British Journal of Pharmacology (2008) 154, 397–405
 0007–1188/08 $30.00
www.brjpharmacol.org

REVIEW

Addiction: the clinical interface

D Nutt and A Lingford-Hughes

Psychopharmacology Unit, University of Bristol, Bristol, UK

This review gives an overview of what we see as the key issues in the human pharmacology of drugs of addiction. We review evidence of efficacy and mechanisms by which treatments act and point out areas where further work is needed. The role of agonist, partial agonist and antagonist treatments for opioid addiction is detailed and current issues relating to the mechanisms of actions at the receptor level and how to improve on compliance are discussed. The role of the brain dopamine and GABA-A systems in drug dependence is considered in relation to the growing pharmacology of these receptor systems, and the current status of novel preclinical targets reviewed. In addition, the different roles of dynamic and kinetic factors in both addiction and its treatment are discussed in relation to the underlying neuropharmacology of the disorders as defined from human and preclinical studies. Finally, some pointers to future research and especially to drug development by pharma are elaborated.
British Journal of Pharmacology (2008) **154,** 397–405; doi:10.1038/bjp.2008.101; published online 14 April 2008

Keywords: addiction; opioid; benzodiazepine; GABA-A; dopamine; alcohol; cocaine; nicotine; human

Abbreviations: PET, positron emission tomography; LAAM, L-a-acetylmethadol hydrochloride

Introduction

In this review, we cannot cover the whole clinical addiction arena or even that part dedicated to current treatments—but these are available in other sources, for example, recent treatment recommendations are in the British Association of Psychopharmacology guidelines (Lingford-Hughes *et al.*, 2004). What we have decided to do is focus on key areas in the human pharmacology of addiction where there is either a clinical need for new preclinical studies or where preclinical theories need testing in humans. The reader should be aware that when we talk of pharmacological treatments, they should almost always be given in the context of other psychosocial interventions to maximize their efficacy, with perhaps the only exceptions being for detox.

Pharmacological approaches to reducing the harm of addictive drugs

Agonist substitution treatment

It is generally accepted in most of the western world that the primary goal of addiction medication treatments should be to reduce harm—rather than to reduce supply or punish use. One of the very few proven pharmacological treatment approaches to harm reduction is the use of substitute prescribing, especially in opioid addiction. This approach was pioneered by the early studies of methadone that showed efficacy in terms of reducing the use of heroin, reducing crime, limiting the spread of HIV infections and engaging users in treatment regimes (see Lingford-Hughes *et al.*, 2004 guidelines and NICE-HTA review, 2007). It has been estimated that investment in methadone leads to a threefold economic benefit in terms of reductions in health and social care costs and reduced criminal activity and the price of policing. Methadone acts as a substitute for heroin because it is a (relatively) full opioid agonist that mimics the pleasurable actions of heroin. However, it has a slower onset of effect; so when taken orally, it gives less of a 'rush' and hence is less preferred than heroin. In addition, as methadone has a much longer $t_{1/2}$, it can be given once a day, rather than 2–4 times a day as observed for short $t_{1/2}$ of heroin. This stabilizes the patient's life, as when taken once, they are relatively free from cravings and the need to find money to buy heroin hits. Also, once methadone is taken, the value obtained from a subsequent heroin hit is significantly reduced (see Figure 1).

But methadone is still a very addictive drug that can not only be fatal in overdose but can also be diverted into street use. For this reason, methadone is usually given under supervised consumption in pharmacies or other treatment outlets; the patient takes the liquid formulation under the supervisor's surveillance. Providing space for consumption, preparing the liquid doses of methadone and paying the

Correspondence: Professor D Nutt, Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitsun Street, Bristol, UK.
E-mail: David.J.Nutt@bristol.ac.uk
Received 30 October 2007; revised 29 February 2008; accepted 3 March 2008; published online 14 April 2008

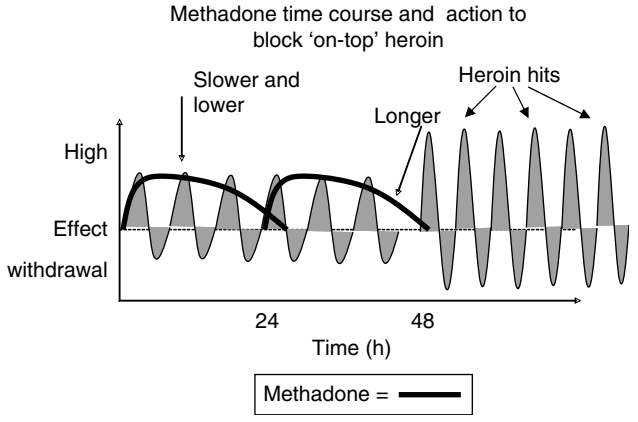

Figure 1 A schematic time course of the actions of methadone when given once daily dosing regime (black lines) superimposed on a schematic time course of multiple daily heroin doses (filled areas). The different kinetics of the two drugs is illustrated and also their interactions. When methadone is taken, the effects of any 'on-top' heroin use are blocked, but if methadone is omitted, for example, at weekends, then the full effect of heroin is achieved (right side).

supervising personnel is a relatively expensive process (much more than the cost of the drug itself), and so in many countries, this is done only during the working week (to avoid overtime costs). The usual solution to this is for the patients to be given two take-home doses on Friday; however, urine testing on Mondays often indicates that these doses are not taken—in many cases, they are sold on to addicts not in treatment regimes—and the proceeds used to finance heroin purchase. Occasionally, the doses are found by children, who drink it as it is usually in a sugar solution and then die of overdose; this results in several deaths per year in the United Kingdom (Milroy and Forrest, 2000).

Although methadone is effective, it is a very sedative drug that leaves many patients 'stoned'. Whereas some like this sense of being out of the world, others find it limiting in terms of job seeking or success as well as in interpersonal relationships (Lingford-Hughes *et al.*, 2004). Moreover, the long-term use of methadone seems to lead to adaptive brain changes that lead to a withdrawal reaction that lasts for several weeks, although the insomnia that occurs during withdrawal may be much more enduring, often not resolving in months, and is a major reason for relapse (Beswick *et al.*, 2003).

