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Substitution therapy for alcoholism: time for a reappraisal?

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Abstract

A number of compounds already in use as medications for various indications substitute for ethanol at clinically relevant brain pathways, in particular, at gamma-aminobutyric acid (GABA) receptors. Nevertheless, although substitute medications have been recognized for heroin and tobacco dependence, patients with alcohol dependence are rarely offered an analogous approach. Benzodiazepines may have paradoxical effects, and abuse and dependence are known. Baclofen ($GABA_B$ agonist) has not been associated with dependence or misuse and has been effective in several trials in preventing relapse, although research is required to establish the optimal dosing regimen. GABA-ergic anticonvulsants, helpful in treating withdrawal, have yet to emerge as effective in relapse prevention. Clomethiazole and sodium oxybate, the latter having been shown to be effective in relapse prevention, have incurred a reputation for dependence and abuse. However, data have emerged showing that the risk of abuse of sodium oxybate is lower than many clinicians had foreseen. For a condition where existing therapies are only effective in a proportion of patients, and which has high morbidity and mortality, the time now seems right for reappraising the use of substitute prescribing for alcohol dependence.

Keywords

Alcohol, alcohol dependence, baclofen, benzodiazepines, $GABA_A$ receptors, $GABA_B$ receptors, GHB, sodium oxybate, substitution therapy

Introduction

Substitution or maintenance therapy for some forms of drug dependence has been used for centuries and is well established since the 1950s when heroin was prescribed in the UK for addicts and methadone became popular in the USA. More recently tobacco smoking has been successfully reduced by making available substitution nicotine in the form of patches or lozenges – initially on prescription but now direct from pharmacists. Substitution therapy can be defined as a medication that has one or more of the pharmacological effects of the substance that are believed to be relevant to the addiction. Substitutes are generally effective in preventing withdrawal from the abused drug and usually reduce craving and the desire to use as well. For these reasons they are often liked by the patients and this can lead to long term use. Whether this is a problem or a desired outcome is the subject of intense debate but where such drugs are licensed then proof of their value reducing harms has been established, as for example for opioid dependence.

However, for drugs other than opioids and tobacco the use of substitutes has developed more slowly. This is partly due to the lack of available substitution drugs but more importantly because society and the medical/pharmaceutical professions have not viewed some addictions as being suitable for such interventions. Thus cannabis is not prescribed for cannabis dependence nor cocaine or methylamphetamine for stimulant users although there are limited randomized controlled trials published on substitute prescribing for stimulant dependence syndrome using dexamphetamine and modafinil (Castells et al., 2010, 2007).

Alcohol dependence has similarly not been seen as suitable for substitution therapy even though for decades there have been a number of safer alternatives to alcohol that could be prescribed as substitutes. Some of these have an extensive evidence base for this indication in other countries. Of the treatments currently recommended for use in England by the substantial systematic review of the National Institute for Health and Clinical Excellence (NICE, 2011), almost all have only a small effect size, or at most (for marital behavioural therapy) a moderate effect; i.e. many patients following current treatments are relapsing (and there are also sufferers who do not request treatment because they doubt the efficacy of available treatments). Thus, there has been a massive increase in alcohol-related health damage in the UK (Academy of Medical Sciences, 2004; NHS Statistics on Alcohol, 2010; Information Services Division, 2009; Leon and McCambridge, 2006). For these reasons, we think it

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timely to review the evidence for substitution treatment as a method to help reduce alcohol dependence and damage.

