Alcohol and Alcoholism, 2017, 52(2) 213–219
doi: 10.1093/alcalc/agw093
Advance Access Publication Date: 7 January 2017
Review

Review

Supervised Disulfiram's Superior Effectiveness in Alcoholism Treatment: Ethical, Methodological, and Psychological Aspects

Colin Brewer[1,*], Emmanuel Streel[2], and Marilyn Skinner[3,4]

[1]The Stapleford Centre, London SW1W 9NP, UK, [2]Unité de recherche en psychophysiologie de la motricité, Université Libre de Bruxelles, Avenue F Roosevelt, 50 – 1050 Bruxelles, Belgium, [3]AP-HP, Service d'addictologie, Hôpital Emile Roux, Limeil-Brévannes, Hôpitaux Universitaires Henri-Mondor, 94010 Créteil, France, and [4]CESP, INSERM, Univ. Paris-Sud, UVSQ, Université Paris-Saclay, Limeil Brevannes, France

*Corresponding author: The Stapleford Centre, London SW1W 9NP, UK. Tel: +44 (0)20 7823 6840.
E-mail. Brewerismo@gmail.com

Received 14 November 2012; Revised 9 October 2016; Editorial Decision 12 November 2016; Accepted 21 November 2016

Abstract

Disulfiram (DSF) causes the ALDH-mediated deterrence of alcohol consumption. We review recent meta-analyses showing the superior effectiveness of supervised disulfiram (SD) in alcoholism treatment compared with oral naltrexone or acamprosate (ACP). The success of SD is also consistent with the almost complete absence of alcoholism in Japanese homozygotes for 'inefficient' ALDH. However, SD is an underused treatment and some clinicians have ethical objections to DSF. We examine these objections and argue that they are based on a misunderstanding of how DSF works. In particular, we argue that SD is not as is often claimed a variety of aversion therapy but aids cognitive, behavioural, educational and psychosocial interventions. It has some unique features that need to be better understood if it is to be properly compared with other treatments and effectively employed to help alcoholic patients, especially those who have not responded to other evidence-based interventions.

INTRODUCTION

> 'We become temperate by abstaining from indulgence and we are the better able to abstain from indulgence after we have become temperate'. (Aristotle, Nichomachean Ethics, II)

Disulfiram (DSF) effectively deters alcohol consumption by inhibiting the enzyme aldehyde dehydrogenase (ALDH). Alcohol dehydrogenase (ADH) converts ethanol to acetaldehyde, which is then converted by ALDH to acetic acid and CO_2. ALDH inhibition causes a marked rise in blood acetaldehyde levels with unpleasant effects such as flushing, nausea, vomiting and headache that constitute the disulfiram-ethanol reaction (DER). Patients may be deterred by the planned or unplanned experience of a DER or more usually by learning about it from the prescribing physician, the internet or other alcoholics. DSF is often described as 'aversive' and DSF treatment is often confused with aversion therapy, but as discussed shortly, deterrence and aversion are very different psychological processes and involve different ethical considerations. In particular, while aversion therapy involves repeated exposure to an unpleasant stimulus, most DSF patients never experience the DER and do not need to.

The main objective of this paper is to increase understanding of some intriguing ethical issues raised by DSF, a treatment used for alcoholism since the late 1940s. Evidence from controlled studies for its effectiveness, when its consumption is supervised by health professionals or by suitable delegated associates of the patient, has been growing since the 1970s. The evidence of success with unsupervised DSF, however, is unimpressive, essentially due to failures of compliance. Furthermore, in placebo-controlled trials, compliance with medication is a marker for a more general compliance with healthy behaviour—the so-called 'healthy adherer' effect—that correlates with better outcomes generally, even for patients in the placebo wing of the trial (Simpson *et al.*, 2006).

The evidence base has now been subjected to meta-analysis, three of which we summarize here. Jørgensen *et al.* (2011) using 10 studies concluded that supervised disulfiram (SD), typically combined with appropriate psychosocial interventions, is effective and probably more effective than the main current alternative medications naltrexone (NTX), acamprosate (ACP) and topiramate. A large Swedish meta-analysis of treatments for substance abuse (SBU, 2002) came to similar conclusions; average treatment effect sizes for NTX and ACP in alcoholism were a modest 0.28 and 0.26, respectively, against 0.53 for SD. Skinner *et al.* (2014) in the most recent meta-analysis including 23 studies left no doubt as to DSF efficacy for maintaining abstinence or preventing relapse vs ACP (3 studies) and NTX (9 studies). In light of these uniformly positive meta-analyses, this paper addresses and updates several longstanding ethical and clinical issues that arise regularly despite the advances in DSF research.

