DRUG & ALCOHOL FINDINGS *Matrix cell*

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Alcohol Treatment Matrix cell A3

Interventions; Medical treatment

Seminal and key studies and reviews on the effectiveness of medical interventions and treatment in medical settings.

S Seminal studies **K** Key studies **R** Reviews **G** Guidance **MORE** Search for more studies

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S Handing patients responsibility matches extended treatment (1977). Effectiveness Bank essay includes an analysis of a mould-breaking study in London which found a brief session handing responsibility to the couple to overcome the husband's dependent drinking worked as well as extended treatment (which generally involved medications). See also this retrospective (2015) from a study researcher. Similar Scottish study later found (1988) more evidence for extended treatment, but still no statistically significant advantage over brief advice. For discussion click and scroll down to highlighted heading.

S Offenders prefer disulfiram-enforced abstinence to a return to prison (1966). Conducted in early-'60s USA, the first test of whether problem-drinking offenders can be pressured to take a drug which enforces abstinence by generating deterrent reactions to alcohol. Among offenders for whom sanctions had repeatedly proved ineffective, the prospect of yet another spell in prison provided the motivation to take the medication witnessed by their probation officers, which seems to have provided about 6 in 10 with the prop they needed to avoid drinking. For related discussion click and scroll down to highlighted heading.

S Disulfiram only works with compliant patients (1986). Despite overall negative findings, from the USA the first rigorous trial of the medication which causes deterrent physical reactions after drinking found that it helped some older and more socially stable patients who completed the study to drink less frequently after lapsing. The study became seen as confirming the need to supervise disulfiram's administration so more patients took more of the pills. For discussions click here and here and scroll down to highlighted heading or text.

S Impressive results from first clinical trial of acamprosate (1985). Three months later the success rate among alcohol-dependent patients detoxified and discharged from a French inpatient unit was 61% if they had been randomly allocated to acamprosate versus 32% on placebo. It was a notable result among severely dependent patients with a record of failed treatments.

S Benzodiazepines best withdrawal treatment (1969). Study which clarified the dangerous confusion over how to prevent the life-threatening complications of alcohol withdrawal.

K Acamprosate fails for UK patients (2000). Despite positive findings elsewhere, large UK trial did not find acamprosate prevented relapse among detoxified alcoholics. The findings highlighted the importance of an accompanying support programme to help keep patients in treatment and taking the pills, and also perhaps the type of patients – steady drinkers rather than the study's 'bingers' – who respond best to the acamprosate. For discussion click and scroll down to highlighted passage.

K Supervised disulfiram works in Britain (1992). In the major UK trial, disulfiram significantly reduced drinking by nearly 10 UK units a day relative to a vitamin-pill placebo, though effects waned over the prescribing period. For the researchers their results showed the importance of supervising consumption and making patients aware of the potential consequences of drinking while taking disulfiram. For discussion click and scroll down to highlighted passage. For related discussion click and scroll down to highlighted heading.

K Naltrexone works in the UK among patients who take the pills (2000). Among patients randomly allocated to naltrexone versus a placebo in conditions typical of British alcohol treatment clinics, the active medication was associated with reduced drinking, craving, and need for treatment at the end of the 12-week prescribing period, but these results were rarely statistically significant. Naltrexone's advantages were more clear among the 'compliant' minority (just 40%) who stayed in the study and in treatment and took at least 8 in 10 of their active or dummy tablets. For discussion click and scroll down to highlighted passage.

K In the USA, naltrexone boosted the impact of primary care treatment (2006). In the large US 'COMBINE' trial, supplementing medication plus primary care-style care with psychological therapy elevated drinking outcomes on a placebo to those of the most effective trial medications. Without therapy, naltrexone boosted outcomes to about the same degree, but acamprosate was not found to improve outcomes. Results of this and another US trial supported prescribing naltrexone in primary care-based treatment with relatively compliant patients but also suggested that psychological therapy can match medication's effects. Partial replication in Germany listed below. For discussion click

and scroll down to highlighted heading.

K In Germany, naltrexone was not shown to boost the impact of primary care treatment (2012). Closely replicated the US COMBINE trial listed above but did not test psychological therapy. Unlike in the USA, did not find that supplementing primary care with naltrexone (or acamprosate) improved on a placebo, perhaps because the patients in Germany were more severely dependent, came directly from inpatient detoxification wards, and were already about 20 days abstinent. Supported by long-term outpatient medical care, they may have been progressing as well as they would do, regardless of medication. For discussion click and scroll down to highlighted heading.

R Full range of medical treatment expertly assessed (2017; free source at the time of writing). A review from a task force of the World Federation of Societies of Biological Psychiatry offers a well-evidenced overview of psychosocial, pharmacological and other medical treatments for alcohol dependence and also for co-occurring psychiatric conditions.

R The power of the placebo (2013; free source at time of writing). Across relevant trials, end-of-treatment improvements in alcohol patients randomly allocated to an inactive placebo preparation on average dwarfed estimates (for which see following reviews) of additional benefits due to the preparation being an active medication. For related discussion click and scroll down to highlighted heading.

R Evidence strongest for acamprosate and oral naltrexone (2014; also available as a journal article). Report amalgamates findings from 123 trials of the full range of medications when prescribed for at least 12 weeks. Evidence for reduced drinking was strongest for acamprosate and oral naltrexone, though health improvements were unclear. The few head-to-head comparisons yielded no significant differences between the two medications, but other reviews listed below have found minor differences. Confined to 'double-blind' trials, the review did not offer a practice-relevant evaluation of disulfiram, which requires the patient knows what they have been prescribed; instead see review below.

R Prescribing in primary care and general medicine (2011). Based on studies offering minimal psychosocial support, recommends oral naltrexone, topiramate or (with abstinent patients) acamprosate – and given supervised consumption and motivated, abstinent patients, also disulfiram. Medication should be accompanied by support to promote compliance with treatment. However, not too much can be expected; even when little other support was provided, improvements due to medication were "modest". For related discussion click and scroll down to highlighted heading.