How can we improve on methadone? One approach is to understand exactly how it works. The reinforcing effect is mediated through the mu-opioid receptor, although the other actions, especially those leading to the prolonged withdrawal reactions, may have other sources. Given its wide and long-term use, methadone is a relatively less studied drug and interactions with other neurotransmitter or enzyme systems have not been systematically researched. Our study has shown that the blockade of on-top heroin use by methadone, although dose-related (Melichar *et al.*, 2003a), is not simply as a result of competition in brain opioid receptors. Positron emission tomography (PET) studies have found that methadone, in contrast to buprenorphine or antagonists (for example, naltrexone), occupies too few receptors for this to be detectable by human imaging methods (Greenwald *et al.*, 2003; Melichar *et al.*, 2003b; Melichar *et al.*, 2005). A similar lack of receptor occupation in rats has recently been reported for several opioid agonists, including methadone (Hume *et al.*, 2007). From these observations, we presume that the methadone blockade must reflect some degree of receptor subsensitivity, perhaps due to internalization of receptors. In this regard, methadone differs from morphine, which does not internalize mu receptors (Williams *et al.*, 2001). One obvious opportunity that thus arises is whether a methadone alternative with the same or better kinetics, but a different profile of secondary receptor effects, could be made that might be free of the long-term adaptive changes in the brain that methadone produces.

LAAM (l-α-acetylmethadol hydrochloride) is another opioid agonist that has even longer kinetics than methadone and so has the potential advantage of less-than-daily dosing (Law and Nutt, 2000). Currently, LAAM is not available in Europe owing to concerns regarding cardiac toxicity from an effect on QT interval in the heart.

Partial agonist substitution treatment

A proven alternative pharmacological approach to substitute treatment with full agonists is to use a partial agonist such as buprenorphine that is still reinforcing and so holds patients in treatment, but which has several theoretical advantages over full agonist treatment such as methadone (Law *et al.*, 2004). First, it is potentially much safer in overdose if a partial agonist with maximal efficacy below the threshold for respiratory depression is used (Figure 2)—buprenorphine fits this bill, and deaths from overdose alone are much reduced compared with methadone. Second, higher doses can be given so that a full occupancy of brain opioid receptors can be achieved, thus effectively blocking the value of any on-top heroin use (Figure 3). Third, a partial agonist may produce less receptor adaptation, so it may be easier to come off; and fourth, the patients will be less 'stoned'. In common with methadone, the treatment would reduce intravenous injecting, as patients would be getting a hit without the need to score and inject street drugs.

In practise, buprenorphine treatment confirms these assumptions. PET imaging has shown a dose-related blockade of the mu-opioid receptor (Greenwald *et al.*, 2003) and clear dose-related blockade of the effects of full agonists such as hydromorphone (Strain *et al.*, 1992). Withdrawal reactions to buprenorphine are lower in severity than those of methadone, but the interpretation of this is complicated by the different kinetics of the two drugs—buprenorphine has a considerably longer $t_{1/2}$. This latter fact can be used to clinical advantage, in that if high doses of buprenorphine are given, cover from heroin use can be achieved for 2–3 days, thus protecting against weekend heroin use (see Figures 2 and 3). Buprenorphine also makes users feel more normal and less stoned; however, this is not always liked by the patient, and in practise a significant proportion opt for methadone.

Additionally, buprenorphine is not free of risks; even partial agonists can produce a degree of respiratory depression that can be fatal in association with other respiratory depressants such as benzodiazepines. This risk is magnified if buprenorphine is given intravenously, a practise that is possible

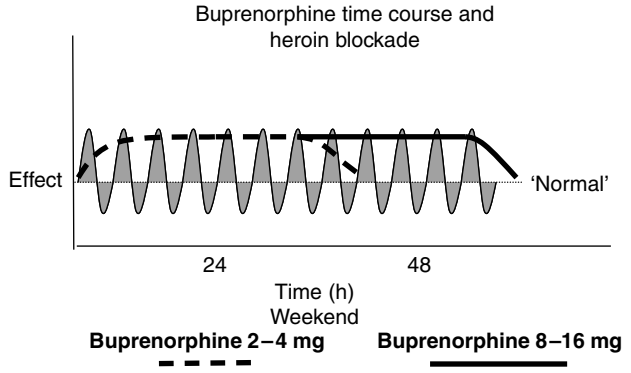

Figure 2 Same as Figure 1, but here the kinetics and actions of different doses of buprenorphine are superimposed on the pattern of heroin use. The longer half-time of buprenorphine means that even if it is not given every day, it still protects against the 'on-top' use of heroin.

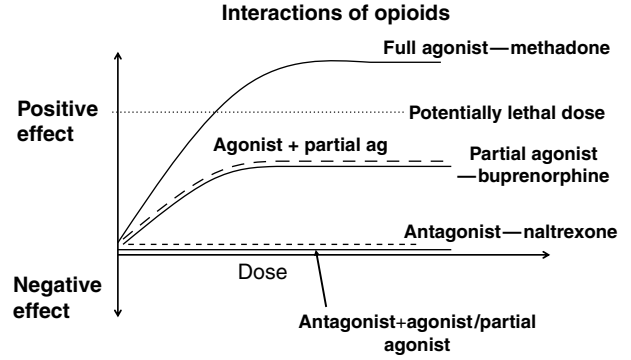

Figure 3 Schematic dose–effect relationships for opioid receptor agonists, partial agonists and antagonists, as well as their combinations.

as it is very water soluble. One way to minimize this risk is to make a combination treatment—buprenorphine plus a mu-receptor antagonist—and this has been done in such a way that a naloxone–buprenorphine combination is now widely used. If the tablet is taken by the normal route (sublingually), then the adsorption of naloxone is slight and the full buprenorphine effect is achieved. However, if the tablet is crushed and dissolved and then injected intravenously, naloxone enters the brain readily and more quickly than buprenorphine. This means that if there is a residual mu-agonist—for example, heroin or methadone—in the brain, naloxone will displace it, so precipitating withdrawal, an aversive experience that will hopefully dissuade users from trying it again! In a drug-naive user, the entry of naloxone before buprenorphine will to some extent attenuate the hit from the intravenous buprenorphine, so reducing the drive to inject. Combination treatments with opioid agonists and antagonists have been used before—for example, pentazocine/naloxone with a degree of success, so what about using a pure antagonist as treatment? This is discussed below.

Partial agonists have now been proven to be effective in another addiction—nicotine—where varenicline (an alpha4-beta2 partial nicotinic agonist) is now licensed on the basis of efficacy data showing a clinical effect that exceeds that of the other licensed medications—bupropion and nicotine replacement therapy (Rollema *et al*., 2007). The principles are the same as with buprenorphine for opioid dependence—substitution treatment sufficient to prevent the need to smoke, with attendant health benefits. Interestingly, there is emerging evidence that varenicline may also reduce alcohol consumption (Steensland *et al*., 2007)—perhaps suggesting a common nicotinic pathway in several addictions—as animal evidence suggests some effects of related compounds in opioid dependence (Glick *et al*., 2002).