The pharmacology of substitution treatments: how alcohol works in the brain

Alcohol (ethanol) is a pluripotent drug that affects many neurotransmitter systems. However, its major effect is on the endogenous inhibitory neurotransmitter GABA where it affects GABA receptors. Alcohol acts as an indirect agonist at the $GABA_A$ receptor (Korpi, 1994; Nutt, 1999) and possibly also the $GABA_B$ receptor. These actions explain many of the effects of alcohol including its sedative, anxiolytic, amnestic and disinhibiting actions. Compensatory adaptive changes in these GABA systems lead to a hyperexcitable state when alcohol intake is stopped, which explains many of the symptoms of withdrawal (Glue and Nutt, 1990). A number of other drugs act on $GABA_A$ and $GABA_B$ receptors and many of these have been shown to reduce alcohol withdrawal. The most well known are the benzodiazepines which currently provide the mainstay of alcohol withdrawal treatment. These drugs act on some subtypes of the $GABA_A$ receptor system to potentiate the actions of GABA so mimicking the actions of alcohol and substituting for it in withdrawal. However, benzodiazepines are much less dangerous in overdose than alcohol because they have only an indirect action on the $GABA_A$ receptor whereas at high concentration alcohol can directly open the $GABA_A$ receptor linked chloride channel so producing terminal respiratory depression (Nutt and Malizia, 2001).

Baclofen acts as an agonist at the $GABA_B$ receptor. These are mostly pre-synaptic in location where they regulate the release of various neurotransmitters especially the amines such as dopamine and noradrenaline (Bowery et al., 1980). Baclofen therefore reduces brain excitation which is why it works in states of spasticity and probably why it reduces the hyperexcitable state of alcohol withdrawal. Baclofen also works to reduce craving for alcohol and other drugs (Tyacke et al., 2010) through an as yet unknown mechanism but which may involve reducing dopamine release (Brebner et al., 2005). Because baclofen metabolism, unlike that of most benzodiazepines, is not affected by liver damage it is popular with hepatologists who wish to help their patients with alcoholic cirrhosis to stop poisoning their livers.

Other approaches to enhancing GABA function use directly acting $GABA_A$ agonist modulators such as clomethiazole or indirectly acting drugs such as tiagabine or vigabatrin (gamma-vinyl-GABA). The latter two drugs are anticonvulsants that work by increasing GABA levels, but by different mechanisms. Tiagabine is a selective GABA reuptake inhibitor (Fink-Jensen et al., 1992), while vigabatrin inhibits the catabolism of GABA by irreversibly inhibiting GABA transaminase. Thus both compounds work by elevating GABA levels either acutely (tiagabine), or chronically, (vigabatrin). This elevation of GABA in the brain will affect both the $GABA_A$ and $GABA_B$ receptors.

Clomethiazole is a $GABA_A$ acting drug with similar actions to other alcohol sedative hypnotics e.g. choral hydrate and to barbiturates. In low doses it acts to augment the actions of GABA acting at the $GABA_A$ receptor but at higher concentrations, especially in overdose, it can mimic the effects of GABA to open the chloride channel itself and this can result in terminal respiratory depression. Adaptive changes on chronic use also lead to significant withdrawal reactions (Cowen and Nutt, 1982).

GHB (gamma-hydroxybutyrate) is a neurotransmitter found in the human brain and which has actions similar to that of GABA. Both GHB and its precursor GBL (gamma-butyrolactone) act as metabolic precursors of GABA, enhancing its supply. It seems very likely that the GABA receptor profile includes actions on the $GABA_B$ as well as $GABA_A$ receptors (Lingenhoehl et al., 1999). There is also evidence for distinct GHB receptors (Cash et al., 1999), whose role is at present unclear although they are found throughout the brain with high density in the basal ganglia. GHB is a sedative drug that promotes sleep and in the form of sodium oxybate is licensed for the treatment of narcolepsy where its ability to consolidate sleep reduces daytime cataleptic attacks (Wong et al., 2004). In recent years GHB and GBL have become drugs of misuse in many western countries on account of their ready availability and low price. Cases of dependence and, rarely, death in overdose have been recorded (Gonzalez and Nutt, 2005) and for these reasons both these drugs are now controlled under the misuse of drugs act in the UK in Class C. (An early reference to 'substitution' with respect to alcohol-seeking was a study of GHB in alcohol-preferring Sardinian rats by Agabio et al., 1998).