R Who benefits most from naltrexone versus acamprosate? (2013). Amalgamated findings from randomised trials comparing each to a placebo or to each other indicated that overall naltrexone was best for patients who want to reduce heavy drinking, acamprosate for those seeking abstinence, findings confirmed by a different kind of analysis (2014; free source at time of writing). Another review (2015) did not find evidence that the medications' impacts differed between European and (mainly) US caseloads. In all three reviews, differences between the medications were slight as were their effects compared to placebo, and individual trials often failed to find benefits. For related discussion click and scroll down to highlighted heading.

R Authoritative analysis finds modest benefits from UK's most commonly prescribed medication for dependent drinking (2010). Amalgamated findings on acamprosate (the most popular pharmacotherapy for alcohol dependence in the UK; 1 2) from the Cochrane collaboration, whose work is often relied on to inform national policy and guidelines. Found that the medication offers worthwhile if modest benefits in preventing drinking after detoxification. Another Cochrane review on naltrexone (2010) and allied medications found inconsistent and generally small effects. For related discussion click and scroll down to highlighted heading.

R Disulfiram needs supervised consumption and patient awareness (2014). Amalgamated findings indicate that disulfiram substantially improves on alternatives or a placebo when (and on average, only when) compliance is bolstered by supervising administration and patients know they are taking a drug which causes unpleasant reactions if they drink. Given the careful patient selection typical of research trials, disulfiram has not been associated with excess deaths or serious adverse events. Different kind of analysis (2011) confirmed findings on supervised consumption. For related discussions click here and here and scroll down to highlighted headings.

R Antiepileptic medication more effective than standard pharmacotherapies (2014; free source at time of writing). Amalgamating the limited research on topiramate suggests it reduces drinking more than naltrexone and acamprosate. Review listed above agrees, but highlights topiramate's undesirable side effects, said to (2014; free source at time of writing) limit its clinical utility. However, a textbook (2014) on addiction medication says these are generally mild or moderate, and that topiramate is among "the most promising agents that directly reduce alcohol consumption". In the UK topiramate is not licensed for treating dependent drinking.

R How to help ensure patients take the pills (2004). Because the reasons why alcohol treatment patients skip their medication are varied, so too must be ways to address this, from reducing side-effects and adjusting dose to compliance-enhancing counselling and enrolling the family. For discussion click and scroll down to highlighted heading.

R Benzodiazepines make withdrawal safer and easier (2010). Rigorous review and synthesis of randomised trials confirms the superiority of benzodiazepines for controlling the potentially serious medical consequences (especially seizures) of withdrawing from dependent drinking.

R Motivational interviewing is for medics too (2013). Reviews randomised trials of this popular counselling style (which importantly for non-specialist settings, lends itself to brevity) as applied typically for patients seeking treatment for physical illnesses affected by the behaviours (such as substance use) targeted by counselling. Concludes that "if you can devote a small amount of extra time with your patients to build relationship and evoke change talk, you can expect

10–15% additional improvement". Impacts on problem drinking were among the strongest. Related review (2014; free source at time of writing) focused on primary care. Overall motivational interviewing generated positive behaviour change (mostly in substance use) relative to usual care.

R Psychological therapies improve on usual care for depressed drinkers (2014). Amalgamated findings show that psychological therapies based on cognitive-behavioural principles and/or motivational interviewing modestly but significantly improve on usual care (typically counselling and/or medication) for depressed problem drinkers, further ameliorating both depression and drinking.

G Official English guidelines on treating harmful drinking and alcohol dependence (National Institute for Health and Care Excellence [NICE], 2011). Britain's gatekeeper to the public provision of health care interventions recommends considering acamprosate or naltrexone after withdrawal, but relegates disulfiram to a second-line option. Treatment and care should take account of the individual's needs and preferences. See also Scottish primary care guidelines (2004). For discussions click here and here and scroll down to highlighted headings.

G Treating withdrawal (Royal College of Physicians, 2010). Guidance developed for the UK's National Institute for Health and Care Excellence (gatekeeper to the public provision of health care interventions) on medical care of patients suffering alcohol-related ill-health conditions, including acute withdrawal.

G Assessment and management of alcohol use disorders (2015). Focuses on practical aspects from the perspective of the non-specialist hospital doctor or general practitioner. Structured around clinical guidelines developed by the National Institute for Health and Care Excellence, the UK's gatekeeper to the public provision of health care interventions. Authorship team led by the substance use treatment specialist later to become the UK government's 'recovery champion'. For discussion click and scroll down to highlighted text.

G US consensus clinical guidelines ([US] Substance Abuse and Mental Health Services Administration, 2009). From experts convened by the US health department, how approved medications in both the USA and the UK (acamprosate; oral and injectable naltrexone; disulfiram) can be incorporated into medical practice, including choosing suitable patients.

G Treating severe mental illness and co-occurring substance use (National Institute for Health and Care Excellence [NICE], 2016). Guidelines from the UK's gatekeeper to the public provision of health care interventions on how to improve services for people aged 14 and above diagnosed with both severe mental illness and substance use problems. Another guideline (NICE, 2011) has dealt specifically with psychosis and substance use problems. Both are reflected in NICE quality standards (NICE, 2019).

G Treating substance use service clients with mental health problems ([Australian] National Drug and Alcohol Research Centre, 2016). Funded by the Australian government; recommends services screen all patients for mental health problems and that mental illness should not be a barrier to treating substance use problems. Research shows these patients can benefit as much as others from routine treatments for problem drinking.