Partial agonists have potential in the treatment of addiction to other drugs—especially that to benzodiazepines and stimulants. In an attempt to make benzodiazepine anxiolytics less abused (that would also be less sedating), several partial agonists were made and tested in humans (see Potokar and Nutt, 1994). These proved to be more sedating in humans than was predicted from animal pharmacology, so they were not progressed in anxiety and have not been taken up by the addiction community, for reasons that are discussed below in the last section. Dopamine partial agonists offer an interesting potential for stimulant addiction, as they might be predicted to provide some dopamine input where it is deficient, for example, in withdrawal states, although not themselves being abused. Moreover, they might block the effects of high dopamine levels, for example, after the use of cocaine. Considerable excitement in this field was produced by the report on BP897, which showed that it would stop cue-induced cocaine behaviour in rats (Pilla *et al*., 1999), although it was not itself self-administered. However, it did not stop cocaine self-administration once it had started. Clinical trials have, we believe, not been conducted owing to issues of toxicology, but other compounds of the same pharmacology are under investigation. Aripiprazole, an antipsychotic recently available for treatment of schizophrenia, is a dopamine receptor D2 type (DRD2) partial agonist. However, recent trials have not shown it to be helpful in stimulant abuse (Tiihonen *et al*., 2007), and the authors are not aware that it is any better in reducing substance misuse in patients with schizophrenia than other antipsychotics. Why drugs targeting the dopamine D2 receptor are of limited efficacy in addiction is perplexing given the large body of both human and rat data that this system is involved in addictive behaviours? (see below) One target for the future might be a compound with both dopamine D3 partial agonism and D1 antagonist properties (Morris *et al*., 2006; and see other papers in this issue).

Antagonists as treatments for addiction

As heroin and other abused opioids act on mu-opioid receptors in the brain, the idea of preventing their use by blocking their actions with an antagonist has been a long-term ambition of treatment providers. Mu antagonists exist, including naloxone, naltrexone and nalmefene, and are effective in reversing and/or blocking the acute effects of heroin. However, their utility in prevention of opioid misuse is limited by several factors. The key factor is that compliance with these drugs is much more difficult to ensure than that of the agonist treatments, for they provide no reinforcement or pleasure so there is little incentive to stay compliant. If compliance can be enforced, then outcomes can be good, because if the blockade of brain mu

receptors is high, then it cannot be overcome—even huge doses of heroin have little or no effect, a fact soon appreciated by the addict who rapidly gives it up. The best evidence of the therapeutic value of naltrexone is currently in health-care professionals such as doctors and pharmacists, where case working can be made conditional on daily consumption of the antagonist under supervision—usually by a spouse or partner.

However, if compliance is poor, then naltrexone therapy may be risky, because with a $t_{1/2}$ of about 24 h, stopping for a day or two will allow the full effect of heroin to be felt. If the patient has been on naltrexone for a few weeks, then the tolerance to heroin gained during the period of addiction before naltrexone treatment will be lost. If the addict stops the naltrexone to restart heroin—even for a one-off—and if they use the same dose as before, then they can experience serious problems with respiratory depression that may ultimately lead to death. For this reason, the use of non-compliant naltrexone has been criticized as being less harm reducing than either methadone or buprenorphine. This concern could be overcome if a long-acting preparation could be used, and several have been used in clinical treatment settings. The best data so far are with a long-acting naltrexone implant developed in Perth by Drs O'Neil and Hulse. They have tested a naltrexone containing polymer implant that is inserted subcutaneously and releases the antagonist over several months (Hulse *et al*., 2004a, b). The implant appears to be very well tolerated, with the only adverse effects being infection at the injection site and some localized itching in $<1\%$ of patients (Hulse *et al*., 2005). So far, they have treated many hundreds of opioid addicts with good outcomes, including an impressive reduction in opioid overdose deaths (Hulse *et al*., 2005) and lower incidence of blood-borne viral infections (Jeffrey *et al*., 2007). Subjective reports suggest positive impacts on work and family life, as well as on drug use alongside improved mental health and more normal sleep (Ngo *et al*., 2007). They can also be used in pregnant heroin addicts, where drugs effects on the foetus have to be carefully considered (Hulse *et al*., 2004b). Clearly, more work in this field is needed to fully characterize the dose and duration of this treatment in more extensive multisite-controlled clinical trials.

Other variants on naltrexone implants and other depot preparations are being developed and some are in clinical trials, and so it may be that this is an arena that will open up in the next few years. However, the risk of death once the antagonist is stopped or the patient removes the implant is a real one, so there is a need for consideration in minimizing such event, for example, through education or take-home antagonists to be used by friends or family in the case of an accidental overdose. It should be noted that the risk of overdose is present when any opioid treatment regime is stopped, so this is not unique to antagonist treatment, although it might emerge sooner with this approach.

Can we use antagonists for other addictions?

With the same caveats as mentioned above, the answer is yes. Naltrexone is licensed in some countries for treatment of alcohol dependence by facilitating abstinence, where it is thought to work by reducing the risk of a drinking lapse leading to a full relapse to loss of control drinking (see below). In this way, naltrexone has a different profile of action compared to other alcohol treatments, such as acamprosate and Antabuse (see Figure 4). A newer mu-opioid receptor antagonist (which may have some kappa partial agonist actions) has recently been shown to have efficacy in treating alcohol dependence, that is nalmefene (see Srisurapanont and Jarusuraisin, 2006).

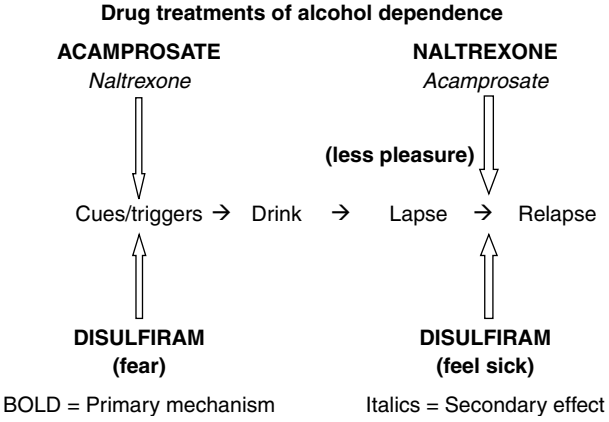

Figure 4 The possible mechanisms of actions of the three drugs that are used in the treatment of alcohol dependence. Presumed main therapeutic effects are shown in caps and lesser effects in italics.