Criteria for a substitution treatment

Any potential substitution treatment should comply with certain criteria:

1. It should reduce the use of alcohol and so reduce the secondary alcohol related harms such as liver, gut, heart and brain toxicity
2. It should ideally be free of harms but as this is never the case for any drug then, it should be less harmful than alcohol
3. Misuse should be less than that of alcohol
4. It should be shown that it can substitute for alcohol and not be used along with alcohol
5. It should be safer in overdose than alcohol
6. It should ideally not potentiate the effects of alcohol especially if either drug is taken in overdose
7. It should offer significant health economic benefits.

Clinical evidence

Benzodiazepines

The literature on the effects of benzodiazepines on alcohol consumption presents us with some apparent paradoxes. This paradox is seen in some animal studies. For example, Hedlund and Wahlström (1998) in a rat model found that diazepam caused a dose-dependent *decrease* in voluntary ethanol intake in naive rats, and in the immediate withdrawal period in rats that had been exposed to ethanol for one year. However, continuing the dose of diazepam beyond the immediate withdrawal period was associated with a *larger* ethanol

intake than in the pre-alcoholization period, when the animal was once more given access to ethanol. Deutsch and Walton (1977) had also found that whereas after withdrawal rats gradually lost their preference for alcohol, diazepam served to maintain that preference.

In human studies, a paradox has emerged in several situations. As might be expected if benzodiazepines partially substitute for alcohol, Zack et al. (1999b) showed that problem drinkers medicated with benzodiazepines as part of their treatment exhibited a complete absence of priming of alcohol-directed thinking when shown negative affect stimuli, such negative affect stimuli being previously shown to trigger alcohol cognitions in recovering patients with psychiatric symptoms (Zack et al., 1999a). They showed that this was not due to general reduction of memory and reaction time due to the benzodiazepine.

This ability of benzodiazepines to substitute partially for alcohol and perhaps induce a degree of satiety was suggested in the experiment in social drinkers given lorazepam by Jackson et al. (2003). Likewise, a laboratory study in community-recruited, non-abstinent problem drinkers found that a dose of 15 mg diazepam reduced alcohol associations, whether or not primed by a stimulus causing anxiety (Zack et al., 2006). However, in that latter study, a low dose (5 mg diazepam) that had been expected also to reduce alcohol associations, albeit to a lesser extent, was found to cause the opposite and increased the salience of alcohol-associations. Similar findings have been reported in other settings, for example, low-dose diazepam (5 mg) was found by Poulos and Zack (2004) to increase consumption of placebo (de-alcoholized) beer in problem drinkers.

These laboratory studies corroborate some clinicians' impressions that taking 'therapeutic' doses of benzodiazepines after the withdrawal period, even for the treatment of anxiety, prolongs rather than reduces the risk of relapse to drinking in some patients.

A further endorsement of this paradox emerged in a study of early relapse after alcohol withdrawal. Malcolm et al. (2002) compared the drinking status on the 12th day after the commencement of alcohol withdrawal treatment of patients who had been randomly allocated for a 5-day treatment for withdrawal to either carbamazepine or to lorazepam. They found that lorazepam-treated patients had a significant rebound of alcohol withdrawal symptoms post-treatment and a 3-times greater risk of having a first drink than the carbamazepine-treated patients.

Although this paradoxical effect on alcohol-seeking of low and 'therapeutic' doses of benzodiazepines has been noted by some clinicians for many years, its clinical significance has never been properly evaluated and so the chief reluctance of UK clinicians in prescribing benzodiazepines is the fear of inducing dependence. This was enshrined in the recommendation of the American Psychiatric Association Task Force (1990): 'Special caution should be taken when benzodiazepines are prescribed to patients with a current or prior history of substance abuse or dependence'. Ciraulo et al. (1988) had found that there had indeed been widespread use of benzodiazepines by alcoholics in former years. In some countries today there continues to be considerable prescribed and non-prescribed use. Nevertheless, Mueller et al. (2005) monitored the clinical course of patients in their anxiety research programme over 12 years and reported that there was little actual misuse of benzodiazepines in those with co-existing anxiety disorders and alcohol use disorders.