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What is this cell about? About the treatment of alcohol dependence in a medical context and/or involving medical care, typically by GPs or by alcohol treatment or psychiatric units in hospitals. Clinical staff are responsible for medications, so the centrality of these to an intervention distinguishes it most clearly as medical. Drugs (primarily benzodiazepines) help patients withdraw from alcohol more comfortably and safely, but of greater interest in the current context are the medications (primarily in the UK acamprosate, but also naltrexone and disulfiram; 1 2) intended to tackle dependence itself by sustaining post-detoxification abstinence or promoting abstinence or moderate drinking. An interesting history (2014; free source at time of writing) of pharmacotherapy for problem drinking records that the modern era of these treatments began with the evaluation in 1948 of disulfiram's power to make subsequent drinking an unpleasant experience.

However, medications are never all there is to medical care. Typically guidelines see psychosocial support as an essential accompaniment, and 'medical' treatment may consist entirely of advice and psychosocial support from clinicians. When they are prescribed, the role of medications is usually to help forge a relatively alcohol-free space during which patients can lose the habit of regular drinking, be supported to find other ways to cope, and construct a life incompatible with a return to dependent drinking. Even if there is no formal psychosocial therapy, medication-based treatments also entail potentially therapeutic interactions with prescribers and other staff. Arrangements or programmes to help ensure patients take the medications may themselves be therapeutic, and provide a 'hook' on which to enlist family and other associates in the patient's recovery. Without these supports, any benefits of medication may be lost once the medication phase of treatment ends. All these approaches have been succinctly summarised in guidance listed above for the non-specialist clinician, which along the way provides an overview of recommended medical treatments for drink problems in the UK.

Though use of alcohol-treatment medication has been increasing in the UK, treatment usually still consists entirely of advice and support. Drugs are almost universally used to ease withdrawal in inpatient units, but in 2018/19 in England in non-residential community settings or primary care, of the 73,556 drinkers not also being treated for drug dependence just 19% were prescribed medication; specifically in primary care, the only identifiably medical setting, it was 47%. As we'll see later in this commentary, relegation of medications to a minority option seems to reflect their generally minor effects relative to the other influences which constellate into what is misleadingly dismissed as the 'placebo effect', to which a section is devoted below. For this 'disease', medications usually add little (but on average, *do* add a little) to the patient's impetus to get better, the processes in their life which help them realise and sustain this ambition, and the impact of deciding to enter and get actively engaged in treatment, one manifestation of which is regularly taking medication.

Where should I start? Exemplifying that last point is a seminal study from England listed above, which questioned the orthodoxy of the time that alcoholism requires intensive treatment. Griffith Edwards and colleagues found that male alcoholics (accompanied by their wives) seen by a psychiatrist-led team at an alcohol clinic did as well after a single brief session as after fully fledged treatment, which for about two-thirds of patients included medications in the form of calcium cyanamide, a drug which causes unpleasant physical reactions to subsequent drinking. Looking back over nearly 40 years, a researcher on the study interpreted the results (document listed above) as meaning formal treatment had been less important than aspects of the process shared by both sets of couples regardless of the intensity and extensity of the treatment: "all the negotiations and arguments that must have gone on between husband and wife prior to and after the visit to the [GP]; the referral to a psychiatric hospital and the wait for the appointment letter; the whole morning spent going over one's drinking and one's marriage with a group of expert strangers; the unequivocal advice, delivered in the presence of one's spouse; ... knowing that the hospital was keeping a watching brief and that questions were being asked about your behaviour every month and that you would be asked to account for yourself at the year's end".

A similar study in Scotland (listed above) included patients randomly allocated to just five minutes of advice, up to one hour, or fully fledged extended treatment, which in this case rarely involved medications. Two years later 58% of the extended-treatment patients were abstinent or trouble-free drinkers compared to 39% of the two advice groups, a difference which verged on the statistically significant. It seemed to be largely due to a significantly greater reduction in alcohol-related problems rather than drinking itself, which was substantially reduced in both advice and extended-treatment patients. For several reasons the

advantage gained by extended treatment was probably greater than the results suggest, but still the improvements in patients given the briefest of interventions was considerable. Speculating on the causes, the researchers highlighted the "unequivocal diagnosis and … injunction to abstain" or "the decision of the patient to do something about his drinking" – or both, since the "injunction" explicitly left their recovery up to the patient.

In both studies we seem to see in action the "patient's impetus to get better, the processes in their life which help them realise and sustain this ambition, and the impact of deciding to enter and get actively engaged in treatment" referred to above, influences which could dwarf into statistical insignificance any added value of extending that treatment and supplementing it with a potentially powerful medication.

Highlighted study Actually a trio of studies from the UK's most prominent researcher into medication-based treatments of alcohol dependence, Dr Jonathan Chick of the University of Edinburgh. Dr Chick led the Scottish study of psychosocial treatment summarised in the previous section, but is best known for his major studies on all three of the medications approved for use in the UK to treat alcohol dependence.

Dr Chick evaluated all three of the medications approved for use in the UK to treat alcohol dependence

Published in 1992, his evaluation of disulfiram (listed above) remains the most robust UK foundation for the treatment. A medication which causes very unpleasant reactions to alcohol seems a sure-fire deterrent to repeated drinking, but this and other studies showed that even such powerful treatments rely on the patient's motivation and social support – for disulfiram, especially the relatives and partners who with the patient's agreement help ensure the pills are taken. Nevertheless, for many patients that will not be enough. The study gave disulfiram the advantages of supervised consumption (usually by a spouse), the patients' awareness that they were taking a deterrent drug, and a 'placebo', vitamin-pill comparator which patients were not led to expect would help control their drinking. Whatever they were prescribed, nearly half the patients effectively rejected or dropped out of treatment. Yet even when drop-outs were included in the analysis, over the six-month treatment period disulfiram patients had reduced their drinking days and amounts drunk by significantly and substantially more than placebo patients. In the final month, when many patients must have withdrawn from treatment, extra drinking reductions remained apparent, but were no longer significantly different from that achieved by placebo patients. Still, these results were the most convincing of those yielded by the three studies.

