Neuropharmacology of addiction and how it informs treatment

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Our knowledge about the neuropharmacology of addiction is increasing and is leading to more informed development of pharmacotherapy. Although the dopaminergic mesolimbic system plays a central role in ‘liking’, reward and motivation, medications directly targeting it have not proved a very fruitful approach to treating addictions. A review of the literature was performed to find articles relating current and developing pharmacological treatments in the clinic and their underlying neuropharmacology. We focussed on the most common addictions for which pharmacology plays an important role. By characterizing what neurotransmitters modulate this dopaminergic pathway, new medications are now in the clinic and being successfully applied to treat a variety of addictions. In addition to modulating this reward pathway, alternative approaches in the future will target learning and memory, improving impulse control and decision-making.

Keywords: neuropharmacology/addiction/treatment/alcohol/opioid/nicotine

Many individuals try substances to see what they are like, often during late adolescence or early adulthood, and for most individuals and for most substances, the use or misuse will be time limited. However, for some individuals, use becomes misuse and they then become dependent on, or addicted to, the substance. In this transition to dependence, loss of control over consumption is the key diagnostic criterion in both the diagnostic and statistical manual (DSM), the American taxonomy of psychiatric conditions, and the international classification of diseases (ICD), a similar classification system used by the World Health Organisation. DSM and ICD. Once dependent, it is rare that someone ever regains control when consuming that substance. This review will describe the underlying neurobiology of dependency and how this
### Table 1: Substances of abuse—their key neuropharmacology and current clinical pharmacotherapeutic approaches.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary target</th>
<th>Main effects/transmitters</th>
<th>Adaptations in addiction</th>
<th>Other actions</th>
<th>Clinical pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>GABA-A; glutamate: NMDA</td>
<td>Inc. GABA; decrease in levels or function of glutamate</td>
<td>Reduced GABA sensitivity; upregulated NMDA glutamate</td>
<td>Many other systems, e.g. reward: opioid, GABA-B, dopamine</td>
<td>Not generally used Benzodiazepines or anticonvulsants to increase GABA-ergic function; reduce glutamatergic activity with anticonvulsants or acamprosate</td>
</tr>
<tr>
<td>Opiates</td>
<td>MOR</td>
<td>Increase opioid activity</td>
<td>Reduced sensitivity of MOR; upregulation of noradrenergic (NA) activity</td>
<td>Kappa and delta opiate receptors</td>
<td>Methadone; buprenorphine; diamorphine Reducing regimens of methadone; buprenorphine; reduce NA hyperactivity with alpha2 agonist, e.g. clonidine or lofexidine Opiate antagonist to prevent access to receptor, naltrexone</td>
</tr>
<tr>
<td>Stimulants: cocaine; amphetamine; methamphetamine</td>
<td>DAT</td>
<td>Inc. dopamine</td>
<td>Reduced DA-ergic activity; enhanced glutamatergic activity</td>
<td>Local anaesthetic? Inc NA/SHT</td>
<td>Controversial: can prescribe stimulants, those with longer on-off kinetics, e.g. oral methylphenidate None: symptomatic</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicotinic ACh receptor</td>
<td>Inc. dopamine</td>
<td>Reduced DA-ergic activity; enhanced glutamatergic activity</td>
<td>Nicotine formulations, e.g. patches, gum, etc.</td>
<td>Nicotine formulations, e.g. patches, gum, etc., varenicline: a nicotinic partial agonist; bupropion: a DAT/NAT</td>
</tr>
<tr>
<td>Drug</td>
<td>Receptors/Activity</td>
<td>Effect on GABA-A receptors</td>
<td>Effect on GABA-B receptors</td>
<td>Effect on Dopamine/Opioid Systems</td>
<td>Effect on Serotonin Transporter</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------</td>
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<td>-------------------------------</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Inc. GABA-ergic</td>
<td>Reduced GABA-A activity</td>
<td>Reduced GABA-A sensitivity</td>
<td>Unclear</td>
<td>None</td>
</tr>
<tr>
<td>GHB</td>
<td>Metabolic precursors of GABA</td>
<td>Increase GABA, likely involves GABA-A and GABA-B receptors</td>
<td>Clear</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cannabis</td>
<td>CB1 receptors</td>
<td>Modulation of dopamine and opioid systems</td>
<td>Controversial though reduced SERT been reported</td>
<td>Some DA release also</td>
<td>None</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>SERT</td>
<td>Inc. SHT</td>
<td>Some DA release also</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ketamine/PCP</td>
<td>NMDA</td>
<td>Dec glutamate</td>
<td>Controversial</td>
<td>Some DA release also</td>
<td>None</td>
</tr>
<tr>
<td>LSD</td>
<td>5HT2 receptors</td>
<td>Dec glutamate</td>
<td>Clear</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Adapted from Lingford-Hughes and Nutt, 2003.
Inc., increase in levels or function; Dec., decrease in levels or function; DA, dopamine; NA, noradrenaline; MOR, mu opiate receptor; SERT, serotonin transporter; ACH, acetylcholine; GHB, gammahydroxybutyrate.
relates to pharmacotherapy for substance misuse commonly seen by clinical teams—nicotine, alcohol, opioids and stimulants. For other substances of abuse (e.g. cannabis, ecstasy, hallucinogens, see Table 1), there is little current evidence to support pharmacotherapy and psycho-social interventions remain the best approach to treatment.

