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Through a glass darkly: can we improve clarity about mechanism and aims of medications in drug and alcohol treatments?

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Introduction

The treatment of addiction and dependence on, and misuse of, alcohol and other drugs is one of the largest unmet needs in medicine today, so the development of new treatments is a pressing need. However, we have seen the development and use of different terminologies for different drug addictions, which confuses prescribers, users and regulators alike. Here we try to clarify terminology of treatment models based on the pharmacology of treatment agents. This editorial covers all drugs that are used for their pleasurable effects and which therefore can lead to harmful/hazardous use, dependence and addiction. These include nicotine, alcohol and abused prescription drugs such as benzodiazepines, as well as opioids and stimulants.

The goals of treatment and disease terminology

Drug and alcohol use is not inevitably harmful or problematic; however, as use escalates, there is an increased likelihood of it causing adverse consequences or harm, which has been termed 'hazardous' or 'risky' use, though these are not yet diagnostic terms. The World Health Organization (WHO) ICD-10 defines harmful use as '*a pattern of psychoactive substance use that is causing damage to health*', and this could be physical or mental, though solely social consequences are not sufficient.

'Progressive use of alcohol/drugs can then result in 'Dependence' a term defined as a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state'.

These definitions have been used in recent NICE guidance on management of harmful drinking and alcohol dependence. Diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) are broadly similar for alcohol abuse and dependence, though abuse includes social consequences. DSM criteria are those commonly used in trials. DSM is currently under revision with publication due in 2013 and it seems likely that 'addiction' will replace dependence, since the use of the term 'dependence' has led to confusion, for example, describing anti-depressants as addictive due to some aspect being present such as withdrawal, whereas the core of addiction, 'compulsive' drug use, is lacking (see Nutt, 2003). Dependence is proposed to be used to describe 'physiological dependence' that happens on repeated doses of drugs such as opioids, benzodiazepines; again, many users do not abuse or escalate their use, so are not 'addicts'.

Treatment approaches

In general, there are three types of treatments for addiction/dependence on alcohol/drugs which for convenience can be called withdrawal treatment, substitution therapy and abstinence-promoting therapy, respectively (Table 1). We do not consider withdrawal treatments in this editorial: because there is more general consensus about their meaning, although the context may vary, being sometimes elective (as a prior step in a patient s abstinence oriented therapy) or urgent, when some crisis has precipitated cessation of the addictive substance and withdrawal reaction if severe might be life-threatening, as in severe alcohol addiction.

Substitution therapy

This can be defined as a medication that has one or more of the pharmacological effects of the substance which are believed to be relevant to the addiction. Substitutes are effective in preventing withdrawal from the abused drug and so in many cases can be started once a decision is made to stop using the abused drug. They reduce craving and the desire to use the abused drug as well. Substitution treatments are preferred by patients, which encourages compliance. As they have to be prescribed, often under supervision, they can

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Table 1. Types of treatment medications and other medical interventions for three major drugs of abuse

	Medications	Other interventions
Heroin	*Substitution*	Needle exchange
	Methadone	Foil (-> smoking not i.v.)
	Buprenorphine	Citric acid
	Prescribed heroin	Filters
	Abstinence-promoter	
	Naltrexone/nalmefene	
Alcohol	*Substitution*	Thiamine (B1) and other vitamins
	(Sodium oxybate)	Magnesium
	(Benzodiazepines)	
	(Clomethiazole)	
	(Baclofen)	
	Aversion	
	Disulfiram etc	
	Abstinence promoter – primary clinical effect	
	Acamprosate	
	(Baclofen)	
	(Topiramate)	
	Drinking regulators – primary clinical effect	
	Naltrexone	
	Nalmefene	
Tobacco	*Substitution*	
	Varenicline	
	Safer forms of nicotine	
	Patch/gum/lozenge	
	Nasal spray	
	Electric cigarette	
	Abstinence promoter	
	Bupropion, Baclofen	

The drugs in () means putative mechanism though not yet proven.

also engage patients with treatment providers, which means that other interventions can be offered that can help sort out other problems. Patients on substitution therapy are still *dependent* on a drug, though albeit one with less harms than the original one. Often they will be working towards coming off the substitution treatment over time.