A notable and significant finding in the Skinner *et al.* (2014) meta-analysis was that DSF is more effective than controls only in studies where patients were informed as to whether the tablet issued to them was a placebo or active DSF. In the blind studies, no significant difference between DSF and the control groups was found. Some can be discounted because the consumption of the tablet was not directly supervised as is necessary for maximal effectiveness (Fuller and Roth, 1979; Fuller *et al.*, 1986; Carroll *et al.*, 2004). In addition, two other blinded but supervised studies were incapable of showing superiority of DSF (Ling *et al.*, 1983; Yoshimura *et al.*, 2014). As with most outcome studies of pharmacological treatments in alcoholism, many of those cited in the reviews above covered periods of months or even weeks, but we refer in the section on supervision to an unusually long-term treatment approach involving SD that looked at outcomes after several years.

These blinded trials suggest that DSF is ineffective, but we can explain this by the atypical deterrent mode of action of DSF: DSF functions as a psychological deterrent for patients who know they are taking it and how it works. It therefore follows that if placebo group patients think they are taking DSF, they will respond in the same manner, being deterred as effectively as the DSF group of patients. This also explains a similar finding in a study by Krampe *et al.* (2006) in which directly supervised DSF played an important part. Some patients with medical conditions that were thought to contra-indicate DSF were openly given sham DSF and informed that a 'disulfiram-like' ethanol reaction would occur if they drank alcohol. Because these medically vulnerable patients were presumably even more deterred from drinking alcohol by the possibility of an unpleasant reaction, it is not surprising that they had an even higher cumulative abstinence score than the group who actually took the DSF. DSF deters drinking in the same way that speed cameras deter speeding and as with sham DSF, sham or inactive cameras are just as effective as active ones, provided that drivers cannot tell that they are not active (Wilson *et al.*, 2010).

NATURE'S VERSION OF SUPERVISED DSF

Approximately 36% of East Asians (Japanese, Chinese and Koreans) show a characteristic response to drinking alcohol, predominantly due to ALDH2 deficiency (Brooks *et al.*, 2009). Therefore, SD's long-term effectiveness would not surprise those who are homozygous for a gene that gives them a very inefficient variant of ALDH and who thus experience the lifelong and unavoidable effects of Nature's version of SD. As regards the Japanese, most of those who are homozygotes would presumably grow up to become regular users and sometimes abusers of alcohol, yet both social alcohol drinking and alcoholism are extremely rare among them (Sun *et al.*, 2002). Opinions differ slightly about the precise degree of rarity but not about the rarity itself. In a survey of 655 Japanese alcoholics and 461 controls, Higuchi (1994) concluded 'The ALDH2(2)/2(2) genotype was found in none of the alcoholics, suggesting that individuals with homozygous ALDH2(2) never become alcoholics.' Chen *et al.* (1999) qualified this view by stating 'The gene status of ALDH2*2/*2 alone can give very considerable but not—as previously thought—complete protection against the development of alcohol dependence.'

The rather simple explanation for this protection is that alcohol in more than minimal, gustatory quantities causes an unpleasant reaction that is virtually identical to the DER that accounts for SD's deterrent (and thus therapeutic) effect. The extremely rare reported exceptions typically involve homozygous patients with comorbid anxiety who occasionally try to use alcohol as an anxiolytic despite the unpleasant consequences, but such patients never manage to drink more than relatively modest amounts of alcohol spread over 24 h. It is possible that other genetic factors enable these exceptional ALDH2*2/*2 homozygotes to tolerate these levels of alcohol consumption. For example, less efficient variants of ADH could reduce the level of acetaldehyde production (Chen *et al.*, 1999). Genetically and/or psychologically determined differences in cardiovascular responses or tolerance of discomfort might also play a part. In large Japanese surveys such as those cited above, the incidence of alcoholism in homozygotes is indeed very low. However, these low figures do not signify an absence of addictive vulnerability, especially for other types of drugs and it is possible that some patients will substitute other drugs for alcohol. In addition, treatment conditions (e.g. residential vs outpatient) can also be a confounder that could explain success of SD treatment, although DSF is quintessentially an ambulatory treatment. It is also relevant that Japanese household surveys use small sample sizes and novel psychoactive substances might be under-reported. Recently, Yoshimura *et al.* (2014) evaluated the efficacy of SD for the treatment of alcohol dependence but while they noted the effectiveness of DSF for the maintenance of abstinence in patients with inactive ALDH2, they also mentioned the need for further studies of DSF in Japan. Indeed, while the efficacy of DSF is recognized by agencies such as the World Health Organization, documented in peer-reviewed publications and acknowledged by clinicians worldwide, there remains a need to investigate and clarify the underlying mechanisms of its superiority to other pharmacological approaches.