It is probably true, as stated some years ago by Lejoyeux et al. (1998), that there continues to be caution among clinicians about prolonging a prescription for benzodiazepines after the acute withdrawal period. But one often hears a physician caring for a damaged alcoholic express the view: 'Surely the harm from dependence on benzodiazepine is far less than the suffering my patient will continue to cause to himself and others if he drinks'. This may, of course, be true, given the remarkable physical safety record of the benzodiazepines established over the past 50 years.

Other $GABA_A$ acting drugs

Clomethiazole (Heminevrin) is a $GABA_A$ acting sedative which has been used as a hypnotic agent for several decades, and can be given i.v. to produce rapid sedation and anti-epilepsy effects. Its therapeutic ratio is not as high as that of the benzodiazepines and related hypnotics which is one reason it has fallen out of favour. Clomethiazole is effective in the treatment of alcohol withdrawal and for this reason was used in the 1970s and 1980s in the UK by some practitioners as a substitution treatment to prevent relapse to drinking. It caused less liver and other systemic toxicity than alcohol but often did not provide full substitution, exacerbated by emerging tolerance, so that some people drank alcohol on top of it. When taken deliberately in overdose, especially if with alcohol, fatal respiratory depression occasionally occurred. Resistance to its use developed and it is not currently recommended except as an alternative to benzodiazepines in alcohol withdrawal treatment (NICE, 2011).

Both tiagabine (Myrick et al., 2005) and vigabatrin (Stuppaeck et al., 1996) have also been shown to be effective in treating alcohol withdrawal syndrome. In addition there was a trend for the patients in the tiagabine study to have less post-detoxification drinking indicating a decreased tendency to relapse (Myrick et al., 2005). However no systematic relapse prevention studies appear to have been conducted as yet.

Sodium oxybate

For several decades it has been known that sodium oxybate protects against alcohol withdrawal and can prevent relapse to alcohol drinking (see below). For these reasons it has been licensed in a liquid formulation taken up to four times a day as a treatment for alcoholism in Italy and Austria for many years. Recently a solid form of GHB has been developed [Alcover] which is bioequivalent to the marketed liquid formulation. The solid formulation suppresses or reduces the risk of misuse, particularly of criminal use and dosing errors. It is easier to carry and use. Alcover has recently been made available in the UK for prescription on a 'named patient basis'.

There are a series of studies detailing the efficacy of this compound in the treatment of alcohol withdrawal (see Cochrane Review by Leone et al., 2010; Sewell and

Petrakis, 2011). In these studies there is undoubtedly evidence of alleviation of withdrawal symptoms with similar efficacy and faster onset to benzodiazepine schedules. Several studies detailing efficacy in maintaining abstinence have also found evidence of efficacy. Early open studies by the same group found moderate-good alcohol abstinence rates with sodium oxybate (Gallimberti et al., 1992; Addolorato et al., 1996). Subsequently, Addolorato et al. (1998a, 1998b) reported that, although 2/3 patients could be controlled on 3 sodium oxybate doses a day, those that relapsed could have abstinence restored by increasing the dose fractioning to 6 doses per day.

Two studies have compared sodium oxybate with naltrexone alone (Caputo et al., 2003) or with naltrexone plus sodium oxybate (Caputo et al., 2007) (both trials using GHB in liquid formulation, with medicines entrusted to a member of the family). The first study found in 35 patients that sodium oxybate was significantly better at maintaining abstinence than naltrexone in spite of a trend to more frequent relapse in heavy drinking with sodium oxybate than with naltrexone (e.g. Volpicelli et al., 1992). In the 2007 study they randomized 55 patients to either GHB or naltrexone alone or the two drugs in combination. All groups did reasonably well considering their heavy degree of dependence but with respect to abstinence, the combination group did strikingly better. Adverse effects were few. Although craving for alcohol was reduced in all groups, two of the sodium oxybate alone group developed craving for this drug. One of the reasons for adding naltrexone to sodium oxybate is that in theory it would reduce such experiences, just as it does for alcohol.