> *Even when it was a placebo, there was a striking gap in abstinence between patients who took their pills and those who did not*

The seminal US disulfiram trial listed above had thrown up a striking finding seemingly nothing to do with the medication's effects – the huge difference in abstinence rates between the minority of patients who largely complied with their treatment and took the pills versus those who were less compliant – *even when those pills were effectively an inactive placebo*, and even when patients knew this was the case. Of the compliant patients, 50% told their placebo was disulfiram (it was an inactive low dose) and 43% told it was a vitamin were abstinent compared to just 9% and 6% of the less compliant patients. Listed above, another study from Dr Chick found that compliance was also important for naltrexone, a medication intended to moderate rather than block drinking – but this time compliance helped boost the medication's performance relative to a placebo. With generally low social support and no supervised consumption, before the end of the 12 weeks during which naltrexone or a placebo were prescribed nearly 60% of patients had terminated both the study and the treatment early. Despite this degree of loss, across all patients there remained signs that naltrexone had reduced drinking, but the effects were not statistically significant. When the analysis was confined to patients who had largely complied with treatment by

attending all appointments and taking at least 8 in 10 of their pills, relative to a placebo there was still no evidence that naltrexone had delayed a return to drinking, but the extra reduction in the amount subsequently drunk (on average half that in the placebo group) was substantial and statistically significant, seemingly a sign that the experience of drinking on naltrexone was not so 'moreish' as it had been without the drug.

Dr Chick completed the treble with his acamprosate study listed above. Hampered by high drop-out and non-compliance rates (by the end of the six-month trial fewer than 30% of patients were taking at least 90% of their tablets) it found no significant reductions in drinking relative to a placebo.

Results of these three British studies emphasise measures to keep patients in treatment and taking their medication. Well appreciated for disulfiram, the same applies to less absolutist medications like naltrexone and acamprosate, which the British studies cited in this section suggest may also benefit from supervised consumption. Not only does this help ensure pills are taken, but also more deeply involves family and associates in the patient's recovery. The next section addresses this issue directly.

Issues to consider and discuss

▸ If 'compliance' is crucial, how *do* we encourage patients to take the pills? No single or best way, concluded a comprehensive review listed above. A basic strategy stressed by UK guidelines listed above is to build a trusting relationship with patients and relate to them in a supportive, empathic and non-judgmental manner. Any qualified practitioner can prescribe anti-drinking medications, but it takes particular skills and qualities to give patients confidence in the treatment, encourage them to take the medication, and to maximise its effects. Improving client-clinician relationships addresses some but not all of the reasons for non-compliance. Patients may skip doses because of side-effects, because they do not feel they have a problem, don't believe the medication is doing any good, are overcome by cravings, simply forget, are disorganised (perhaps by intoxication), or lack the right kind of support from family or associates – and so on!

Note that some of these reasons may be 'legitimate' – and not just from the patient's point of view. Side-effects *can* be distressing or life-diminishing, conceivably some patients' problems (UK guidelines have recommended medications for non-dependent alcohol 'abusers') *do not* warrant taking side-effect producing pills several times a day, and often medications *do not* help. Another reason to pause before taking strong measures to promote compliance is that diligent pill-taking may be a *marker* of a pre-existing good prognosis rather than a cause of that prognosis. This is almost certainly part of the reason why even with an inactive placebo, good compliance is associated with good outcomes – as in the seminal US disulfiram trial referred to above. Good compliers may tend to be diligent, health-conscious and well-organised people, traits likely to facilitate recovery from any illness, condition or misfortune. If this is the case, 'artificially' boosting compliance will not improve outcomes to the degree expected from how well naturally good compliers do in research trials. On the other hand, even highly effective medications cannot exert their effects unless they are taken.

Given these considerations, how far should we go to overcome resistance to regularly taking pills: offer inducements for complying, impose sanctions for not complying? As a last-ditch measure, criminal justice sanctions have been tried with some success in Britain to persuade offenders otherwise facing several months in prison to take disulfiram to reduce their alcohol-related offending. Loss of employment or professional status and 'tough-love' pressure are other tactics. As long as the patient is free to refuse and does not suffer sanctions simply for refusing, everyone can benefit: offenders avoid prison; prisons are relieved of some pressure; public money is saved; doctors facing being struck off can practice; their patients continue to be treated by them; employees can continue to contribute to their work and to society; and families are preserved.

Such benefits depend on how far medications really do protect patients and others from the serious consequences of continued heavy drinking, and that in turn depends on patients taking their medication. However, with naltrexone it is possible at least for a month or so to ensure the drug is active and take patient choice out of the equation by irreversibly injecting a long-acting formulation of the drug. It can help some patients cut down their drinking, as in this freely available pilot study (2005). But there is a downside; in this trial, at least a third of full-dose patients experienced side-effects, and if they had needed opiate-based pain relief, it would have been blocked by the injection. Long-acting naltrexone is one of the measures which by improving compliance also seems (2011) to have improved drinking outcomes relative to naltrexone pills taken every day.

Is disulfiram defunct? Of the main medications used to treat dependent drinking, disulfiram ('Antabuse') is the one which most sharply divides opinion: its deterrent effects raise safety and ethical issues, its *modus operandi* taps into conflicting understandings of addiction, and the evidence can be interpreted as supportive or negative, depending on what you think counts as an appropriate methodology.

In the mid-'80s overall negative results from the first rigorous trial (listed above) led the researcher to expect disulfiram prescribing to wither. That did not happen in the USA nor in the UK, but its use has declined and mainstream guidance envisages a more niche role than for other medications. Here we invite you to consider whether this is justified by the evidence or whether more of Britain's dependent drinkers should be benefiting from a medication which makes drinking such an unpleasant experience that – if they take the pills – most will avoid the bottle.