In those who are heterozygous for inefficient ALDH (and thus experience the equivalent of lifelong treatment with a sub-optimal dose of DSF that may not completely deter drinking), Sun et al. (2002) found the incidence of alcoholism to be around 5% compared with around 10% in those with 'normal', 'efficient' or 'western-style' ALDH. This represents a clear dose response in terms of ALDH inhibition and also points very strongly to the primacy of ALDH inhibition in the pharmacological component of SD's effectiveness. Conversely, Bickel *et al.* (1989) document the fact that if patients continue drinking on standard doses of DSF, raising the dose will usually secure abstinence. Some patients need doses of 600 mg daily or more (Brewer, 1984, 1993), and some preparations of DSF have higher bioavailability than others. It is not sufficiently recognized that DSF is a prodrug and needs to be converted to an active metabolite. In a few patients, this conversion may be inefficient for various reasons (Andersen, 1992).

ABSTINENCE AND THE LANGUAGE-LEARNING ANALOGY

It has been argued (Brewer, 1988, 1990; Brewer and Streel, 2003) that this process of acquiring enduring habits of abstinence has important and therapeutically relevant parallels in the processes by which students of a foreign (i.e. second) language acquire fluency in that new language. In particular, it is argued that both processes rely on the techniques and principles of Exposure and Response-Prevention (ERP) which is the standard, evidence-based psychological approach for changing maladaptive patterns of repetitive behaviour. In foreign language learning (FLL), the goal is to suppress the habit of speaking only in, say, English and replace it with the ability to make, say, speaking in French (when necessary) as fluent and automatic as speaking in English. In alcoholism treatment, the goal is to suppress the habit of drinking alcohol as the sole response to many stimuli and to replace it with alcohol-free cognitive and behavioural habits. In FLL, controlled studies show that fluency is most effectively achieved by strongly discouraging the speaking of English and requiring the student to use French from the beginning, however inexpertly and however uncomfortable or anxious this may initially make the student feel (Brewer, 1988).

Educational research also shows clearly that continuous, uninterrupted teaching is more effective and efficient than the same amount of teaching spread intermittently over months or years. Similar findings come from studies of the cognitive-behavioural treatment of phobias, presumably because new, adaptive habits are more likely to become established if they are not constantly interrupted by succumbing to the temptation to revert to old, maladaptive habits. Thus, Hawkins states 'No one seriously doubts how foreign languages should be learnt', noting that using intensive, all-day 'immersion', it is possible to get a class of adults up to GCE 'O' level [the school-leaving exam for 16 year olds] Italian Grade 1 in 80 h spread over 2 weeks, compared with 5 years for the normal school Italian syllabus (Hawkins, 2000). Similarly, a single 2-h session of exposure for phobias or compulsions has been found to be more effective than four half-hour sessions (Stern and Marks, 1973). Furthermore, exposure to real snakes gives better results in snake phobias than exposure to simulated or imagined snakes (Sherman, 1972).

This strongly suggests that SD's ability to facilitate abstention every day, despite powerful real-life temptations, has certain proximal advantages over more distal methods such as AA meetings and typical psychotherapy and skill training for relapse prevention. Most SD-assisted learning takes place in the natural environment of the patient, whereas conventional counselling occurs in the protective setting of the clinic and essentially involves simulated temptations. While exposure to high-risk situations is vital if patients are to learn how to deal with them, and while exposure is an important component of CBT, the crucial advantage of SD is that it adds response-prevention (RP) to exposure. It is as if patients had their own personal therapist present and supporting them every time they encounter major risk factors for relapse until RP becomes automatic. RP can also be regarded as the application of urge-specific coping skills, a component of cognitive-behavioural treatment particularly associated with positive outcomes (Dolan *et al.*, 2013).

Alcoholics can develop self-efficacy by extinguishing any automatic responses that involve drinking and repeatedly practicing alternatives. Often they need to develop new patterns of coping with solitude and negative emotions as well as participate in rewarding activities with others that do not involve drinking. Using the analogy of language learning, these new habits need to be practised in the real world for long enough for them to become automatic. The studies summarized above indicate that encouraging students to practice (with increasing confidence) and then to converse in a foreign language, even imperfectly, leads to better outcomes than having a good theoretical knowledge of vocabulary and grammar but inadequate confidence to use it (Brewer, 1988). Similarly, it may be more important to acquire confidence and automaticity in the new non-drinking responses, even imperfectly, than to be theoretically competent but lack confidence in practice.

Two neuroimaging studies strongly support this argument. Controlled comparisons of expert vs less-expert golfers found significant differences in both the site and the level of brain activity when mentally rehearsing golf swings. The most expert golfers had the lowest levels of activity and fewer areas were involved (Ross *et al.*, 2003). The authors suggest that the differences reflect a higher level of automaticity in experts and less interference from the need to decide or think about what to do. Ross *et al.* explain 'The fact that these differences are apparent before the golfer swings the club suggests that the disparity between the quality of the performance of novice and expert golfers lies at the level of the organization of neural networks during motor planning. In particular, we suggest that extensive practice over a long period of time leads experts to develop a focused and efficient organization of task-related neural networks, whereas novices have difficulty in filtering out irrelevant information' (Milton *et al.*, 2007). Similarly, in surgical practice, '…a defining trait of experts is that they move more and more problem-solving into an automatic mode' (Leape, 2003). We suggest that similar considerations apply to experienced vs inexperienced abstainers; indeed, alcoholism itself often involves an 'automatic-pilot' process of anticipation followed immediately by drinking. The process is aggravated by alcohol's immediate and therapeutically disabling effects on important brain areas, mainly in the frontal lobes, that might otherwise inhibit such maladaptive behaviour.