The potential for misuse of sodium oxybate has been voiced widely (e.g. Miotto et al., 2001; Wong et al., 2004; Snead and Gibson, 2005). A laboratory study in recreational users of street GHB found that they perceived a euphoric effect of GHB, just as they did with a 0.7 g/kg dose of ethanol and 1.26 mg of flunitrazepam (Abanades et al., 2007). However, this was not surprising given that the dose of GHB used was four times greater than the dose used in the alcohol treatment studies.

Post-marketing surveillance as well as specific abuse liability studies have identified subgroup of patients where abuse or misuse of sodium oxybate are at increased risk: patients with co-addictions (heroin, cocaine) and patients with certain psychiatric co-morbidities e.g. personality disorders. Following the licensing of sodium oxybate, (Xyrem) for narcolepsy in the USA, Carter et al. (2009) summarized data from the scientific literature; from national surveillance systems in the USA, Europe, and Australia regarding illicit use of GHB; and from clinical trials and post-marketing surveillance with Xyrem. They reported that in the USA, the prevalence of illicit GHB use, abuse, intoxication, and overdose had declined from 2000, the year that GHB was scheduled, and was lower than that of 'most' other licit and illicit drugs of misuse. They concluded that,

> 'Abuse and misuse of the pharmaceutical product, sodium oxybate, has been rare over the 5 years since its introduction to the market, which is likely due in part to the risk management program associated with this product. Differences in the accessibility, purity, dosing, and misuse of illicit GHB and sodium oxybate suggest that risks associated with illicit GHB are greater than those associated with the pharmaceutical product sodium oxybate.'

Nevertheless, there are cases where illicit GHB (or GBL) have been regularly consumed, albeit in doses very much higher than doses used in medical treatment, and withdrawal has been extremely serious (e.g. Craig et al., 2000; van Noorden et al., 2009; Wojtowicz et al., 2008). That withdrawal syndrome, as predictable from an understanding of pharmacology, can be helpfully managed using baclofen or a benzodiazepine agent (LeTourneau et al., 2008).

$GABA_B$ drugs

Currently there is only one selective $GABA_B$ agonist available for human use, baclofen. Baclofen was originally developed as an anti-epileptic in the 1920s but its effectiveness was disappointing. However, it was found to have anti-spastic effects and is currently used for the treatment of spastic movement, especially in instances of spinal cord injury, spastic diplegia, multiple sclerosis, and amyotrophic lateral sclerosis. It is an orally active GABA derivative, p-chlorophenyl gamma-aminobutyric acid, with a half-life of 2 to 4 hours. Over its many years of use it appears to be a very safe drug with few side effects, the main ones being somnolence, dizziness, muscle weakness and headache; but these are not universal and can be minimized by titrating doses up over a few days. Baclofen has good absorption after oral administration (75%), with peak serum concentrations achieved in 2–4 h. Its half-life is 3–4 h. It is eliminated primarily via the kidneys, 85% as the unchanged parent compound which makes it relatively easy to use in patients with liver disease.

Building on a number of preclinical experiments, two open-label trials testing the effect of baclofen on alcohol reduction/abstinence and craving (Addolorato et al., 2000; Flannery et al., 2004) gave encouraging results. In the first study, two participants continued to drink alcohol although they substantially reduced their daily drinks in the first week of treatment, whereas the seven remaining completers were abstinent for the entire 4 weeks. Alcohol craving was significantly reduced, and liver function improved. Some participants also reported that their obsessional thinking about alcohol had disappeared. In the second study, 12 alcohol dependent individuals were given baclofen titrated up to 30 mg/day (10 mg tid) for the 12 weeks of the trial (Flannery et al., 2004). Although the subjects in this trial were alcohol dependent they were not necessarily seeking to give up. Significant reductions in the number of drinking days, the number of drinks per drinking day and the number of heavy-drinking days were found even though only 6 were completers.