Current status

Disulfiram remains one of the three main medications licensed in the UK for the treatment of alcohol dependence and endorsed in national guidance for Scotland and England and Wales. The other medications are naltrexone (licensed in 2011) and acamprosate, for which the guidance envisages a more routine and/or first-line post-detoxification role than for disulfiram. With disulfiram comes the caution that total abstinence is required to avoid unpleasant and potentially dangerous reactions, and that the positive evidence derives only from situations where consumption has been supervised.

Compared to the main alternative medications, the experts behind the guidance for England and Wales found the evidence for disulfiram "much weaker and the potential for harm was greater [so] did not consider disulfiram as a suitable first-line pharmacological treatment for relapse prevention in individuals with alcohol dependence". They saw the evidence as most supportive of its role among patients who are relatively older, socially stable, highly motivated, enjoy strong home-based or clinical support, especially in the form of someone to supervise consumption, but who are also "impulsive", presumably because taken in the morning the medication deters such patients from acting on a later impulse to drink ▸ panel above right. Even one of the medications's staunchest advocates agrees that naltrexone or acamprosate are more appropriate first-line pharmacotherapy choices, and that disulfiram should be reserved for patients who do not respond well to these or persistently relapse, patients for whom early relapse would have adverse life-changing or potentially fatal consequences, or those who after being appraised of the options, believe disulfiram will work for them and request it. Especially given the inconsistent effects of naltrexone and acamprosate (see section below), this remit would still leaves a large potential patient population for whom trying disulfiram would be appropriate.

What is disulfiram?

From: Edwards G. *et al. The treatment of drinking problems. A guide for helping professions*. 3rd edition. Cambridge University Press, 1997.

Disulfiram blocks the breakdown of alcohol at the acetaldehyde stage by inhibiting the hepatic enzyme aldehyde dehydrogenase. This leads to an accumulation of acetaldehyde in the body and to the disulfiram-ethanol reaction, characterised by flushing of the face and upper trunk, throbbing headache, palpitations, tachycardia, nausea, vomiting, and general distress. With large doses of alcohol, arrhythmias, hypotension and collapse may occur. The reaction usually starts within 10 to 30 minutes of drinking and can last several hours … The rationale of this treatment is that a patient cannot drink while under protective cover of the drug and they will thus only have to make a daily decision to take the medication rather than have to resist the sudden temptation at any moment to drink.

Despite the cautions in the guidance, in 2017 in England disulfiram was dispensed 35,807 times, making it still a substantial player in the treatment of dependent drinking. However, it was well behind the 134,673 prescription items recorded for acamprosate, and disulfiram has been on a downward trend from its peak of 60,842 items dispensed in 2012. In hospitals as opposed to GPs' surgeries, disulfiram used to be dispensed more often than acamprosate. From 2010, an account of its routine and seemingly successful prescribing after detoxification at Leeds' alcohol treatment unit illustrates its place in the medication armoury. However, by 2013 disulfiram's prescribing lead over acamprosate had reversed and after that, even in hospital settings acamprosate was well ahead, by 2017 totalling 3,325 prescriptions to disulfiram's 1,089.

Trends in Scotland were similar, but less pronounced. In terms of patient numbers, acamprosate overtook disulfiram in 2012/13, but even in 2018/19 the gap remained smaller than in England, at 4,235 patients prescribed disulfiram versus 5,647 acamprosate.

Origins … in rubber

Disulfiram can lay claim (2014; free source at time of writing) to being the earliest medication still prescribed for this purpose which specifically targets problem drinking. In the 1800s it was used for an entirely different purpose – vulcanisation in rubber production. Factory workers who absorbed the substance through the skin were found to develop unpleasant symptoms including palpitations, nausea and flushing almost within minutes of drinking. By 1937 the possible therapeutic application of these reactions had been noted, but not until 1948 was disulfiram tested for this purpose after one or two Danish scientists experienced its anti-drinking potential while evaluating it as a medication to expel parasitic worms; after taking it, they became violently ill when they drank cocktails at a party or their evening lager – the details differ in different accounts (1; 2, free source at time of writing).

Rather than solidifying its position in alcohol treatment, this long history has probably contributed to its falling out of fashion, since there remains little money to be made from a medication long past its more lucrative patent-protected period, meaning little industry-funded promotion and research in comparison with newer products.

Staunchest UK advocate

The most consistent and staunchest UK advocate for disulfiram has been the psychiatrist Dr Colin Brewer. His writings on the treatment are used here as hook on which to explore its pros and cons. Appropriately for a controversial medication, Dr Brewer's long and distinguished career in the addictions has itself not been without controversy. In 2006 he ran into serious trouble with the General Medical Council for reasons unrelated to disulfiram, but remained a respected figure in the eyes of some of his professional peers.

Published in 2018, he was first author of the textbook, *Antabuse Treatment for Alcoholism*, an attempt to help reinstate disulfiram to what the authors saw as its rightful prominence in alcohol treatment. A foreword by William Miller, originator of motivational interviewing, depricates the medication's under-utilisation and expresses his pleasure at this "important textbook". As the figurehead for a counselling style predicated on client autonomy and freedom to make (or not make) therapeutic choices, Professor Miller's endorsement is significant for a medication sometimes critiqued as depriving patients of autonomy and choice.

Then at the alcoholism treatment service of Westminster Hospital, Dr Brewer's enthusiasm for disulfiram had been stoked by the results of a study published in 1983 in the *British Medical Journal*, on which he was lead author. It evaluated disulfiram treatment of 18 habitual offenders, typically with a considerable history of alcohol-related convictions. Persuaded by the offer of leniency to try disulfiram, 12 were either completely successful in abstaining or had only brief and comparatively harmless lapses.