In the case of heroin addiction where methadone and buprenorphine are used the issue of whether dependence on the substitution therapy is a problem or a desired outcome of the treatment is a subject of intense and polarized debate amongst therapists and even the general public. This debate occurs despite proof that such drugs have clear value in terms of reducing the harms of heroin use such as crime, HIV spread and overdose deaths (Lingford-Hughes et al., 2004). Heroin when prescribed to reduce street heroin use could also be considered in this category.

Substitution therapy for alcohol dependence, for example the use of benzodiazepines or sodium oxybate (GHB), even when the person is abstinent, is even more controversial. It is not supported by some guidelines (e.g. NICE, 2011), despite evidence that they can be effective and not lead to abuse (Chick and Nutt, 2011).

For tobacco dependence the term 'substitution' is not currently used. This is somewhat illogical, since many effective harm reduction treatments for smoking use substitute forms of delivering nicotine, such as patches, gum and lozenges. Although these were developed as an aid to quit smoking, in practice many patients stay on these for years, proving that they are in fact substitution therapy.

Abstinence

Abstinence is the most widely recognised goal for addiction treatment, and yet can have subtly different meanings. In the strict sense, abstinence should refer to not taking the substance of abuse, for example heroin, **nor** taking substitute treatments, for example methadone; but for some, abstinence means no longer taking 'street drugs' whilst on substitute medication. Some therapists and support groups such as Alcoholics Anonymous have traditionally taken the view that abstinence must be achieved without the use of any medication. However, use of anti-depressants or anti-psychotics is now more widely allowed or supported if the person's mental health problems are seen as separate from their dependence. This means that medications which target 'addiction', or its component processes are not allowed, which reflects a narrow perspective on the treatment of addiction.

However, most authorities now accept that those drugs which promote abstinence from the drug of abuse are worthwhile since they are likely to reduce drug/alcohol harms. Such drugs help reduce relapse risk factors such as cravings (e.g. bupropion for smoking, possibly acamprosate or naltrexone

for alcoholism) or provide a threat of harm if the drug is taken, which is called aversion (deterrent) treatment (e.g. disulfiram for alcoholism) – see the following.

Harm reduction

This is a term that strictly refers to any intervention that reduces the harms of drug/alcohol use. It includes social measures such as needle exchange for heroin users as well as medicines such as opioid substitution therapy, and in the case of alcohol will include vitamin B1 supplements. In recent years, particularly in the UK, the term 'harm reduction' has become used by some to equate to substitution treatment, particularly that for heroin addiction.

New developments

There are several new approaches available or under investigation and these do not fall easily into current terminology. For instance, there are alternative but safer nicotine delivery systems, for example electric cigarettes which deliver nicotine but not tar and other combustion products or carbon monoxide. These are in essence a variant of substitution therapy, though using a pure preparation of the addictive substance in a safer way – nicotine is substituted for tobacco. Whether these are medications or variants of the commodity of tobacco needs clarifying. Until now the nicotine patch/gum/lozenge and spray have been considered as treatments (to aid quitting) but the electric cigarette is being sold as a safer cigarette.

In alcohol dependence the idea of interventions that might regulate excessive intake is being tested using opioid antagonist drugs such as nalmefene. This approach has developed from findings with another opioid antagonist naltrexone when used to assist abstinence. It was found instead that naltrexone was more effective at preventing a lapse becoming a full relapse, than in promoting complete abstinence (Rösner et al., 2008). The idea that drugs might reduce the damage from drinking by helping patients control their drinking better is relatively new and there is no agreed terminology, so we discuss this issue below.