MORAL AND ETHICAL ARGUMENTS AGAINST DSF—UPDATING THE ETHICAL DEBATE

In 2004, an editorial in *Addiction* conceded that SD is an effective intervention and was accompanied by several positive commentaries (Edwards, 2000; Ehrenreich and Krampe, 2004; Fuller and Gordis, 2004). Only 4 years previously, however, *Addiction's* senior editor, the late Prof Griffith Edwards, had strongly criticized DSF treatment as both unethical and lacking an adequate evidence base (Zullino *et al.*, 2010). More recently but before the publication of further substantial meta-analytical evidence for the effectiveness of DSF, Zullino *et al.* (2010) and Thorens *et al.* (2010) argued that the use of DSF had no theoretical justification. They claimed that its apparent effectiveness in comparative trials against purely psychosocial interventions or against other drugs such as ACP and NTX was an artefact that could be explained without invoking any true pharmacological effects of DSF. Furthermore, they argued that because DSF treatment involved the threat of an unpleasant experience, it was morally unacceptable and that the use and marketing of DSF for alcoholism should end. These criticisms, which could make some clinicians feel uncomfortable about using DSF, reveal a misunderstanding of the mechanisms by which DSF achieves its therapeutic effects. They are cognitive-behavioural and educational rather than pharmacological or psychopharmacological. We summarize below the principal objections to DSF presented by these authors, followed by our responses and comments.

An important objection held by DSF opponents is that DSF treatment involves the threat of 'punishment' and that it is therefore

inappropriate for physicians to take part in it. There are a number of possible responses to such objections, including the obvious ones—that treatment is not compulsory and that 'punishment' usually means something unwelcome, unpleasant and degrading done to a person by society or individuals. In the case of SD, any unpleasantness is not done by physicians to patients but by patients to themselves and they can easily avoid it. Most SD patients do just this by not drinking, which is after all the usual mutually agreed long-term aim of the treatment. Another response is to regard the use of DSF as a matter rather like abortion or contraception, on which good men and women may hold opposing opinions. In such situations, most developed and democratic societies (Eastern as well as Western) allow both patients and doctors to make their own ethical choices and to participate in or refrain from treatment as they think fit.

There are also pharmacological objections. For example, some researchers state 'DSF represents a very notable pharmaco-therapeutic anomaly. Normally, we regard a medication as effective if it deploys its pharmacological effect (this being the basis of placebo-controlled trials). However, DSF is supposed to be effective when it isn't producing a pharmacological effect.' (Zullino *et al.* 2010) (*Our translation*). While it is true that DSF's efficacy is due to a unique mechanism of action, this pharmacological effect has two facets. First, if the mere probability of an unpleasant DER is a sufficient deterrent, then DSF is doing its job. Second, if the patient needs to experience the DER personally before deterrence reaches adequate levels, then DSF is also doing its job. In both cases, the pharmacology of DSF is ultimately what causes the deterrent effect.

In our experience, it is exceptional for patients to expose themselves repeatedly to a DER unless an inadequate dose makes the DER so mild that it has insufficient deterrent effect. If they do test it and experience a sufficiently unpleasant effect, they will only try it once or twice. Rather than expose themselves to it repeatedly, they are more likely to drop out of treatment despite attempts to help them to stay, thereby demonstrating that they are not really willing to accept even a period of abstinence. This avoids much wasted time and effort for both doctor and patient.

Opponents' also question whether the ritual of taking a tablet is the crucial factor in the decision to drink or abstain, whether or not the tablet contains DSF. That, we would argue, depends on whether the patient is informed as to the composition of the tablet. For example, in an open label study, Chick *et al.* (1992) showed that SD, even at rather modest doses, is more effective than supervised ascorbic acid.

Opponent's final objection is that the deterrent effect depends on the patient behaving like a rational actor, 'able to evaluate the costs and benefits of his choices. But it is precisely the inability to make such evaluations that is the central element in the definition of an addiction' (e.g. Thorens *et al.* 2010). In reality, most addicts have no general 'inability' to act rationally. They may react irrationally or inappropriately in relation to alcohol, as spider phobics do to spiders, but the agreed object of treatment, achieved more effectively with SD than without it, is precisely to assist them in acting more rationally in alcohol-related situations. Their ability to act rationally in other situations is not usually in question, otherwise how would a person with a history of alcohol dependence ever gain employment?