Benzodiazepine abuse is common and there is an effective antagonist licensed for human use—flumazenil (Anexate). This is a highly potent, high-affinity antagonist that is active only via the intravenous route as first-pass metabolism is extensive. Using similar technology to the naltrexone implants, the Western Australia group has made an implantable flumazenil formulation that can provide antagonist cover for several months, so in theory it could be used in the treatment of benzodiazepine dependence. Other benzodiazepine antagonists have been made, often inadvertently, in the search for valium look-alikes but none have been taken into human trials because the indication of the treatment of benzodiazepine dependence has not yet been considered; hopefully, this volume will revive an interest in these compounds!

Cannabis dependence is becoming more recognized and it is known that the actions of this drug are mediated via the cannabinoid CB_1 receptor for which a number of potent and selective antagonists have been made. Their target indication is weight loss but there is no reason why these antagonists should not be used for other indications such as cannabis dependence (Nutt, 2005). They certainly block the effects of cannabis and can precipitate withdrawal, so therapeutic potential as functional antagonists is clearly there. Again, issues such as compliance and kinetics need to be taken into account but should not be insuperable.

One of the great concerns in the addiction field is the treatment of stimulant dependence, as many compounds have been tested but few have been found to be even minimally effective. As stimulants work indirectly on neurotransmitter pumps to increase release and/or prevent

reuptake, the use of antagonists is more problematic. However, there have been attempts to make dopamine uptake blockers with less abuse potential than cocaine, and animal studies have shown a degree of efficacy, although human trials to our knowledge have not been reported (Lindsey *et al.*, 2004; see Morris *et al.*, 2006, chapter). Another, perhaps more promising, use of antagonists in stimulant abuse is the dopamine D3 receptor, where in animal studies antagonists have been shown to reduce drug-seeking behaviours (Vorel *et al.*, 2002). Similarly, dopamine D1 agonism may be stimulant-like (Graham *et al.*, 2007), then antagonism could attenuate cocaine-seeking behaviour, as it seems to do for novelty-induced behaviours (Peters *et al.*, 2007). Perhaps, a drug that combined both actions would have even greater utility. Such a theory could easily be explored in animals.

Withdrawal

Managing withdrawal from substances of abuse is often a clinically challenging, as distress during withdrawal is a common reason for restarting drug use. For some substances of abuse, such as psychostimulants, symptomatic support is the mainstay of treatment, for example, for insomnia. For other substances, such as alcohol and opioids, knowledge about the underlying brain process has led to rationale pharmacotherapy that has altered clinical management.

Opioid withdrawal, for instance, can be managed without giving opioids—although the most common way to detoxify someone off opioids is to gradually reduce their substitution medication (methadone or buprenorphine) (Lingford-Hughes *et al.*, 2004). Preclinical studies noted, however, that increased activity in the noradrenaline system contributed to opioid withdrawal symptomatology. So α2-adrenoceptor agonists began to be used in the clinic to ameliorate the so-called 'noradrenergic storm' (Maldonado, 1997) by acting on inhibitory autoreceptors to dampen noradrenaline neuronal activity. Symptoms such as tachycardia, sweating, runny nose, hair standing on end, goose bumps (hence the term 'going cold turkey') are reduced by α2adrenergic agonist medications, such as clonidine or lofexidine. However, other medication is also needed to deal with insomnia or gastrointestinal (GI) disturbances, for example, diarrhoea.

Although withdrawal from many substances of abuse can be unpleasant or even distressing, it is rarely life threatening—except for alcohol. For people who are alcohol dependent, stopping drinking can lead to seizures or delirium tremens. Therefore, to prevent such problems, benzodiazepines such as chlordiazepoxide or diazepam are given in reducing doses for about a week to provide effective symptom control (Lingford-Hughes *et al.*, 2004). However, elsewhere in the world, anticonvulsants such as carbamazepine, are used for this purpose (Lingford-Hughes *et al.*, 2004). Benzodiazepines provide symptom control by increasing activity in the brain's inhibitory system (GABA-A) that has been reduced by chronic drinking (Lingford-Hughes and Nutt, 2003). However, there is preclinical evidence that benzodiazepines may not prevent or offset changes in brain function occurring in withdrawal episodes that contribute to seizures and neuronal loss (Mhatre *et al.*, 2001; Becker and Veatch, 2002). This toxicity appears primarily related to an overactive excitatory glutamate system (NMDA type) that is present when alcohol-dependent patients are in withdrawal (Lingford-Hughes and Nutt, 2003). In a number of preclinical models, reducing glutamate overactivity is associated with reduced excitability in alcohol withdrawal (Tsai and Coyle, 1998).

Therefore, anticonvulsants being used that have a direct 'anti-glutamatergic' activity may have greater neuroprotective effects than benzodiazepines—although this has never been directly examined in humans. One study, however, did report that those who had more than those previous detoxes (and therefore potentially greater glutamatergic dysfunction due to kindling) had better outcomes with regard to symptom control and drinking (Malcolm *et al.*, 2000). However, carbamazepine is associated with significant side effects and whereas it is widely used in some countries, in the United Kingdom, it has not been so acceptable to patients or clinicians. Notably, acamprosate (used clinically to maintain abstinence) in animal models has been shown to reduce glutamate overactivity or release in the nucleus accumbens and hippocampus during early ethanol withdrawal and to prevent associated hypermobility (Gewiss *et al.*, 1991; Spanagel *et al.*, 1996; Dahchour *et al.*, 1998; Dahchour and de Witte, 1999) or cell death (al Qatari *et al.*, 2001; Mayer *et al.*, 2002). In one study, diazepam appeared to worsen withdrawal-associated hyperactivity (Gewiss *et al.*, 1991). Interestingly, in low levels of alcohol withdrawal, acamprosate alone reduces brain hyperexcitability and improves sleep (Boeijinga *et al.*, 2004; Staner *et al.*, 2006). Therefore, examination as to whether current clinical treatments for alcohol detoxification minimize underlying neurobiological dysfunction leading to toxicity is urgently needed.

Future needs centre on the withdrawal from other drugs, especially stimulants and cannabis, neither of which are well served by current pharmacologies.

Craving—and how to reduce it?