The impact of problematic drug and alcohol misuse on global health is high. The WHO reports that tobacco contributes to 8.8% of all deaths worldwide, alcohol to 3.2% and illicit drugs to 0.4%. In terms of years lost due to disability in men, alcohol use disorders are second only to unipolar depression and are particularly prominent in high-income countries.¹ For example in England, it is estimated that 24% of adult men and 13% of adult women drink in a hazardous or harmful way and alcohol-related harm to cost £20 billion.² The economic and social costs of class A drug use in the UK are estimated at £15.4 billion, or £44231 per problem drug user per year for 2003/04.³ Ninety per cent of this cost is attributed to drug-related crime, but health-care costs amount to £1.4 billion per year.

**Neurobiological pathways in addiction and the role of dopamine**

The neural pathways involved in addiction are much the same as those that underlie processes of motivation, the processing of rewards and making decisions about how to deal with rewards. In terms of dynamical equilibrium in the brain, what starts off as a system in a state of homeostatic balance may undergo an allostatic shift so that equilibrium can only be maintained by the continuing consumption of drugs.⁴

The dopaminergic mesolimbic system is key in the circuitry of reward and motivated behaviour and includes the following:

- The nucleus accumbens (NAcc), which is implicated in learning to predict rewards and to express adaptive behaviours.
- The orbitofrontal cortex (OfCx), which is involved in stimulus evaluation—telling us ‘what we want’, being able to wait for larger rewards over immediate but smaller ones, and impulse control.
- The amygdala, which responds to the intensity of rewarding and aversive stimuli and also links motivationally relevant events with neutral stimuli and the autonomic and endocrine systems.

The dopaminergic mesolimbic system arises in the ventral tegmental area (VTA) in the brainstem and projects to the NAcc in the ventral striatum and the prefrontal cortex (PfCx). Preclinical studies have shown that increased levels of dopamine in the NAcc are critical in
mediating rewarding effects or positive reinforcement for all drugs of misuse except possibly benzodiazepines. This increase in dopamine may occur directly as a result of:

- binding at the dopamine transporter (DAT), which blocks dopamine reuptake in the NAcc (e.g. cocaine)
- reuptake blockade combined with direct dopamine release from the terminals (e.g. amphetamine)
- increasing dopaminergic neuronal firing via disinhibition in the VTA (e.g. alcohol, opiates, nicotine).

Consistent with the abundant evidence from preclinical studies, increases in dopamine in the ventral striatum have been shown to be associated with the pleasurable or euphoric effects of stimulants. Increases in dopamine have also been demonstrated with nicotine and alcohol but not consistently and not always associated with ‘high’. No increases in dopamine have been seen with opioids, indeed a reduction has been reported. Whilst it may be that the amount of dopamine released is too small to be reliably detected, reinforcement may also result from non-dopaminergic pathways.

Several studies in man have now shown the low dopamine D2 receptor (DRD2) availability is associated with drug liking for stimulants. Preclinical studies have also demonstrated a similar association. A study in primates demonstrated that re-housing individuals into groups of four resulted in an increase in DRD2 in those monkeys that became dominant, whilst DRD2 levels remained lower in subordinate monkeys. When given access to cocaine, the subordinate monkeys consumed more than the dominant monkeys, consistent with the hypothesis that low DRD2 is associated with greater liking for substances of abuse. Further studies with these monkeys have shown that increased social interaction can reduce the reinforcing effects of cocaine. Thus, the environment can alter striatal dopaminergic function. Psychogenetic traits, e.g. higher levels of impulsivity, also increase vulnerability to addiction, for example impulsive rats had lower levels of striatal DRD2 and consumed greater amounts of cocaine than less impulsive rats. Notably the cocaine reduced their level of impulsivity (Fig. 1).