Uncompromising physical effects but works through the mind

Together with other experienced clinicians, in 2000 Dr Brewer explained (free source at time of writing) the medication's *modus operandi*. First is the patient's knowledge that disulfiram will cause an unpleasant reaction after drinking. Secondly, "taking disulfiram … has certain symbolic connotations. It tells us that here is a patient who is willing … to surrender some control over his freedom or urge to drink. Such a patient announces both to himself and to the wider world that he is not merely talking about changing his drinking habits … but is actually doing something about it." The final element derives from the need for administration to be supervised if more than a small minority of patients are to benefit, providing "additional opportunities for involving family members in the broader therapeutic and monitoring enterprise." Effective supervision is critical, because without it typically as many as 80% of the tablets will not be taken, undermining the treatment's anti-drinking impact.

As this account makes clear, though disulfiram is uncompromising in its physical effects after drinking, even for this drug, social, cognitive and symbolic influences mediate its effectiveness as a treatment. With another colleague, in 2003 Dr Brewer likened disulfiram treatment to placing language-learners in an environment where resort to their native tongue is in effect barred, and they are forced to communicate and understand in the new language, a 'sink or swim' method which can be rapidly effective. Similarly, taken regularly disulfiram forces the dependent drinker to learn new ways of responding to everyday feelings and situations which used to prompt drinking. Rather than the artificial and limited "drip-feed" of other treatment programmes, the result is to immerse the patient in 24-hours-a-day relearning in the environment where they aim to survive without regular resort to drinking.

Are ethical misgivings justified?

Apart from the equivocal evidence from the first rigorous trial (listed above) , ethical misgivings among some clinicians may have contributed to disulfiram's waning. After all, it works through its capacity to inflict a very unpleasant experience which at the extremes can be dangerous, not a mainstream medical tactic.

Speaking in 2014 at a meeting in Tokyo of the International Society of Addiction Medicine, Dr Brewer stressed that disulfiram worked primarily as a deterrent rather than an aversive medication. The aim was not to inflict unpleasant effects in order to "punish" patients for drinking, but for the prospect of these effects to deter drinking, *avoiding* 'punishment'. In this he reflected the general consensus that patients do not have to experience disulfiram's aversive effects in order for it to prevent drinking. Instead, "expectations following ingestion of disulfiram and the mental anticipation of an aversive interaction with alcohol is decisive". From this perspective, disulfiram shares its ethical and theoretical foundations with other deterrent mechanisms, such as mandatory sobriety checks allied with the threat of immediate brief imprisonment for breeching a court-ordered abstinence requirement or the prospect of losing a valued career, programmes which have attracted considerable support.

In Tokyo Dr Brewer was responding to a survey which showed that Geneva's addiction treatment specialists generally disagreed with their department's decision just under two years before to terminate disulfiram treatment due to what was seen as insufficient evidence. Most of the clinicians whose patients had to stop taking the medication thought they had deteriorated. For this report's authors, the fact that "the perception of disulfiram utility is still strong in Geneva's addictology caregivers" showed that "personal clinical habits" were resistant to scientific evidence, and perhaps too betrayed an attachment to "aversive treatments such as disulfiram". For Dr Brewer, the bulk of the clinicians were right and their critics wrong, both about evidence of effectiveness and disulfiram's ethical credentials.

Showing that what seems alien and artificial is in fact merely an extension of natural mechanisms is one way to disarm concerns. One of Dr Brewer's latest essays (free source at time of writing) on disulfiram was published in 2017 in the journal *Alcohol and Alcoholism*. As he has done consistently, he highlighted nature's 'experiment' in disulfiram-type protection from dependent drinking – the gene shared by a substantial minority of the population of some East Asian countries which, like disulfiram, obstructs the metabolism of alcohol in a way which generates an unpleasant reaction. In Japan, it means dependent drinking is very rare among this section of the population, especially those who inherited the characteristic from both parents.

A chemical handcuff?

But the main contribution of the paper is its consideration of the ethical dimensions of supervised consumption of disulfiram. Central to the argument is that substance dependence is not so disabling that patients are unable to make rational choices in their best interests, a view shared by some of the field's leading ethicists. Among these choices may be the decision to collaborate with clinicians and whoever is supervising their disulfiram consumption to achieve the shared aim of suppressing drinking and learning to live without regular resort to inebriation. At any time the patient can decide they would prefer to drink and abandon the treatment, but have to accept the consequences, which for some offenders might include reversion to a harsher sentence. The essay in which these and other arguments were made is freely available and accessibly written; we suggest you read it and ask yourself if you are convinced, or feel disulfiram blockade is too controlling a measure, which offers the opportunity to arm-twist patients into a Hobson's-choice acquiescence.

A related ethical concern is that the treatment illiberally 'handcuffs' patients into abstinence. Indeed, some guidelines insist that total abstinence is the only appropriate objective for disulfiram patients, and that its effects mean that during treatment they must stay abstinent. However, clinical experience and a little research indicate otherwise. Rather than taking it continuously to maintain a blockade against drinking, reviewers have suggested patients could take the medication 'as needed', and this need not necessarily be with a view to sustaining total abstinence.

In 1987 the ways this might work were documented in a report on patients in Norway recruited for a trial of minimal versus more intensive treatment, who could also choose whether to take disulfiram. Only about a third were aiming for abstinence. Some who chose the medication and took it 'as needed' did so to sustain abstinence by countering urges or to cope with high-risk situations. However, others deliberately took it in a way which permitted some drinking, for example at weekends but not on workdays, or only on special occasions, while others used it during stressful periods or to stop a drinking episode turning into an extended 'binge'. Followed up 15–21 months after starting treatment, on average disulfiram patients had sustainably more than halved their alcohol consumption. The researchers

commented, “the majority of our patients did not want lifelong abstinence, but wished to have as their goal some form of reduced consumption. Our results indicate that also for these people Antabuse could be a helpful device in securing adherence to their reduced drinking goals.”