In the clinic, craving receives a lot of attention, as it is implicated in causing relapse—although this has been hard to show definitively (Lowman *et al.*, 2000). In part, this may be due to the fact that it likely means different things to different people and can be time and context dependent. Preclinical models are unlikely, therefore, to fully represent all aspects of human craving. Broadly, craving can be used to describe a desire or drive to experience a 'high' from a drug (positive reinforcement), overcome a negative state such as anxiety or withdrawal (negative reinforcement) or simply an 'urge' or 'compulsion'. These are likely to have different neuropharmacologies leading to a range of potential targets for development of 'anti-craving' drugs for the clinic.

The dopamine mesolimbic system

A number of pharmacotherapies have been developed that alter the activity of the dopaminergic mesolimbic pathway

that is intimately involved in reinforcing effects of the drug. Such pharmacotherapy aims to prevent relapse once abstinence has been achieved or alternatively to minimize the reinforcing effects of drugs of abuse so that use decreases as the individual tries to stop.

Fortunately, the availability of *in vivo* imaging techniques such as PET has enabled us to image many facets of dopaminergic neurotransmission in the striatum, including levels of monoamine oxidase-type A (MAO-A), dopamine transporter, dopamine D1 and D2 receptors and dopamine turnover. Studies of D2 receptor binding using ^{11}C-raclopride displacement (see Laruelle, 2000) have allowed the effects of drugs on dopamine release to be measured. Many human studies have shown that drugs of abuse such as nicotine, alcohol and a variety of stimulants result in increased dopamine levels in the striatum of naive or non-dependent individuals (Volkow *et al.*, 2004), which fits with the animal microdialysis literature (see Di Chiara, 2002). In addition, in some cases, the increase in dopamine parallels the 'high' experienced, suggesting a direct effect of this neurotransmitter to cause pleasure with these drugs (although interestingly not for mu-opioid agonists such as alfentanil (Hagelberg *et al.*, 2002) or heroin (Daglish *et al.*, 2007)). Therefore, clinically, it was hoped that by blocking this dopaminergic effect, the 'high' would be reduced and that the individual would then not continue to take the drug. Several dopamine antagonists, principally antipsychotics, have been tested under laboratory conditions and can block craving or effects of a variety of drugs, but in the clinic they are not efficacious neither are the side effects tolerable.

However, in stimulant addicts or alcoholics, D2 receptor levels are often reduced in number compared with healthy controls—perhaps, in a compensatory manner to alter the effects of excess dopamine simulation or perhaps as a pre-existing vulnerability factor (Volkow *et al.*, 1997; Martinez *et al.*, 2005). Abstinence may result in recovery of DRD2 levels but not in all individuals. In heroin addicts, a study similarly showed reduced DRD2 levels, which we have, however, failed to replicate, suggesting that the dopamine system may not be as hard hit by heroin as in the case of other drugs of abuse (Wang *et al.*, 1997; Daglish *et al.*, 2007). It is likely that this reduced activity in the dopaminergic system mediates the lack of pleasure or anhedonia that addicts often experience in their recovery; this can lead to their relapse. As already described, partial agonists are able to boost (to overcome hypodopaminergic state) or block (when drug of abuse is taken), but their preclinical promise has not been realized as yet in the clinic.

An intriguing alternative strategy is to use disulfiram (Antabuse). This has a long track record in the treatment of alcohol dependence where it blocks aldehyde dehydrogenase, a liver enzyme necessary for clearing this metabolic product of alcohol. The resulting build-up of acetaldehyde if alcohol is drunk leads to an aversive reaction, thus limiting future intake. However, it has recently been shown that disulfiram can also block dopamine B-hydroxylase in the brain, thus resulting in an increase in dopamine and depletion in noradrenaline, both of which changes may be beneficial in stimulant dependence. Currently, disulfiram is showing promise in treating cocaine addiction and it is hypothesized that this may be due to its effects on the dopaminergic system, although clear evidence of this is needed (Preti, 2007).

The role of dopamine in substance abuse is now seen as more complicated than simply mediating the positive reinforcement, and its role in learning and expectation is seen as important. Schultz (2001) has elegantly shown that ventral tegmental area dopaminergic neurons initially fire more in response to a pleasurable, unconditioned stimulus (food), but this increased firing then transfers to a cue that is paired with the pleasurable stimulus. Importantly, no increase in dopaminergic activity is then seen in the food condition, rather, if it is not present, a reduction in dopaminergic cell firing is seen. It is often clinically evident that salient cues can mimic drug effects and this may be the reason why. In PET studies of addicts, stimulant-induced (amphetamine) or enhanced (methylphenidate) dopamine release is measurable, although it can be blunted. However, notably, dopamine release in response to their drug of choice has not been measurable in two studies—with heroin (Daglish *et al.*, 2007) and stimulant (Volkow *et al.*, 1997) users, whereas cues have been shown to result in increased dopamine levels (Volkow *et al.*, 2006; Wong *et al.*, 2006). This supports the idea that once someone has become addicted, dopamine plays a more important role in signalling the significance of a cue rather than mediating the effects of the drug of misuse itself.

Targeting other neurotransmitter systems

Pharmacotherapeutic approaches that act directly on the dopaminergic system have not been successful clinically; however, those that target neurotransmitter systems that modulate the dopaminergic system are showing much greater promise.

GABA-ergic system

The dopaminergic cell bodies in the ventral tegmental area are under GABA-ergic control and the GABA-B receptor plays a critical role here (Cousins *et al.*, 2002). GABA-B agonists, such as baclofen, can reduce the reinforcing effects of several different classes of abused drugs, (for example, heroin, psychostimulants, alcohol) in animal models under a variety of conditions. Studies in man have also shown baclofen to be promising in treating cocaine addiction and alcoholism, and large clinical trials are currently underway (Cousins *et al.*, 2002).

Other approaches to altering GABA neurotransmission include the use of anticonvulsants—which, in fact, are being used clinically for a variety of conditions, including mood stabilizers in bipolar disorder. The exact pharmacology of these drugs is not fully characterized but all also affect the glutamatergic system. Anticonvulsants, such as valproate, tiagabine and topiramate, are showing promise in treating psychostimulant misuse and alcoholism, whereas others appear to have no utility (Lingford-Hughes *et al.*, 2004; Sofuoglu and Kosten, 2006; Johnson *et al.*, 2007).