Subsequent controlled trials confirmed these early findings. For example, Addolorato et al. (2002a) studied 39 alcohol dependent subjects randomized to either baclofen, titrated up to 30 mg/day (10 mg tid, $n = 20$) or placebo ($n = 19$) in a 4-week double-blind trial. Subjects were only included if they had a family member who could be entrusted with the study medication and its administration. Three subjects in the

baclofen group and eight in the placebo group failed to complete the study. Baclofen resulted in significantly more abstinent subjects, the duration of abstinence was significantly greater in the baclofen group and there was also a significant reduction in overall alcohol craving measured with the Obsessive-Compulsive Drinking Scale. In addition state anxiety was also significantly reduced in the baclofen group, but there was no effect on the depression score.

These results were confirmed in a larger ($n = 84$) 12-week double-blind placebo controlled trial in patients with alcohol-related liver disease of baclofen 30 mg/day (20 mg tid, $n = 42$) versus placebo ($n = 42$) (Addolorato et al., 2007). In addition to confirming the finding of the previous study, that baclofen is effective at promoting and maintaining alcohol abstinence in alcohol-dependent individuals, it also found there were no hepatic side-effects or worsening of liver function tests.

There has however been a trial that had a negative result (Garbutt, 2009), for which explanations relating to patient characteristics have been offered: that the patients were recruited in this study by advert, did not require detoxification medication, wanted 'controlled drinking' rather than abstinence, were less anxious than typical patients and had had fewer adverse health consequences of their drinking. Heydtmann (2011) postulated that patients without liver disease would need a higher dose of baclofen than used by Garbutt and this was also implied in a dose-comparison study of Addolorato et al. (2011).

There have also been case studies describing beneficial effects of baclofen in treatment-resistant alcoholics (Ameisen, 2005; Bucknam, 2007) and in a schizophrenic alcohol dependent patient (Agabio et al., 2007). These case studies showed that baclofen was effective in suppressing alcohol craving, preventing relapse and was apparently safe when co-administered with medications for depression (Bucknam, 2007) and schizophrenia (Agabio et al., 2007). In two of these reports the subjects used very high doses of baclofen 100 mg/day (Bucknam, 2007) and up to 120 mg/day (Ameisen, 2005) increasing the dose (respectively, to 140 mg/day or 160 mg/day and at peak, 270 mg/day) in stressful situations or periods. This 'as required' use presents an interesting option for physician-monitored treatment. However, there are very occasional reports of disinhibition tending towards hypomania (Soufia et al., 2010) when the compound is taken by alcohol dependent patients, an unwanted effect that may be commoner on higher doses.

The acute safety of baclofen and alcohol taken together was tested in a human laboratory-based study (Evans and Bisaga, 2009). Baclofen (0, 40 and 80 mg) was given 2.5 hours before alcohol (1.5 g/L body water or approximately 0.75 g/kg) or placebo. They found that baclofen, alone or with alcohol, caused only modest increases in heart rate and blood pressure, did not have its own positive subjective effects and did not alter either alcohol craving or positive subjective effects. However, baclofen did increase alcohol-induced sedation, and dose escalation of baclofen is often difficult because of a marked dose-dependent sedative effect severely impacting daily functioning.

Baclofen has also been effective in alcohol withdrawal (Addolorato et al., 2002b; Addolorato et al., 2003). These authors formally studied its use in alcohol withdrawal in a comparison with diazepam (Addolorato et al., 2006). For 10 days 37 patients with alcohol withdrawal syndrome were given either baclofen 30 mg/day (10 mg tid, $n = 18$) or diazepam (0.5–0.75 mg/kg/day, $n = 19$) and the Clinical Institute Withdrawal Assessment (CIWA-Ar) was used to evaluate the efficacy of the treatments. The study found that there was no significant difference between the treatments. Diazepam appeared to act slightly more rapidly to reduce the sweating, anxiety and agitation sub scale scores of the CIWA-Ar. However, these data suggest that for treating alcohol withdrawal syndrome baclofen provides an alternative to the benzodiazepines, which might be clinically important in patients with a history of benzodiazepine abuse.