Preclinical models demonstrate that sensitization, i.e. greater increases in dopamine and behaviour, occurs with less drug after repeated exposure. In healthy volunteers, 14 days and a year after a single exposure to amphetamine, greater increases in dopamine resulted from the subsequent amphetamine doses accompanied by greater behavioural responses. However, in addicts, reduced dopaminergic function is found as measured by release, dopamine synthesis and DRD2 levels, suggesting that such sensitization is not a prominent
feature of dependence in man. In addition, abstinence does not always result in ‘normalization’ of dopaminergic function. Given low DRD2 levels are associated with greater vulnerability to drug consumption and liking, are these reduced levels a cause or consequence of their substance misuse? Owing to recall difficulties, it is problematic to demonstrate in man associations between the amount of substance misuse and dopaminergic function; however, preclinical studies in monkeys described above have shown that cocaine misuse can reduce DRD2 levels. Notably, in the monkeys, abstinence was variably associated with increases in DRD2 levels. It will be important to characterize how to optimize recovery or normalization in the dopaminergic system since it also plays a key role in mediating pleasure in daily life. Recovering addicts often have depressive symptoms or dysphoria, which increase risk of relapse and may be related to low dopaminergic function.

Dopamine does still play a critical role in dependence but is released to the cue rather than reward. Consistent with this is that cues have been shown to increase dopamine in cocaine or heroin dependence but the actual drug does not. The release is more prominent in the dorsal striatum, which may reflect a move from ‘limbic’ to ‘habit’ striatum as proposed by Everitt and Robbins. However, if the reward does not actually arrive following the cue, then dopaminergic activity is reduced. These changes in dopaminergic function are thought to be described clinically as craving.
Accompanying these striatal adaptations are changes in the prefrontal cortical projection areas of the dopaminergic mesolimbic system (Fig. 2). There is a reduction in OfCx and ventromedial PfCx activity at rest in addicts. This is thought to reflect a switch from prefrontal control, with reflective decision-making, to more compulsive striatal control over substance use. This switch from the pleasure and liking of drug use, to the compulsive wanting of drug dependence, is underpinned by changes in synaptic plasticity and neurotransmitter function.

Pharmacotherapy in the clinic

Given that increases in dopamine are associated with pleasurable effects, a wide range of dopaminergic antagonists targeting the DAT and DRD2 receptors have been studied but have limited clinical efficacy. An exception may be bupropion, which is used to treat nicotine dependence and is a dopamine and noradrenaline reuptake inhibitor. Promisingly, several recent studies looking at bupropion for the treatment of methamphetamine misuse have shown it to reduce cue-induced craving; to reduce methamphetamine use itself; and to reduce methamphetamine self-administration in rats. However, it is unclear how
much altered dopaminergic activity contributes to its therapeutic effect. Antagonists more specific for DRD3, the subtype predominantly found in the NAccs, show promise in preclinical models but clinical effectiveness has yet to be determined.\textsuperscript{26}

Given that dependence has been shown to be associated with reduced function in the dopaminergic system and lower DRD2 levels are associated with drug-liking, increasing dopaminergic activity might be a more appropriate approach. In alcoholism, a dopaminergic agonist, bromocriptine, has shown efficacy but not widespread effectiveness.\textsuperscript{27} In cocaine addiction, a variety of medications that increase dopamine, e.g. methylphenidate have shown efficacy, however concerns about abuse limit their utility.

Disulfiram is well known for its ability to block aldehyde dehydrogenase in the liver, resulting in increased acetaldehyde levels when alcohol is consumed, which cause aversive symptoms such as flushing, nausea and palpitations. Dopamine B-hydroxylase is from the same family and can also be blocked by disulfiram. This enzyme catalyzes the conversion of dopamine to noradrenaline and disulfiram, therefore results in increased dopamine and reduced noradrenaline levels in the brain. It is not clear whether the ability of disulfiram to increase dopamine contributes to its effectiveness in alcoholism but does provide a mechanism for its potential effectiveness in cocaine addiction since increased dopamine may be aversive from the combination.\textsuperscript{28}

**Other neurotransmitter systems that modulate the mesolimbic system and are involved in reward and/or motivation**

**Gamma-aminobutyric acid-B**

A key tonic inhibitor of mesolimbic dopamine neuronal firing is the gamma-aminobutyric acid (GABA) system through GABA-B receptors on dopamine neurons. Increased inhibitory activity can be achieved either with anticonvulsants, which can increase GABA, e.g. vigabatrin or by baclofen, a GABA-B agonist. In preclinical models, baclofen reduces drug seeking and consumption of a number of addictive substances, including alcohol, cocaine and nicotine.\textsuperscript{29} Baclofen has been shown to reduce dopamine release in the dorsal and ventral striatum in animal studies\textsuperscript{30} and is showing promise in the clinic.