Opioid system

The mu-opioid receptor on the GABA neurons also plays a key role in modulating ventral tegmental area dopaminergic activity. A link between alcohol use and endogenous opioid activity was suggested by animal models, and the opioid antagonist naltrexone reduced alcohol self-administration by blocking this mu-opioid receptor. PET studies have also revealed increased levels of the mu-opioid receptor in recently abstinent cocaine, alcohol or heroin addicts, which in alcohol and cocaine addicts are associated with craving (Zubieta *et al*., 1996; Heinz *et al*., 2005; Williams *et al*., 2007). In probably the best example of translation from 'lab to clinic', as mentioned above, naltrexone has now been shown in a number of different clinical trials in alcoholism to reduce the risk of a full-blown relapse—particularly after a lapse (that is, one or two drinks) (Pettinati *et al*., 2006). It does not work for everyone and recent studies, suggest that it is most beneficial in those that are less severely alcohol dependent and mu-opioid polymorphisms also play a role in its effectiveness (Anton *et al*., 2006; Ray and Hutchison, 2007). Although other drugs of abuse also work through the opioid system and PET studies suggest increased availability of opioid receptors in humans, naltrexone does not appear to be efficacious in treating either nicotine or cocaine addiction (Vocci and Ling, 2005). Indeed, for cocaine addiction, currently the best treatments, by far, are psychosocial.

Kinetic considerations

The emphasis in the present review is very much on the dynamic receptor-based pharmacology of drugs in addiction. However, it is very important to realise that kinetic factors—especially rate of drug delivery to the brain—are also important in the initiation and maintenance of drug dependence. They also influence efficacy and compliance of drug treatments. In the opioid treatment section, we explained how the kinetics of agonists and partial agonists, particularly those with longer half-lives such as methadone and buprenorphine, has assisted in their use as substitution therapies. Similar considerations apply with other addictions—for example, the nicotine patch offers a continuous supply of nicotine to obviate the need to smoke cigarettes to prevent withdrawal. Also, nicotine is the only addiction for which a wide range of different substitutions with different kinetic profiles is readily available—from the fast-acting nicotine inhalator to the nicotine gum and patch with a partial agonist varenicline as a further alternative. This serves as a model for seeking new interventions in other addictions.

Future needs

Some of these have already been touched upon; however, there is one area of great interest at present that needs emphasis, that is, using drugs implicated in learning and memory to UNLEARN addiction. The value of glutamate enhancers, especially D-cycloserine, to promote the learning of safety behaviour—that is, equivalent to unlearning fear—has been shown by the Davis group and is now being translated into clinical evidence. For example, in clinical populations, D-cycloserine has been shown to accelerate learning to overcome fear of heights (Ressler *et al*., 2004) and social situations (Hofmann *et al*., 2006).

As several of the other papers in this volume identify learning mechanism, especially glutamate based, that are central to many aspects of addiction, could the same principles of accelerating learning of new non-addiction strategies or behaviours be promoted by glutamate-enhancing drugs? We are in the process of completing a study of D-cycloserine augmentation of exposure therapy in alcohol dependence, and other trials in smoking cessation are underway. Hopefully, in a few years, the potential of such interventions will be apparent. However, D-cycloserine may not be the ideal pro-glutamate drug; indeed, it is being used in these studies simply because it is available for clinical use, being an old treatment for tuberculosis that was also trialed in dementias and schizophrenia; other drugs that may have a stronger pharmacological rationale are yet to be cleared for research on humans.

For such developments to work, there will need to be considerable investment in translational tools so that preclinical evidence can be properly tested in human models. Over the years 'big pharma' has shied away from major investment in addiction. There are many reasons for this, the major ones being

(1) A dislike of having their 'clean' health-giving drug treatments being associated with a 'dirty' disorder, as addiction has been seen for decades—'stockholders would not like it' is a common supposition that is probably close to the truth. Now evidence that such treatments can bring financial rewards (for example, bupropion for nicotine dependence) is going some way to offset this view.
(2) Addiction is not an illness that can be treated with drugs. Thankfully, advances in medicine and neuroscience in the last two decades have revealed addiction to have a brain basis and be amenable to treatments, with outcomes equivalent to those achieved in other diseases.
(3) Uncertainty that governments will reimburse new addiction treatments should they be made. This is a fair point, although the utility of nicotine replacement therapy has been long established, it is only in the last few years that the UK government has made them available on the national health service (NHS). It is incumbent on both clinical and non-clinical researchers to lobby hard to ensure that such anomalies are exposed and overturned.

As indicated, each of these premises is clearly false and we hope that the continued progress in the pharmacology of addiction, as detailed in these reviews, will help progress in the field and further encourage pharmaceutical inputs into this hugely important medical problem.

Conclusions

The neuroscience of addiction has made remarkable advances in the past 20 years. Pharmacology, especially that

applied to the treatment of humans with drug addiction, has a long way to catch up. Nevertheless, there are good examples already of how basic pharmacological principles, both kinetic and dynamic, have been used to develop effective treatments, for examples, in the field of opioid and nicotine dependence. With a little more creativity and effort, similar advances can be expected for other drugs where there is still a grea, or even a growing problem, especially for crack cocaine and methamphetamine. Translational medicine approaches—in both directions—offer the best way to progress in this field, and this volume gives a substantial underpinning and considerable impetus to such a goal.

Conflict of interest

Nutt—in past 5 years

- Consultancies—Pfizer (W-L), GSK (SKB), MSD, Esteve, Novartis, Asahi, Organon, Cypress, Lilly, BMS, Janssen, Takeda, Phamacia, Therasci, Passion for Life, Hythiam, Servier, Roche, Sanofi-Aventis, Actelion, Lundbeck, Wyeth, Teva
- Speaking honoraria (in addition to above) Reckitt-Benkiser, Cephalon
- Grants or clinical trial payments—Reckitts, MSD, GSK, Novartis, Servier, Janssen, Yamanouchi, Lundbeck, Pfizer, Wyeth, Organon, AZ, Cephalon, P1vital, MoDefence, NHS,
- Shares ~300 GSK (ex-Wellcome)
- Worked for the UK Government's Committee on Safety of Medicines; Advisory Council on the Misuse of Drugs, British National Formulary

Lingford-Hughes

- Consultancies—BMS, Sanofi-Aventis
- Speaking honoraria—Janssen-Cilag
- Grants or clinical trial payments—Wyeth

Worked for NICE on opioid detox guidelines and DoHealth.