Undisciplined past stokes concerns over safety

Beyond ethics, doubts about disulfiram have other roots. One dealt with only briefly here is its safety, a prominent consideration because – very rarely and almost exclusively in the past – its effects have proved fatal. Safety concerns linger in the record and perhaps too in the consciousness of clinicians from the days more cautious dosing and patient selection and monitoring had yet to be developed. But by 1999, Dr Jonathan Chick, the UK’s foremost researcher into pharmacotherapies for alcohol dependence (see above), was able to contrast the medication’s “moderate record of adverse effect” with the “high morbidity and mortality” it can help prevent by interrupting dangerously heavy drinking. In particular, probably due to more restrained dosing and exclusion of patients at special risk, “There have been no reports of death due to the disulfiram-alcohol interaction in recent years”, while “Serious hepatotoxicity and neuropathy probably occur at less than 1 case per 10,000 patients per year.” Nine years later a US team reassessed safety (free source at the time of writing) in the context of treating cocaine dependence, including cases complicated by dependent drinking. Their verdict was, “When patients are screened for medical and psychiatric stability, and are evaluated for drug interactions, disulfiram has an acceptable side-effect profile.” Especially if reserved for last-ditch cases facing life-changing or life-ending consequences and/or severely dependent drinkers for whom less constraining treatments have failed, its risks in careful hands pale in comparison to unfettered alcohol addiction.

Only a short-term fix?

Safety is critical to practice, but of greater theoretical interest is the argument that while ‘drip-feed’, clinic-based therapy may be artificial, so too is learning to live without depending on drink while constrained by disulfiram. Even if this learning takes place 24 hours a day in the patient’s natural environment, consumption may resume once that constraint is removed, because they have not learnt to *themselves* control their drinking, merely to *have it* controlled by the medication. Also suggesting effects will be short-lived is the presumption that underlying problems not addressed by taking an anti-alcohol medication will re-express themselves in drinking once disulfiram is stopped.

A theory-based rejoinder (explored in cell D2) to concerns that disulfiram’s effects will be short-lived is that this would simply show the medication is effective, and that it is the role of longer term continuing care or aftercare to build on the sober space it created. Another is that while dependence may be sustained by unresolved underlying problems, for others it may simply be an ingrained habit or a way of dealing with current circumstances – and that if there are underlying problems, supervised disulfiram will aid psychotherapy by enabling those problems to be exposed and addressed during a period of sobriety (1; 2, free source at the time of writing).

In practice, a German study (2006) suggested that disulfiram’s impact can last. It evaluated intensive two-year treatment of severely dependent drinkers using another deterrent medication followed by disulfiram. The result was high rates of long-term abstinence, outlasting the treatment period by seven years. In this study, joined by under half the patients who were asked and were eligible, administration was supervised by clinic staff, and few patients dropped out of treatment, perhaps spurred on by what were usually serious medical consequences of highly excessive drinking.

The results highlighted disulfiram’s psychological rather than pharmacological mechanisms of action. On safety grounds a few patients were prescribed inactive pills but told they were a form of ‘Antabuse’; they fared at least as well as patients prescribed deterrent medication. What these psychological mechanisms were has been speculated on by the study’s authors: “patients learned to use disulfiram as a successful coping skill to prevent relapse and … replaced the alcohol deterrent during psychotherapy by a broad spectrum of alternative behavior including participation in self-help groups and lifelong checkup sessions”. However, with no randomly allocated comparison group offered all the therapy elements *except* deterrent medication, this optimistic account is merely consistent with rather than proved by the findings. Whether impacts would have lasted just as well if disulfiram had not been part of the therapeutic mix cannot be determined by the study, though the unpromising nature of the patients suggests this would have been unlikely. Despite multiple problems including mental illness and unemployment, severe and longstanding dependence, and repeated detoxification and relapse, they achieved what would normally be considered enviable reductions in drinking.

What counts as the most reliable evidence?

If results from the first rigorous trial were equivocal, what of the accumulated evidence of effectiveness to date? Clinicians and patients who advocate for disulfiram have support from reviews (listed above: 1 2) published in 2011 and 2014 which found it more effective at curbing drinking than other medications, as long as consumption was supervised.

One of the reviews listed above offered a particularly sophisticated analysis, dividing trials into those which did or did not supervise consumption, and those whose patients (as well as researchers and doctors) were not told who was taking disulfiram ('double-blind') versus when patients knew they were taking a medication which would cause unpleasant reactions if they drank. The results showed that the 'gold standard' double-blind methodology robbed disulfiram of its main active ingredient – the expectation of a nasty reaction if one returns to drinking – and that as well as this knowledge, patients usually need someone to bolster their resolve by making sure they take the pills. Given these circumstances, disulfiram not only substantially bettered a placebo in reducing drinking at the end of the treatment period, but in head-to-head trials also substantially and significantly bettered naltrexone and acamprosate and (there was only one such trial) topiramate.

> *The 'gold standard' double-blind methodology robs disulfiram of its main active ingredient*

Then take a look at the other review listed above and in particular at our commentary on its findings. In it we queried whether disulfiram had been advantaged over other drugs by the use of abstinence as an outcome – one targeted by disulfiram but less so by acamprosate and naltrexone – and the relevance to the UK context of findings in India supportive of the medication which substantially contributed to the overall impression of effectiveness. Note also that on the other hand, British trials have found disulfiram effective, but acamprosate not.

Where do you stand?

With this information at your disposal, do you think the National Institute for Health and Care Excellence (NICE, the UK's authority on medical treatments) was right to say disulfiram (document listed above) should normally only be considered when acamprosate or oral naltrexone are not suitable? Burrow through their report, and you will see that apart from safety concerns, their rationale was that the evidence was weaker than for other drugs, which in turn was due to the lack of 'double-blind' trials – those in which neither patients nor research assessors know who has taken what. One set of disulfiram's reviewers dismissed (document listed above) such concerns as "meaningless", because the main active ingredient of the treatment is precisely that patients know they have taken a drug which will cause a nasty reaction if they drink.