Finally, the future promises new interventions such as vaccines, which though designed to prevent access of the drug to the brain may also work through other mechanisms.

Multiple actions

It also needs to be understood that a medication or treatment may have a different mode of action against different types of drug/alcohol misuse. For example, naltrexone blocks heroin use directly but also can modify alcohol intake. Baclofen may act as an alcohol substitute as well as reducing craving for stimulants.

Specific drugs and their interventions

Opioids

Substitution. Heroin addiction is a major public health problem – not least because of the social impact, especially acquisitive crime, that users engage in to supply their habits. For this reason methadone was introduced in the 1950s as a substitution therapy. It provides a significant degree of the pleasurable (addictive) effects of heroin but has better pharmacokinetic properties, so can be taken once a day. Methadone prevents withdrawal, reduces street heroin use and, because of regular attendance (often daily) to get the medication, it helps the addict engage with treatment staff and so experience other treatment interventions as well. Methadone has been shown to be highly cost-effective and reduces both heroin-related harms, such as blood-borne virus spread, and crime.

Buprenorphine is a mu-opioid partial agonist that is safer in overdose than methadone and with even better pharmacokinetics (it can be given on alternate days). It is taken by the sublingual route and prevents withdrawal as well as blocking on top heroin use.

Both methadone and buprenorphine can themselves be abused, in some cases by i.v. injection which is the most hazardous way of using any drug. With regard to buprenorphine this risk has been attenuated by putting buprenorphine in a combination with the opioid antagonist naloxone (Suboxone). If this combination is injected then precipitated withdrawal is likely which deters such use (Nutt, 2010).

Abstinence promotion. Currently the medications used are antagonists, such as naltrexone and nalmefene. When patients are stabilized on these, then the effects of heroin are blocked so that its use is pointless. However, ensuring compliance is difficult except in specialist circumstances, such as when an individual is under the threat of legal or professional disciplinary sanctions if he or she relapses, or if a partner supervises daily consumption. To improve compliance, long-acting formulations such as depots and implants of naltrexone and nalmefene are now available in some countries.

Many factors such as cravings, conditioned cues and stress can lead to relapse and in future we can expect to see drugs developed to protect against these. It is notable that whilst in alcohol and cocaine dependence a variety of pharmacological approaches are used – for some of which there is evidence in opioid dependence (e.g. baclofen) – their use in the opioid treatment clinic is almost negligible. Given the number of people affected and amount spent on substitute treatment and harm-minimization strategies, helping them to achieve and maintain abstinence appropriately is an important aim.

Alcohol

Substitution. This approach to alcohol addiction is not as well established as that for opioid or tobacco addiction. In reducing withdrawal, the use of medications with similar pharmacology to the pharmacology of alcohol, such as benzodiazepines and clomethiazole, is well established. An extension of this is their use whilst the person is still taking alcohol, with the aim of reducing their drinking. However, use of these medications for this purpose has never been licensed or widely supported (see NICE, 2011) owing to concerns about dependence on these medications, and concerns about safety if alcohol is taken as well.

Other drugs such as sodium oxybate and baclofen have some pharmacological similarities to alcohol, since they target the GABAergic system, and both medications have been shown not only to reduce withdrawal, but also to reduce drinking (Leggio et al., 2010). Sodium oxybate has been licensed for these indications in some European countries (e.g. Italy, Austria). Like taking heroin on top of methadone, there are risks of drinking alcohol on top of either of these medications (e.g. excessive sedation). Although these medications are not currently conceptualized as substitutes, it seems likely that this is a major factor in their mode of action. However, they may have other actions that may help in treatment, for example baclofen when it is used in nicotine dependence (Franklin et al., 2009).

Acamprosate has some but lesser similarities to alcohol, being somewhat GABA-ergic and anti-glutamatergic (Mann et al., 2008). However, it is not perceived as being alcohol-like or sedative-like and there are no examples of abuse and dose escalation. The main use of acamprosate is in promoting abstinence (Boeijinga et al., 2004; Rösner et al., 2008). Acamprosate alone is not sufficient to manage moderate to severe alcohol withdrawal; it has been shown to reduce hyperglutamergic state during withdrawal and can be initiated whilst the patient is still drinking.