References

al Qatari M, Khan S, Harris B, Littleton J (2001). Acamprosate is neuroprotective against glutamate-induced excitotoxicity when enhanced by ethanol withdrawal in neocortical cultures of fetal rat brain. *Alcohol Clin Exp Res* **25**: 1276–1283.

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM *et al.* (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* **295**: 2003–2017.

Becker HC, Veatch LM (2002). Effects of lorazepam treatment for multiple ethanol withdrawals in mice. *Alcohol Clin Exp Res* **26**: 371–380.

Beswick T, Best D, Rees S, Bearn J, Gossop M, Strang J (2003). Major disruptions of sleep during treatment of the opiate withdrawal syndrome: differences between methadone and lofexidine detoxification treatments. *Addict Biol* **8**: 49–57.

Boeijinga PH, Parot P, Soufflet L, Landron F, Danel T, Gendre I *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.

Cousins MS, Roberts DCS, de Wit H (2002). GABA b receptor agonists for the treatment of drug addiction: a review of recent findings. *Drug Alcohol Depend* **65**: 209–220.

Daglish MRC, Williams TM, Wilson SJ, Taylor LG, Eap C, Augsburger M *et al.* (2007). Dopamine response in human opioid addiction. *Br J Psychiatry*, in press.

Dahchour A, De Witte P (1999). Acamprosate decreases the hypermotility during repeated ethanol withdrawal. *Alcohol* **18**: 77–81.

Dahchour A, de Witte P, Bolo N, Nedelec JF, Muzet M, Durbin P *et al.* (1998). Central effects of acamprosate: part 1. Acamprosate blocks the glutamate increase in the nucleus accumbens microdialysate in ethanol withdrawn rats. *Psychiatry Res* **82**: 107–114.

Di Chiara G (2002). Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Brain Res* **137**: 75–114.

Gewiss M, Heidbreder C, Opsomer L, Durbin P, de Witte P (1991). Acamprosate and diazepam differentially modulate alcohol-induced behavioural and cortical Alterations in rats following chronic inhalation of ethanol vapour. *Alcohol* **26**: 129–137.

Glick SD, Maisonneuve IM, Kitchen BA, Fleck MW (2002). Antagonism of alpha 3 beta 4 nicotinic receptors as a strategy to reduce opioid and stimulant self-administration. *Eur J Pharmacol* **438**: 99–105.

Graham DL, Hoppenot R, Hendryx A, Self DW (2007). Differential ability of D1 and D2 dopamine receptor agonists to induce and modulate expression and reinstatement of cocaine place preference in rats. *Psychopharmacology (Berl)* **191**: 719–730.

Greenwald MK, Johanson CE, Moody DE, Wood JH, Kilbourn MR, Koeppe RA. *et al.* (2003). Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* **28**: 2000–2009.

Hagelberg N, Kajander J, Nagren K, Hinkka S, Hietala J, Scheinin H (2002). Mu-receptor agonism with alfentanil increases striatal dopamine D2 receptor binding in man. *Synapse* **45**: 25–30.

Heinz A, Reimold M, Wrase J, Hermann D, Croissant B, Mundle G *et al.* (2005). Receptor availability in detoxified alcoholic patients with alcohol craving a positron emission tomography study using carbon 11-labeled carfentanil. *Arch Gen Psychiatry* **62**: 57–64.

Hofmann SG, Meuret AE, Smits JAJ, Simon NM, Pollack MH, Eisenmenger K (2006). Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry* **63**: 298–304.

Hulse GK, Arnold-Reed DE, O'Neil G, Chan CT, Hansson RC (2004a). Achieving long term continuous blood naltrexone and 6-beta naltrexol coverage following sequential naltrexone implants. *Addict Biol* **9**: 67–72.

Hulse GK, Stalenberg V, McCallum D, Smit W, O'neil G, Morris N *et al.* (2004b). Histological changes over time around the site of sustained release naltrexone-poly(dl-lactide) implants in humans. *J Control Release* **108**: 43–55.

Hulse GK, Tait RJ, Comer SD, Sullivan MA, Jacobs IG, Arnold-Reed D (2005). Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. *Drug Alcohol Depend* **79**: 351–357.

Hume SP, Lingford-Hughes AR, Nataf V, Hirani E, Ahmad R, Davies AN *et al.* (2007). Low sensitivity of the PET ligand [11C]diprenorphine to agonist opiates. *J Pharmacol Exp Ther* **322**: 661–667.

Jeffrey GP, MacQuillan G, Chua F, Galhenage S, Bull J, Young E *et al.* (2007). Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. *Hepatology* **45**: 111–117.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K *et al.* (2007). Topiramate for treating alcohol dependence a randomized controlled trial. *JAMA* **298**: 1641–1651.

Laruelle M (2000). Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J Cereb Blood Flow Metab* **20**: 423–451.

Law FD, Myles JS, Daglish MRC, Nutt DJ (2004). The clinical use of buprenorphine in opiate addiction: evidence and practice. *Acta Neuropsychiatrica* **16**: 246–274, with erratum at 2004; **16**: 326.

Law FD, Nutt DJ (2000). Drugs used in the treatment of the addictions. *New Oxford Textbook of Psychiatry*, vol 2. OUP: oxford, pp 7–10.

Lindsey KP, Wilcox KM, Votaw JR, Goodman MM, Plisson C, Carroll FI *et al*. (2004). Effects of dopamine transporter inhibitors on cocaine self-administration in rhesus monkeys: relationship to transporter occupancy determined by positron emission tomography neuroimaging. *J Pharmacol Exp Ther* **309**: 959–969.

Lingford-Hughes AR, Nutt D (2003). The neurobiology of addiction and implications for treatment. *Br J Psychiatry* **182**: 97–100.

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

Lowman C, Hunt WA, Litten RZ, Drummond DC (2000). Research perspectives on alcohol craving: an overview. *Addiction* **95** (S2): S45–S54.

Malcolm R, Roberts JS, Wang W, Myrick H, Anton RF (2000). Multiple previous detoxifications are associated with less responsive treatment and heavier drinking during an index outpatient detoxification. *Alcohol* **22**: 159–164.

Maldonado R (1997). Participation of noradrenergic pathways in the expression of opiate withdrawal: biochemical and pharmacological evidence. *Neurosci Biobehav Rev* **21**: 91–104.

Martinez D, Gil R, Slifstein M, Hwang DR, Huang Y, Perez A *et al*. (2005). Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry* **58**: 779–786.