Other drugs

Pregabalin (Martinotti et al., 2010; Minozzi 2010) and its precursor gabapentin (Myrick et al., 2009) have also been used as a form of treatment for alcohol dependence especially in the treatment of withdrawal, where efficacy has been demonstrated for both. Despite their names they do not in fact work on the $GABA_A$ system but attenuate calcium influx by acting on the a2delta calcium channel subunit so reducing brain excitability. This explains why they are effective anti-epilepsy treatments and also work in neuropathic pain. Both have anxiolytic properties and pregabalin is licensed as a treatment for generalized anxiety disorder (GAD) so may well work to reduce anxiety in alcoholics. Whether they can be considered substitute therapy is questionable given their very different pharmacological and clinical profile, although trials have yet to be carried out. Similarly acamprosate and topiramate have also been shown to reduce the risk of relapse to drinking in abstinent individuals but for similar reasons neither can really be considered as substitution agents (Lingford-Hughes et al., 2004).

What are the barriers to alcohol substitution treatment?

Barriers to alcohol substitution treatment come in many forms. Abstinence based treatments such as delivered by AA have been the bedrock of alcoholism treatment in the UK and especially the USA for decades. The philosophy of AA cautions against the use of substitution treatments, which are perceived as 'chemical crutches' that delay or obscure the possibility of emotional and spiritual recovery. The general public tends to view alcohol dependence as a failure of will which is therefore best dealt with by psychological approaches to strengthen determination or deal with underlying weaknesses, and few are aware that other options exist. This is seen also in commentaries on opioid addiction where there are those who oppose substitution treatment with methadone partly on moral and philosophical grounds even though many studies have shown it to be a cost effective way of reducing social harm.

Another major hurdle is resistance from the medical professions who tend to the populist view of alcoholism as a moral rather than a medical problem. This is manifest by a degree of hostility to substitution therapy which often emerges as a disproportionate concern over the negative or

adverse effects of alternative agents. Thus the problems of benzodiazepines are exaggerated and much lower thresholds for harms or concerns are tolerated compared with the toxic effects of alcohol itself. This issue is exaggerated by the threat of medical negligence charges that hangs over benzodiazepine prescribing especially in people with a history of drug and alcohol dependence. The very cautious guidance offered by professional bodies such as the Royal College of Psychiatrists (1997) is not helpful in some situations.

Ongoing issues about the dependence liability of the benzodiazepines limit their use even though they are much safer than alcohol. Notwithstanding a risk of paradoxical effects as noted above, a prescription of these drugs might benefit some alcoholic patients with chronic anxiety; yet this is denied while further damage from alcohol ensues. Similar concerns are now being raised about baclofen and GHB substitution therapy even though these agents do not have the toxicity of alcohol and its main metabolite acetaldehyde. Some of this prejudice derives from older experience with more toxic agents such as the barbiturates and meprobamate which could be fatal in overdose.

The fact that people in treatment with these drugs may experience a degree of dependence on them, and indeed some liking or craving for them, should not be a barrier to their use. Indeed in the opioid field such experiences are considered an essential element of the treatment regime for they improve or even drive compliance and so reduces relapse to the more dangerous drug of primary dependence, heroin.

Xyrem was introduced, at least in the USA, with a fairly elaborate and apparently successful system to limit its misuse. Nevertheless concern has been expressed as to the effectiveness of such controls if the patient population are alcohol dependent (Sewell and Petrakis, 2011). Others advise against premature closure on this question (Caputo, 2011). In Italy and Austria, where Alcover® has been marketed since the 1990s, Alcover® is almost only prescribed to outpatients by centres specializing in alcoholism or addiction. This pattern of prescription has effectively prevented the occurrence of drug diversion or abuse.

Such treatments will not be a substitute, however, for the psychological and social changes that many patients will need to make to consolidate their recovery. The role of medications is to allow a period of sobriety so that the planning and practice of those changes can be commenced. One cannot learn to navigate in a sinking ship.

To change the attitude of UK addiction psychiatrists to substitution therapy for alcohol dependence will require considerable education and evidence, but with the high UK death rates from alcohol-related liver disease (Leon and McCambridge 2006; NHS Statistics on Alcohol, 2010; Information Services Division, 2009) now is the time to engage in the debate.

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Conflict of interest

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