Some anti-convulsants also share some of the pharmacology of alcohol and one, topiramate, has shown promise in improving abstinence. However, unlike other 'relapse prevention' medication trials which start the medication in abstinence, topiramate has been started whilst patients were still drinking but aiming for abstinence (Johnson et al., 2007).

Abstinence promotion

Aversion. A long-established treatment for alcohol addiction is that of blocking alcohol metabolism with drugs such as disulfiram (Antabuse) and carbimide (Abstem). These lead to the accumulation of acetaldehyde when alcohol is drunk, which is highly unpleasant, producing nausea/vomiting, headache and flushing. These adverse effects are intended to be so off-putting that they scare alcoholics into not drinking.

Anti-relapse drugs. Until recently the major thrust of alcohol dependence treatments have been to promote abstinence. Whilst most interventions are psychological/social, two drugs have been licensed in many countries, namely acamprosate and naltrexone. Both drugs reduce relapse risk but through different mechanisms. Acamprosate increases abstinence rates probably by attenuating conditioned responses to alcohol cues, and also reduces the amount drunk in a lapse (Chick et al., 2003; Lingford-Hughes et al., 2010). In contrast, naltrexone, as well as slightly increasing absolute abstinence rates, seems to stop a lapse to alcohol use leading to a relapse. The mechanism underlying this behaviour are still uncertain, but it may be due to reducing reward from alcohol by modulating mesolimbic dopaminergic activity or by reducing impulsivity. Newer medications such as baclofen and topiramate might also fit into the 'anti-relapse' category, since they moderate drug liking and motivation and indeed have potential to treat other addictions, though baclofen may also have alcohol-like effects.

Harm reduction

Vitamins. A unique form of harm-reduction treatment in alcohol addiction is that of thiamine, which is used to prevent neurological damage from vitamin B1 deficiency in chronic alcohol use (Wernicke's encephalopathy and subsequent Korsakoff's syndrome). It can and indeed should be used when necessary in patients who are still drinking, and it has been suggested that it could be added to alcoholic drinks as a preventative measure.

Drink-regulating agents (drinking regulators). This is a newer innovation to reduce harmful levels of drinking which involves the use of drugs that reduce the amount of alcohol drunk in a single drinking session, and possibly the number of drinking sessions. Many people with alcohol dependence find that sometimes they can control their intake and have just a couple of drinks. Whereas at other times, even though they set out with the intention of only having a couple of drinks, they lose control once they have had the first drink and then take much more than they wanted to. Often this is in the form of a binge or 'bender'.

The feasibility of interfering with this destructive pattern of drinking came from studies with the opioid antagonist naltrexone, when it was being used as part of a relapse prevention abstinence programme (O'Malley et al., 1992; Volpicelli et al., 1992). Compared with placebo treatment groups the naltrexone ones had a lower level of drinking. More fine-grained analysis revealed that this was because the naltrexone-treated patients showed a reduced likelihood of a lapse to drinking (a couple of drinks) leading to a full relapse to dependent drinking.

The mechanism seems to be that an important initial action of alcohol is to release endorphins which then drive the dependence-prone person to drink more and more – so called loss-of-control drinking. Naltrexone blocks the endorphin effects and so lessens the risk of drinking leading to relapse. In this way naltrexone leads to a lower, more regulated level of drinking with fewer binges/benders.

More recently it has been shown in patients attempting abstinence that naltrexone taken in a targeted (as required) fashion, that is only on those days when the patient felt at risk of drinking, resulted in greater reductions in drinking than when it was taken each day (Kranzler et al., 2009).