Mayer S, Harris BR, Gibson DA, Blanchard JA, Prendergast MA, Holley RC *et al*. (2002). Acamprosate, MK-801, and ifenprodil inhibit neurotoxicity and calcium entry induced by ethanol withdrawal in organotypic slice cultures from neonatal rat hippocampus. *Alcohol Clin Exp Res* **26**: 1468–1478.

Melichar JK, Hume SP, Williams TM, Daglish MRC, Taylor LG, Ahmad R *et al*. (2005). Using [11C]-diprenorphine to image opioid receptor occupancy by methadone in opioid addiction: clinical and preclinical studies. *J Pharmacol Exp Ther* **312**: 309–315.

Melichar JK, Myles JS, Eap CB, Nutt DJ (2003b). Using saccadic eye movements as objective measures of tolerance in methadone dependent individuals during the hydromorphone challenge test. *Addict Biol* **8**: 59–66.

Melichar JK, Nutt DJ, Malizia AL (2003a). Naloxone displacement at opioid receptor sites measured *in vivo* in the human brain. *Eur J Pharmacol* **459**: 217–219.

Mhatre MC, McKenzie SE, Gonzalez LP (2001). Diazepam during prior ethanol withdrawals does not alter seizure susceptibility during a subsequent withdrawal. *Pharmacol Biochem Behav* **68**: 339–346.

Milroy C, Forrest A (2000). Methadone deaths: a toxicological analysis. *J Clin Pathol* **53**: 277–281.

Morris K, Iversen L, Nutt DJ (2006). Pharmacology and treatments. In: Nutt DJ, Robbins TW, Stimson GV, Ince M, Jackson A (eds). *Drugs and the Future: Brain Science, Addiction and Society*. Elsevier: USA, ISBN 0-12-370624-6, pp 169–208.

Ngo HTT, Tait RJ, Arnold-Reed DE, Hulse GK (2007). Mental health outcomes following naltrexone implant treatment for heroin-dependence. *Prog Neuropsychopharmacol Biol Psychiatry* **31**: 605–612.

NICE (2007). *Methadone and Buprenorphine for the Management of Opioid Dependence. NICE Technology Appraisal Guidance 114*. National Institute for Health and Clinical Excellence: London.

Nutt D (2005). Cannabis antagonists: a new era of social psychopharmacology? *J Psychopharmacol* **19**: 3–4.

Peters JR, Vallie B, Difronzo M, Donaldson ST (2007). Role of dopamine D1 receptors in novelty seeking in adult female Long–Evans rats. *Brain Res Bull* **74**: 232–236.

Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM *et al*. (2006). The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. *J Clin Psychopharmacol* **26**: 610–625.

Pilla M, Perachon S, Sautel F, Garrido F, Mann A, Wermuth CG *et al*. (1999). Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist [published erratum appears in *Nature* 1999; **401**: 403]. *Nature* **400**: 371–375.

Potokar J, Nutt DJ (1994). Anxiolytic potential of benzodiazepine receptor partial agonists. *CNS Drugs* **1**: 305–315.

Preti A (2007). New developments in the pharmacotherapy of cocaine abuse. *Addict Biol* **12**: 133–151.

Ray LA, Hutchison KE (2007). Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response. A double-blind placebo-controlled study. *Arch Gen Psychiatry* **64**: 1069–1077.

Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E *et al*. (2004). Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* **61**: 1136–1144.

Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE (2007). Rationale, pharmacology and clinical efficacy of partial agonists of alpha4beta2 nACh receptors for smoking cessation. *Trends Pharmacol Sci* **28**: 316–325.

Schultz W (2001). Reward signalling by dopamine neurons. *Neuroscientist* **7**: 293–302.

Sofuoglu M, Kosten TR (2006). Emerging pharmacological strategies in the fight against cocaine addiction. *Expert Opin Emerg Drugs* **11**: 91–98.

Spanagel R, Putzke JS, Stefferl A, Schobitz A, Zieglgansberger W (1996). Acamprosate and alcohol: II. Effects on alcohol withdrawal in the rat. *Eur J Pharmacol* **305**: 45–50.

Srisurapanont M, Jarusuraisin N (2006). Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* **25**: CD001867.

Staner L, Boeijinga P, Danel T, Gendre I, Muzet M, Landron F *et al*. (2006). Effects of acamprosate on sleep during alcohol withdrawal: a double-blind placebo-controlled polysomnographic study in alcohol-dependent subjects. *Alcohol Clin Exp Res* **30**: 1492–1499.

Steensland P, Simms JA, Holgate J, Richards JK, Bartlett SE (2007). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. *Proc Natl Acad Sci USA* **104**: 12518–12523.

Strain EC, Preston KL, Liebson IA, Bigelow GE (1992). Acute effects of buprenorphine, hydromorphone and naloxone in methadone-maintained volunteers. *J Pharmacol Exp Ther* **261**: 985–993.

Tiihonen J, Kuoppasalmi K, Föhr J, Tuomola P, Kuikanmäki O, Vorma H (2007). A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* **164**: 160–162.

Tsai G, Coyle JT (1998). The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. *Annu Rev Med* **49**: 173–184.

Vocci F, Ling W (2005). Medications development: successes and challenges. *Pharmacol Ther* **108**: 94–108.

Volkow ND, Fowler JS, Wang GJ (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology* **47** (S1): 3–13.

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Hitzemann R *et al*. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine dependent subjects. *Nature* **386**: 830–833.

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR *et al*. (2006). Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* **26**: 6583–6588.

Vorel SR, Ashby Jr CR, Paul M, Liu X, Hayes R, Hagan JJ (2002). Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *J Neurosci* **22**: 9595–9603.

Wang GJ, Volkow ND, Fowler JS, Logan J, Abumrad NN, Hitzemann RJ (1997). Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology* **16**: 174–182.

Williams JT, Christie MJ, Manzon O (2001). Cellular and synaptic adaptations mediating opioid dependence. *Pharmacol Rev* **81**: 299–343.

Williams TM, Daglish MRC, Lingford-Hughes A, Taylor LG, Hammers A, Brooks DJ *et al*. (2007). Brain opioid receptor binding in early abstinence from opioid dependence: an [^{11}C]diprenorphine PET study. *Br J Psychiatry* **191**: 63–69.

Wong DF, Kuwabara H, Schretlen DJ, Bonson KR, Zhou Y, Nandi A *et al*. (2006). Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology* **31**: 2716–2727.

Zubieta JK, Gorelick DA, Stauffer R, Ravert HT, Dannals RF, Frost JJ (1996). Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nat Med* **2**: 1225–1229.