PRACTICAL AND ETHICAL ASPECTS OF SUPERVISION

Careful supervision of DSF consumption is essential to the success of SD treatment. Often this can be delegated to family members who tend to be strongly motivated to help the patient. Supervisors need appropriate training that should include teaching them the tricks some patients use to evade swallowing DSF. Most patients who use these tricks remain in treatment when their attempts are discovered and thwarted (Brewer, 1986). If supervision leads to conflicts and arguments, then they can usually be resolved in therapist-led discussions involving the relevant family members using a cognitive-behavioural approach (Azrin *et al.*, 1982).

There are certainly ethical aspects to SD, but motivating patients to accept a therapeutic contract including SD is not different from motivating them to accept other therapeutic components about which patients may be—and often are—ambivalent. Phobic patients do not initially like graded exposure to feared objects or situations such as flying or spiders and could come to harm if exposure produces panic attacks. Drugs and surgery can have adverse effects. As with all medical, surgical and psychosocial interventions, risks and benefits need to be discussed and choices need to be made. It is both common and widely regarded as legitimate for a clinician to encourage a patient to initiate and persevere with a mutually negotiated treatment plan and to adhere to informed and adequately considered therapeutic contracts.

For patients with no family, or when years of alcoholic behaviour have alienated previously supportive family members or friends, health professionals, hostel staff or probation officers can substitute. A combined breathalyser and DSF breath monitor that can be attached to a mobile phone may facilitate supervision when work or location makes direct personal supervision difficult (Fletcher, 2015). Ehrenreich *et al.* (1997) showed that frequent but brief contact for the first year or two is important for patients with many previous relapses. A minimum of 18 months of SD is advisable in such cases. The features of Outpatient Long-term Intensive Therapy for Alcoholics (OLITA) are the unusually long duration of the programme (minimum 2 years), frequent short-term contacts with gradual tapering, crisis interventions, social re-integration, SD, regular urine analyses, assertive aftercare and planned therapist rotation to ensure continuity.

Even recurrent alcoholic offenders, commonly regarded as a very unpromising patient group, considerably increased their previous maximum abstinence out of prison when they agreed to take SD as one condition of a probation order (Brewer and Smith, 1983). There are additional ethical considerations in any probation order contingent upon medical treatment, but such arrangements are generally not regarded as unacceptable.

Relapse in alcoholism means that the process of learning and routinizing new cognitive-behavioural habits is interrupted. However, what distinguishes relapse during treatment of alcoholism (and many types of substance abuse) from other interruptions in an educational process or a CBT programme is that it involves a reversion to counter-productive behaviours mutually agreed upon as undesirable by the therapist/teacher and the patient/pupil. It also typically involves intoxication for a period of hours, days or weeks, during which the patient's ability to respond to rational argument, to regain control, or even to discuss the situation is severely impaired or absent. This impairment may be aggravated by the 'abstinence violation effect' (Walton *et al.*, 1994) a phenomenon that intensifies the likelihood that a lapse or 'slip' evolves into a relapse. In the event of a lapse, SD treatment sends a strong signal with symptoms of a DER. This can be viewed as a crisis intervention in itself to prevent a slip from immediately becoming a full-blown relapse. ALDH inhibition and the risk of a DER reinforce the treatment in that they usually persist for several days after the last dose of DSF. DSF is an irreversible inhibitor of ALDH. Unlike the effects

of most drugs, the duration of inhibition depends not so much on DSF blood levels as on the rate at which new ALDH is made. This varies presumably for genetic reasons. With efficient supervision and adequate DSF dosage, impulsive relapse to heavy drinking becomes very unlikely. Refusal to take DSF is a usual precursor to a planned relapse, but that refusal inevitably alerts the supervisor and thus enables timely crisis intervention. This unique built-in delay caused by persistent ALDH inhibition means that the patient has to deal with the situation (and with the therapeutic team) while still sober instead of in an intoxicated state. This may give all parties a better chance of resolving the issues and resuming cooperation with SD.

The only way patients can avoid SD in this situation is by formally withdrawing from treatment. Withdrawal has very important implications for patients' relationships with their families and other important figures and institutions, such as employers, clinicians and the courts, and sober patients are much more likely to consider these implications than intoxicated ones. If a patient with many previous relapses consistently refuses cooperation with SD, it becomes easier for the therapeutic team and the patient's family to terminate treatment with a clear conscience unless and until the patient agrees to cooperate again. Sereny *et al.* (1986) found that 68 out of 73 alcoholic patients with at least three relapses despite adherence to intensive drug-free treatment accepted the addition of SD as a condition of further treatment. The important distinction, possible only with SD, between preventing relapse and responding quickly when a relapse occurs is particularly important in a probation or parole setting. A relapse to actual intoxication may not be so tolerantly viewed by the courts, especially where there is a history of alcohol-related violence.