Currently another opioid receptor antagonist, namely nalmefene, is being studied for alcohol dependence in patients who are trying to reduce their drinking rather than to be totally abstinent. The drug is taken on the days they feel they are at risk of drinking excessively and does reduce the amount drunk (Karhuvaara et al., 2007). It is therefore an alternative strategy to abstinence-promotion and targets a group of alcohol-dependent patients who often are not interested in abstinence but want more control over their drinking. However, nalmefene could also be used like naltrexone in patients in abstinence to reduce relapse risk.

It is important to note that the terminology for this new class of alcohol intervention is not yet agreed; as well as 'drinking-regulating agents', the term we have used, other terms have been suggested. These include: drinking-restrictors, drinking-control agents, anti-bingeing agents, and self-control drugs. Although the exact mode of action is not understood, many of the medications with potential have a shared mechanism of action of reducing mesolimbic dopamine neuronal firing through their receptors – for example CB1, nicotinic, mu-opioid – inhibiting the GABA interneuron. In addition opioid antagonists may also increase frontal cortical function to improve self-regulation of behaviour, which is consistent with its efficacy in treating pathological gambling and other impulse control disorders (Grant et al., 2008).

Tobacco

Substitution. This has been the mainstay of treatment for many years by way of alternative forms of nicotine such as patches, lozenges, gum and, more recently, nasal sprays. Although they were ostensibly developed to provide a means of withdrawing from cigarettes, many smokers continue to use them for many years, in which case they are substitution treatments.

The nicotine receptor partial agonist varenicline has recently come to be used in the same way. It substitutes for smoking, stops withdrawal and the urge to smoke, so promotes a less harmful form of behaviour. Varenicline is also being tested with other addictions, and should it be found to work in these then it would have to be viewed as an abstinence promoting agent rather than a substitution treatment (Crunelle et al., 2010).

The electric cigarette is currently becoming quite popular in some countries including the UK. It is promoted on the grounds that it is free of combustion products and carbon monoxide so is presumed (reasonably) to be safer than ordinary cigarettes and can be smoked indoors in public places. Whether it should be viewed as a substitution treatment is a matter of discussion, but currently it is sold as a non-pharmaceutical product, like cigarettes.

Abstinence promotion. The only licensed drug currently in this class is bupropion (Zyban), an anti-depressant that was found to reduce smoking as well as lift mood. It appears to reduce cravings in nicotine withdrawal, so assisting abstinence. Vaccines against nicotine are in clinical trials and show a reduction of smoking when adequate antibody titres are achieved. How they work is still not certain, for although they were developed to prevent access of nicotine to the brain it seems that other factors may also be important, such as the prevention of sudden nicotine withdrawal as the vaccine provides a long-acting supply of nicotine in the blood. Baclofen may also have utility here (Franklin et al., 2009).

Other drugs

As yet there are no proven pharmacological treatments for other drugs of addiction. Many medications have been tested for cocaine/crack dependence without robust success. These include medications to block the access of cocaine to its active sites in the brain (including vaccines) and those to reduce craving, for example, modafinil. As cocaine acts to release dopamine which then leads to depletion, approaches that increase dopamine levels are being tried. These include dopamine-*b*-hydroxylase inhibitors that reduce conversion of dopamine. Similar approaches are being used for metamfetamine addiction.

Cannabis dependence is now a recognized problem without proven pharmacological treatment. The emergence of antagonists to the central CB1 receptor, such as rimonabant, offered hope. Sadly, the removal of these from the market, after their efficacy/safety ratio in weight control was found wanting, has set this field back. Currently there is interest in pharmacotherapy to ameliorate withdrawal; potential treatments include synthetic tetrahydrocannabinol (Marinol) and cannabis spray (Sativex).

There is scope for long-acting forms of benzodiazepine receptor antagonists (e.g. depot flumazenil) in preventing benzodiazepine abuse. A new idea in harm reduction for steroid users is also under evaluation in the form of the product Roid, which it is claimed reduces the aggression seen with this class of drugs.

