists during the day it can often be easily abolished by an appropriate dose of pemoline or dexamphetamine. Misuse is unlikely if patients are selected with care, prescribing is closely controlled and the stimulant, like the disulfiram, is supervised by a third party.

Evasion techniques

Since supervisors are human, they are therefore subject to such typical human faults as forgetfulness, distraction, inefficiency, misplaced loyalty and lack of assertiveness. Alcoholic patients are human too and may prove to be cunning, determined, persuasive and manipulative. Some of them may simply want to try to beat the system.

Whether supervision is carried out by professionals or by family members or colleagues, supervisors need to be instructed in the correct techniques of supervision and the ways in which patients may try to evade it. Azrin et al. (1982) have shown that time spent in educating supervisors is a good investment. Apart from taking the risk of drinking on disulfiram, there are only a few evasion techniques and all of them can be circumvented. In the only study to examine this issue, 10% of patients persuaded their supervisor that careful observation of disulfiram administration was unnecessary, 4% substituted similar-looking tablets for the disulfiram and 2% induced vomiting shortly after swallowing disulfiram (Brewer, 1986). It is essential that disulfiram be dissolved, or at least chewed, before being swallowed under direct vision. Most formulations dissolve quickly but if not, a small pestle and mortar should be used. Disulfiram does not have a strong or unpleasant taste.

Who should do the supervising?

In the absence of studies to guide us, this must be a matter of clinical judgement. Professional supervision has some obvious advantages but usually means that the patient has to visit a clinic regularly. If he fails to attend, someone then has to go to the trouble of finding out whether the absence was more or less accidental or deliberate. Supervision by family members, friends or colleagues may be more difficult for the patient to avoid. It may cause arguments, though usually fewer arguments than a relapse. Appropriate training of
supervisors should include rehearsals of potential disagreements (Azrin et al., 1982). Supervision by visiting community psychiatric nurses may be a useful compromise in some cases. Supervision by the probation service has already been mentioned.

Because ALDH may be inhibited for up to a week after the last dose of disulfiram, supervision thrice or even twice weekly may maintain adequate deterrence and be less disruptive. It is usually advisable to maintain approximately the same total weekly dose but, as already noted, even a pharmacologically inadequate dose will often prove psychologically effective if well supervised.

Disulfiram as an adjunct to other treatments

For the large number of patients without serious underlying psychopathology and with reasonably intact relationships, Azrin et al. (1982) showed that supervised disulfiram by itself may be sufficient to establish either lasting abstinence or a lasting reduction in alcohol intake, even after disulfiram is discontinued. Many patients improve considerably once they stop drinking, and a valid assessment of their mental and physical health can rarely be made until they have had a chance to recover from the effects of alcohol on the brain and other organs, including recovery from withdrawal symptoms if they are present. It is consequently a misuse of therapeutic resources, in most cases, to suggest elaborate psychological interventions or specific psychopharmacological treatments before abstinence has been secured for several weeks. Clearly, urgent problems — such as imminent marital breakdown — may have to be attended to at an early stage, but even Miller and Hester (1986), who are psychologists, do not feel that counselling and psychotherapy, other than of a fairly simple and supportive kind, should be considered unless the need for them is clearly apparent after 2 or 3 months. Numerous studies have shown that many alcoholics have significant cognitive impairment on admission, although this usually improves fairly quickly with abstinence.

Depot injections of disulfiram

Pharmacologically effective long-acting injections of disulfiram would remove the need for frequent oral administration and supervision and minimise the risk of evasion. Unfortunately, existing commercially available depot preparations of disulfiram are pharmacologically inert and in most studies, neither disulfiram nor any of its metabolites were detected in blood taken from patients.

In a controlled study, disulfiram implants tended to cause a higher incidence of local tissue complications than placebo implants. When alcohol was administered blind by the intravenous route, so that fear of a DER did not confound the assessment, no significant differences in cardiovascular measures or acetaldehyde levels were observed between placebo and disulfiram implants (Johnsen and Morland, 1992). Considering the small amount of disulfiram contained in most implants, compared with the usual daily oral doses which are necessary to produce a significant DER, such negative results are not surprising.

However, implants may have a useful placebo effect in some patients. Following the publication of a controlled study in Norway which found no difference in outcome between placebo and allegedly active disulfiram implants, one of the authors received much criticism from patients who had had implants (Johnsen, personal communication). Recently, some encouraging results have been reported with disulfiram injected subcutaneously as a suspension rather than implanted in the solid form (Phillips and Greenberg, 1992).

CONCLUSION

Many patients do well without disulfiram, but for those who fail to respond to simpler treatments, or for whom the consequences of an early relapse would be particularly dis-
astrous, the diligent supervision of an adequate dose of disulfiram by a supervisor who is aware of the possible evasion techniques is probably the most potent specific intervention at our disposal. Despite its effectiveness, supervised disulfiram is generally under-used. I have summarised elsewhere the reasons for reluctance to use it, or outright antagonism (Brewer, 1990). The unopposed evidence of its effectiveness from several controlled trials is the best counter-argument. The development of a well-tolerated and pharmacologically active depot preparation of disulfiram should further increase its usefulness.

REFERENCES

Brewer, C. (1986a) Patterns of compliance and evasion in treatment programmes which include supervised disulfiram. Alcohol and Alcoholism 21, 385–388.


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