THE POLITICS OF DSF TREATMENT

The resistance to the deterrence model of treatment may be only one aspect of a more general trend that regards deterrence as inferior to 'positive reinforcement' (i.e. reward) in programmes for changing undesirable behaviour. This position may be politically correct but is not always scientifically correct. According to Shepherd (2001), 'Deterrence is an established theme in criminal justice, but its role in prevention of assault has been treated with ambivalence and even hostility in medicine.' Shepherd registered no dissent when it was suggested in published comment that '[Shepherd] seems to be saying that although selective deterrence works rather well, there are influential people in medicine, psychology and criminology who fervently wish that it didn't because its success conflicts with their ideologies' (Brewer, 2002). Opposition may also represent reactions to techniques such as electrical or apnoeic aversion that are now considered neither ethical nor beneficial (Johnston *et al.*, 2006).

Therapeutic strategies based on positive reinforcement principles, such as voucher-based contingency management, are relatively popular, though only modestly effective in practice. Even with escalating rewards, they can generate periods of abstinence only for as long as the incentive is provided (Higgins *et al.*, 2007). In contrast, a deterrent technique such as SD offers an opportunity for patients to not only change their drinking habits to avoid potential unpleasant effects, but also through consistent abstinence to create favourable conditions for the acquisition and integration of other components of treatment, such as psychotherapy. These two strategies work synergistically to generate abstinence and maintain it even after SD is discontinued. Negative reinforcement of abstinence (Sheldon, 2011) may also operate when patients find that SD reduces the anxiety normally caused by internal conflicts about drinking vs not drinking that typically occur many times a day. We emphasize that long-term SD's mode of action is primarily an educational process in that it both aims at and optimizes the acquisition by patients of new and useful coping skills, information, insights and responses that become increasingly automatic.

One of the few studies to examine the contribution of the various components of a comprehensive SD treatment package (albeit for a relatively short period) found that 'the contribution of the DSF component…was much greater than that of any of the psychotherapeutic components … and that none of the varieties of specific psychotherapy was clearly superior to any of the others' (Carroll *et al.*, 1998). This adds to the evidence that the mechanism by which SD facilitates the move from alcoholism to lasting abstinence is essentially educational or psychological rather than neurobiological or neuropharmacological.

ADVERSE EFFECTS OF DSF

DSF appears to be a safe medication with carefully screened populations according to the Skinner *et al.* (2014) meta-analysis, which also analysed safety and tolerance. There was no difference between the DSF and control groups in studies reporting deaths and serious adverse events requiring hospitalization. As expected, there were more adverse events reported for DSF than for controls, the most common problems being skin rash, halitosis and fatigue. According to Gitlow (1980), DSF toxicity has often been viewed with disproportionate anxiety and DSF is less likely than aspirin to cause serious side effects (Gitlow, 1980). Fulminant DSF hepatitis, though rare at ~1 case per 25,000 treatment years (Poulsen *et al.*, 1992), is the only life-threatening toxic effect, but in no reported case has death occurred when DSF was discontinued at the first clinical or biochemical signs of serious liver dysfunction. DSF is not contra-indicated in patients with even severe alcoholic liver disease (Brewer and Hardt, 1999) and can be life-saving in cirrhosis and incipient liver failure (Jensen, 1984).

CONCLUSION

Given its demonstrable effectiveness (much of which was persuasively demonstrated in randomized controlled trials several decades before the meta-analyses), it is clear that SD has been very much underused, especially in patients who have not responded well to programmes that do not offer SD and even more so if they have not responded to other relapse-preventing medication, such as ACP or NTX. This underuse is more obvious in some countries than in others but surveys reveal the comparative rarity with which any sort of anti-alcoholism medication is used in many US alcoholism programmes (Mark *et al.*, 2003), though resistance seems to be diminishing despite the traditional opposition to medication in '12-step' programmes.

While serious side effects from DSF are uncommon, the fact that adverse effects from DSF can be more serious compared with ACP or NTX (even though death from the DER or DSF hepatitis is very rare) means that many clinicians may prefer to use NTX or ACP as drugs of first choice for new patients. However, SD should surely be the first treatment choice for patients with several previous treatment failures and no lengthy periods of abstinence, whose domestic, legal, financial or employment situation would quickly become catastrophic if they had further relapses.

Secondly, physicians, counsellors and psychotherapists (as well as patients) should recognize that SD does not imply the 'medicalisation' of treatment. It still places the main responsibility for success or failure on the patient, particularly in persevering with treatment

for as long as necessary. Far from saving the patient from the need to do 'real psychological work', SD makes it easier for that work to proceed without interruption and in a sober state.

Practice makes perfect and as has been noted (Brewer and Streel, 2003) the French equivalent of that phrase is 'c'est en forgeant qu'on devient forgeron' ('by doing the work of a blacksmith, you become a blacksmith'). By practising abstinence for long enough, you become an abstinent person. As [Shakespeare's] Hamlet says to his mother, (Act 3, Sc. 4.): 'Refrain tonight, and that shall lend a kind of easiness to the next abstinence; the next more easy. For use [i.e. getting used or accustomed to refraining] almost can change the stamp of nature, and either curb the devil, or throw him out, with wondrous potency.' We think Aristotle would have agreed.