After making your judgement, you may find yourself agreeing with one or other side of a deep divide in academic and expert opinion: one side sees disulfiram as a poorly evidenced and risky option best kept in reserve; another advocates its more widespread use, arguing that though it needs careful monitoring and usually supervised administration, among patients who will tolerate this option, it is acceptably safe, and at least as effective as other medications. Underlying some of the divergence over disulfiram are differences in understandings of alcohol dependence. According to one view, the treatment merely temporarily suppresses drinking without "target[ing] the core phenomenon of alcohol dependence". Understanding dependent drinking as a learnt reaction to certain cues, another view is that the treatment precisely targets that core by forcing a dislocation between those cues and drinking which with repetition can become cemented, underpinning the construction of an alcohol-free way of living. You might profitably reflect on whether your predispositions with respect to the treatment derive from your understanding of addiction, of the evidence, or from a distaste for versus an appreciation of the utility of deterrence.

▸ **The placebo effect *is* the main active ingredient** Reviews listed above testify to the fact that when the scales are evened out by a randomised trial, commonly used medications have only a modest impact on drinking relative to a pharmacologically inactive placebo (1 2 3 4 5). Disulfiram is a partial exception; in the special circumstances when doses can be and are effectively supervised to make sure pills are taken, effects verge (document listed above) on what is conventionally considered a large impact.

Modest and inconsistent effects mean that most patients do almost or just as well if offered a placebo instead of these medications. We can get a feel for how closely the placebo effect matches that of an active medication from an amalgamation of research on naltrexone and acamprosate listed above. It found that six months after treatment started, 77% of placebo patients had lapsed to drinking compared

to 65% prescribed acamprosate. Three months after treatment started the corresponding figures for naltrexone were 71% and 65%, while for relapse to heavy drinking they were 59% versus 50%. In each case these raw figures amounted to a statistically significant advantage for the medications, but a slight one which in individual trials often failed to materialise.

Usually research and reviews focus on the medication, but one revealing analysis listed above instead focused on the placebos against which alcohol medications have been benchmarked. Across relevant trials, improvements among alcohol patients randomly allocated to an inactive placebo on average dwarfed those attributable to the additional effects of an active medication. The more severe the dependence, the greater was the improvement among placebo patients, and the greater that improvement, the less was gained by prescribing an active medication.

Unusually, the large US COMBINE study listed above directly tested the power of a placebo by including a set of patients allocated to sophisticated psychosocial therapy with neither an active nor a dummy medication. Their abstinence record was significantly worse (67% v. 74% days abstinent) than patients not offered therapy but allocated to medical care plus a placebo. It seemed an inactive medication could not just match the effect of psychosocial therapy, but do better – a testimony to the power of the placebo effect either (as the authors speculated) in a positive form as a response to being prescribed what looks like medication, or in a negative form as disappointment at receiving no medication. "Somewhat unexpectedly," said the researchers, "we observed a positive effect of receiving placebo medication and medical management over and above that seen with specialist-delivered behavioural therapy alone." In a partial replication of this trial in Germany (listed above), patients receiving medical care with no psychosocial therapy actually did slightly (but not significantly) better when prescribed a placebo than when prescribed either acamprosate or naltrexone. Though large in randomised trials of this kind, placebo effects might be larger still normal practice, because in trials patients are normally told they stand a 1 in 2 chance of being prescribed an inactive placebo, dampening expectations that the pills will work.

What the 'placebo effect' consists of has yet to be adequately unpacked, but it is almost certainly far more than a reaction to taking a pill. Some of the apparent effect will be natural remission, but the fact that the more often a placebo is scheduled to be taken, the greater the reduction in drinking (document listed above), suggests that social and psychological influences associated with being actively engaged in treatment might mediate much of the effects of medications. The impact of engaging in a treatment understood in that culture to help 'cure' the condition is one the 'common factors' underlying effective treatment explored in cell A2. In Western societies, taking a medicine is perhaps the prime culturally endorsed way to signal the existence of a curable condition and to cure it.

> *The 'placebo effect' is almost certainly far more than a reaction to taking a pill*

Another factor is how the clinician relates to the patient. A signal of this influence emerged in a spin-off analysis from the COMBINE alcohol treatment trial, the main results from which are listed above. The analysis was confined to the arms of the trial which provided medical care only plus real or dummy medication. Doctor who according to observers credibly conveyed optimism about recovery and confidence in the medical programme – but were also prepared to be flexible in its delivery – had patients who actually did more fully recover. You will find more on relationship issues in cell B3.

These findings should come as no surprise. Across medicine, when a condition is susceptible to expectations (such as depression and pain for example, but not the cancer which may be causing these), placebo effects rival those of active medications, and do so partly because the context, the clinician's words and attitudes, and the expectations of the patient induce biochemical effects which can mimic those of medications, including generation of the body's natural opiate-type chemicals. Doctors appreciate these benefits, and the prescribing or administration of placebos is common in clinical practice.

Once we accept the frequency, reality and benefits of placebo effects, it then becomes legitimate to search for ways to enhance these effects. That placebo effects are manipulable has been demonstrated, for example in a study of dummy tablets administered to students, ostensibly to help curb anxiety about examinations. When a pretend participant in the study said in the hearing of a real participant that the tablets had calmed and relaxed them and slowed their heart rate, these same effects were stronger in the real participant than if the stooge had said they felt no different. In medication-based treatment of physical as well as mental complaints, the physician's enthusiasm for and confidence in the therapy can potentiate improvements in response to a placebo as well as to real medication. As explored in cell B2, such effects can be subtly influenced by the doctor's and patient's attitudes and expectations, the doctor's warmth, and the professional impression given by the clinic environment.

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Raistrick, Co-Director of RESULT. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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