Conclusions

Alcohol/drug dependence and addiction are huge medical as well as social problems for the treatment of which new medications could be helpful. A better understanding of the modes of actions and targets for current treatments is required with clarity about exactly what patient groups or symptom stages they work on. This editorial attempts to provide this as well as providing an underpinning structure to the terminology in the treatment field.

Conflict of interest

DJN has received grants, and/or consulting/speaker's fees from many companies that have/had drugs or research interests in addiction treatment: GSK, Pfizer, D&A pharma, Sanofi, Lundbeck, Schering-Plough, Reckitts, Novartis, Merk-Lipha, Janssen-Cilag.

ALH has received grants, and/or consulting/speakers fees or support to attend conferences from companies that have/had drugs or research interests in addiction treatment: GSK, Pfizer, Janssen-Cilag, Sanofi, Lundbeck, Servier, Merk-Lipha, Reckitts, Wyeth.

JC Has received speaker's fees from D&A pharma.

References

Boeijinga PH, Parot P, Soufflet L, et al. (2004) Pharmacodynamic effects of acamprosate on markers of cerebral function in alcohol-dependent subjects administered as pretreatment and during alcohol abstinence. *Neuropsychobiology* 50: 71–77.

Chick J, Lehert P and Landron F (2003) Does acamprosate improve reduction of drinking as well as aiding abstinence? *J Psychopharmacol* 17: 387-392.

Chick J and Nutt DJ (2011) Substitution therapy for alcoholism: time for a reappraisal? *J Psychopharmacol* 26: 204-211.

Crunelle CL, Miller ML, Booij J and van den Brink W (2010) The nicotinic acetylcholine receptor partial agonist varenicline and the treatment of drug dependence: a review. *Eur Neuropsychopharmacol* 20: 69–79.

Franklin TR, Harper D, Kampman K, Kildea-McCrea S, Jens W, Lynch KG, O'Brien CP and Childress AR (2009) The GABA B agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. *Drug Alcohol Depend* 103: 30–36.

Grant JE, Kim SW and Hartman BK (2008) A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J Clin Psychiatry* 69: 783–789.

Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group (2007) Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 298: 1641–1651.

Kranzler HR, Tennen H, Armeli S, Chan G, Covault J, Arias A, et al. (2009) Targeted naltrexone for problem drinkers. *J Clin Psychopharmacol* 29: 350–357.

Karhuvaara S, Simojoki K, Virta A, Rosberg M, Löyttyniemi E, Nurminen T, et al. (2007) Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 31: 1179–1187.

Leggio L, Garbutt JC and Addolorato G (2010) Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol Disord Drug Targets* 9: 33–44.

Lingford-Hughes AR, Welch S and Nutt DJ; British Association for Psychopharmacology (2004) Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 18: 293–335.

Lingford-Hughes A, Watson B, Kalk N and Reid A (2010) Neuropharmacology of addiction and how it informs treatment. *Br Med Bull* 96: 93–110.

Mann K, Kiefer F, Spanagel R and Littleton J (2008) Acamprosate: recent findings and future research directions. *Alcohol Clin Exp Res* 32: 1105–1110.

NICE (2011) Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence NICE clinical guideline 115. London: National Institute for Health and Clinical Excellence.

Nutt DJ (2003) Death and dependence: current controversies over the selective serotonin reuptake inhibitors. *J Psychopharmacol* 17: 355–364.

Nutt DJ (2010) Antagonist-agonist combinations as therapies for heroin addiction: back to the future? *J Psychopharmacol* 24: 141–145.

O'Malley SS, Jaffe AJ, Chang G, et al. (1992) Naltrexone and coping skills therapy for alcohol dependence. *Arch Gen Psychiatry* 49: 881–7.

Rösner S, Leucht S, Lehert P and Soyka M (2008) Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *J Psychopharmacol* 22: 11–23.

Volpicelli JR, Alterman AI, Hayashida M, et al. (1992) Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 49: 876–80.