ACKNOWLEDGEMENTS

We are grateful to Drs Duncan Raistrick, Henning Krampe and Ivan Montoya and to Professors David Denney, Ted Godlaski, Gary Hulse, Brian Sheldon and David Smith for helpful comments and suggestions.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

Andersen MP. (1992) Lack of bioequivalence between disulfiram formulations. Exemplified by a tablet/effervescent tablet study. *Acta Psychiatr Scand Suppl* **369**:31–5.

Azrin NH, Sisson RW, Meyers R, *et al.* (1982) Alcoholism treatment by disulfiram and community reinforcement therapy. *J Behav Ther Exp Psychiatry* **13**:105–12.

Bickel WK, Rizzuto P, Zielony RD, *et al.* (1989) Combined behavioral and pharmacological treatment of alcoholic methadone patients. *J Subst Abuse* **1**:161–71.

Brewer C, Hardt F. (1999) Preventing disulfiram hepatitis in alcohol abusers: inappropriate guidelines and the significance of nickel allergy. *Addict Biol* **4**:303–8.

Brewer C, Smith J. (1983) Probation-linked supervised disulfiram in the treatment of habitual drunken offenders: results of a pilot study. *BMJ* **287**: 1282–3.

Brewer C, Streel E. (2003) Learning the language of abstinence in addiction treatment: some similarities between relapse-prevention with disulfiram, naltrexone and other pharmacological antagonists and intensive 'immersion' methods of foreign language teaching. *Subst Abus* **24**:157–73.

Brewer C. (1990) Combining pharmacological antagonists and behavioural psychotherapy in treating addictions: why it is effective but unpopular. *Br J Psychiat* **157**:34–40.

Brewer C. (1984) How effective is the standard dose of disulfiram? A review of the disulfiram-alcohol reaction in practice. *Br J Psychiat* **144**:200–2.

Brewer C. (1993) Long-term, high-dose disulfiram in the treatment of alcohol abuse. *Br J Psychiat* **163**:687–9.

Brewer C. (1988) Managing opiate abuse: learning from other addictions. *J Drug Issues* **18**:679–97.

Brewer C. (1986) Patterns of compliance and evasion in treatment programmes which include supervised disulfiram. *Alcohol Alcohol* **21**:385–8.

Brewer C. (2002) The deterrence issue. *Lancet* **359**:982.

Brooks PJ, Enoch M-A, Goldman D, *et al.* (2009) The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. *PLoS Med* **6**:e1000050. doi:10.1371/journal.pmed.1000050.

Carroll KM, Fenton LR, Ball SA, *et al.* (2004) Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiat* **61**:264–72.

Carroll KM, Nich C, Ball SA, *et al.* (1998) Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* **93**:713–28.

Chen Y-C, Lu R-B, Peng G-S, *et al.* (1999) Alcohol metabolism and cardio vascular response in an alcoholic patient homozygous for the ALDH2*2 variant gene allele. *Alcohol Clin Exp Res* **23**:1853–60.

Chick J, Gough K, Falkowski W, *et al.* (1992) Disulfiram treatment of alcoholism. *Br J Psychiat* **161**:84–9.

Dolan S, Rohsenow D, Martin R, *et al.* (2013) Urge-specific and lifestyle coping strategies of alcoholics: relationships of specific strategies to treatment outcome. *Drug Alcohol Depend* **128**:8–14.

Edwards G. (2000) *Alcohol, the Ambiguous Molecule*. London: Penguin.

Ehrenreich H, Krampe H. (2004) Does disulfiram have a role in alcoholism treatment today? Not to forget about disulfiram's psychological effects. *Addiction* **99**:25–8.

Ehrenreich H, Mangholz A, Schmitt M, *et al.* (1997) OLITA: an alternative in the treatment of therapy-resistant chronic alcoholics. First evaluation of a new approach. *Eur Arch Psychiatry Clin Neurosci* **247**:51–4.

Fletcher K. (2015) Disulfiram and the Zenalyser®: teaching an old dog new tricks. *Alcohol Alcohol* **50**:255–6.

Fuller R, Gordis E. (2004) Does disulfiram have a role in alcoholism treatment today? *Addiction* **99**:21–4.

Fuller RK, Branchey L, Brightwell DR, *et al.* (1986) Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. *JAMA* **256**: 1449–55.

Fuller RK, Roth HP. (1979) Disulfiram for the treatment of alcoholism. An evaluation in 128 men. *Ann Intern Med* **90**:901–4.

Gitlow SE. (1980) Antabuse. In Gitlow SE, Peyser HS *Alcoholism: A Practical Treatment Guide*. New York: Grune and Stratton, 273.

Hawkins E. (2000) *Modern Languages in the Curriculum*. Cambridge: Cambridge University Press.

Higgins S, Silverman K, Heil S. (2007) *Contingency Management in Substance Abuse Treatment*. New York: The Guilford Press.

Higuchi S. (1994) Polymorphisms of ethanol metabolizing enzyme genes and alcoholism. *Alcohol Alcohol Suppl* **2**:29–34.

Jensen E. (1984) A proper use of Antabuse: the Danish model of treatment. *Br J Clin Pract* **38**:117–22.

Johnston JM, Foxx R, Jacobson J, *et al.* (2006) Positive behavior support and applied behavior analysis. *Behav Anal* **29**:51–74.

Jørgensen CH, Pedersen B, Tønnesen H. (2011) The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcohol Clin Exp Res* **35**:1749–58.

Krampe H, Stawicki S, Wagner T, *et al.* (2006) Follow-up of 180 alcoholic patients for up to 7 years after outpatient treatment: impact of alcohol deterrents on outcome. *Alcohol Clin Exp Res* **30**:86–95.

Leape L. Cited by Gawande A. (2003) Complications: a surgeon's notes on an imperfect science. 2003; London. Profile. 39.

Ling W, Weiss DG, Charuvastra VC, *et al.* (1983) Use of disulfiram for alcoholics in methadone maintenance programs. A Veterans Administration Cooperative Study. *Arch Gen Psychiat* **40**:851–4.

Mark TL, Kranzler HR, Song X, *et al.* (2003) Physicians' opinions about medications to treat alcoholism. *Addiction* **98**:617–26.

Milton J, Solodkin A, Hlustík P, *et al.* (2007) The mind of expert motor performance is cool and focused. *Neuroimage* **35**:804–13.

Poulsen EH, Loft S, Andersen JR, *et al.* (1992) Disulfiram therapy; adverse drug reactions and interactions. *Acta Psych Scand Suppl* **86**:59–66.

Ross JS, Tkach J, Ruggieri PM, *et al.* (2003) The mind's eye: functional MR imaging evaluation of golf motor imagery. *Am J Neuroradiol* **24**: 1036–44.

Sereny G, Sharma V, Holt J, *et al.* (1986) Mandatory supervised Antabuse therapy in an out-patient alcoholism program: a study. *Alcohol Clin Exp Res* **10**:290–2.

Sheldon B. (2011) *Cognitive-Behavioural Therapy; Chap. 4 Learning Theory and Research*. London: Routledge, 89–135.

Shepherd JP. (2001) Criminal deterrence as a public health strategy. *Lancet* **358**:1717–22.

Sherman A. (1972) Real life exposure as a primary therapeutic factor in the desensitisation treatment of fear. *J Abnorm Psychol* **79**:19–28.

Simpson SH, Eurich DT, Majumdar SR, *et al.* (2006) A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* **333**:15.

Skinner MD, Lahmek P, Pham H, *et al.* (2014) Disulfiram efficacy in the treatment of alcohol dependence: a meta analysis. *Plos One* **9**:e87366.

Stern R, Marks I. (1973) Brief and prolonged flooding: a comparison of phobic patients. *Arch Gen Psychiat* **28**:270–6.

Sun F, Tsuritani I, Yamada Y. (2002) Contribution of genetic polymorphisms in ethanol-metabolizing enzymes to problem drinking behavior in middle-aged Japanese men. *Behav Genet* **32**:229–36.

Swedish Council on Technology Assessment in Health Care (SBU). (2002) Treatment of alcohol and drug abuse: an evidence-based review. *Int J Technol Assess Health Care* **18**:145–54.

Thorens G, Manghi R, Khan R, *et al.* (2010) Le disulfirame, un traitement? Soyons logique. Deuxieme partie: Le disulfirame, peut-il etre considere comme un traitement psychologique? (Is disulfiram really a treatment? Let's be logical. Part 2. Can disulfiram be considered a psychological treatment?). *Rev Med Suisse* **10**:584–7.

Walton MA, Castro FG, Barrington EH. (1994) The role of attributions in abstinence, lapse, and relapse following substance abuse treatment. *Addict Behav* **19**:319–31.

Wilson C, Willis C, Hendrikz JK, *et al.* (2010) Speed cameras for the prevention of road traffic injuries and deaths. *Cochrane Database Syst Rev* **10**:CD004607.

Yoshimura A, Kimura M, Nakayama H, *et al.* (2014) Efficacy of disulfiram for the treatment of alcohol dependence assessed with a multicenter randomized controlled trial. *Alcohol Clin Exp Res* **38**:572–8.

Zullino D, Wullschleger A, Thorens G, *et al.* (2010) Le disulfirame, un traitement? Soyons logique. Premiere partie: Le disulfirame, peut-il etre considere comme un traitement phamacologique? (Is disulfiram really a treatment? Let's be logical. Can disulfiram be considered a pharmacological treatment. Part 1. *Rev Med Suisse* **10**:565–7.