**Pharmacotherapy in the clinic**

Anticonvulsants such as topiramate, tiagabine and vigabatrin have been investigated in a variety of addictions. They all have shown some
efficacy in treating alcoholism and cocaine addiction. However, the adverse side-effect profiles of these drugs include word-finding difficulty with topiramate and visual field deficits with vigabatrin, which limit their development and widespread application despite showing promise in clinical trials.

Baclofen has shown efficacy in preventing relapse in alcoholism but not in all studies in alcoholism, leading to the hypothesis that baclofen is more likely to be efficacious in those that are more severely dependent, require medication for detox and are more anxious. In cocaine dependence, although early studies showed promise, the latest trial failed to support the efficacy of baclofen in reducing cocaine use. Though notably in these studies, baclofen was started whilst cocaine was still being used whereas in the alcoholism trials, abstinence was achieved prior to starting baclofen. Higher doses than original 30 mg/d are being studied with a pilot promising study in nicotine addiction using 80 and 60 mg/d in methamphetamine addiction, which only showed an effect of baclofen in those that were more compliant. It is unknown whether higher doses are required due to altered kinetics, such as increased metabolism or altered GABA-B receptors in addiction.

Opioids

There are three central opioid receptors, mu (MOR), kappa (KOR) and delta (DOR). Effects of MOR include analgesia, respiratory depression and pupillary constriction with KOR-mediating dysphoria, depersonalization and sedation. MOR and DOR activation is associated with reward, whereas KOR activation in the NAcc attenuates reward. MOR receptors are present in the VTA on the GABA inhibitory neurons. Since MORs are inhibitory, their activation by endorphins results in the GABA neuron being inhibited. Therefore, the GABA-ergic ‘brake’ on the dopamine neuron is released resulting in increased firing and dopamine release in the NAccs. Preclinical studies show that mice lacking the MOR no longer find opioids rewarding and a withdrawal syndrome is not apparent. The pleasurable effects of alcohol are also thought to be mediated through this mechanism since alcohol is known to release endorphins.

Alterations in MOR may also be fundamental to addiction since imaging studies have revealed an increase in MORs in individuals recently abstinent from opioid or alcohol or cocaine dependence. In addition, in cocaine or alcohol dependence, increases in MOR receptors are associated with increased craving, and these increases persist into extended abstinence in some brain regions.
More recently a role for opioids in impulsivity has been suggested since MOR knockout mice are less impulsive. Naltrexone, an opiate antagonist (see below) can increase activity in a key part of the OfCx involved in waiting for a larger reward rather than taking an immediate smaller one.

**Pharmacotherapy in the clinic**

Naltrexone, the non-selective opiate antagonist, is used to block reward associated with MOR activation. In opioid addiction, naltrexone prevents any opioid taken from binding to the receptor to have its effects. Whilst naltrexone is a very effective antagonist, compliance tends to be poor unless the individual is highly motivated. Naltrexone also blocks MOR in the VTA, thus preventing endorphins from having their effect. In alcoholism, such MOR antagonism results in no increase in dopaminergic activity making drinking less pleasurable. Consistent with this mechanism of action, naltrexone has been shown to reduce the risk of a lapse becoming a full blown relapse in alcoholism but not to increase abstinence. Naltrexone has shown limited efficacy in other addictions.

**Glutamate**

Glutamate is the brain’s primary excitatory neurotransmitter and of its receptors, the glutamatergic N-methyl-D-aspartate (NMDA) has been shown to be involved in different aspects of addiction with different substances. Glutamatergic projections from the PfCx, amygdala and hippocampus increase dopamine release in the NAcc directly or via the VTA. There is also increasing evidence that glutamate plays a role in sensitization, since glutamate levels are higher in response to cocaine in sensitized compared with non-sensitized rats, and NMDA antagonists block sensitization to cocaine and morphine.

Kalivas and Volkow suggest that there is a final common pathway consisting of projections from the PfCx to NAcc to ventral pallidum in drug-craving and drug-seeking behaviour. Changes in the strengths of synaptic connections in this pathway depend upon glutamatergic fibres from the PfCx, which converge on NAcc dendritic spines with dopaminergic afferents from the VTA. Such changes in the strengths of synaptic connections in this pathway can account for the rapid reinstatement of drug use during a relapse from abstinence. Such reinstatement can be triggered by stress, a drug-specific cue, or a single dose of the drug. Repeated use of drugs may lead to plastic reorganization of these synaptic connections, which then cements changes in neural activity, and so behaviour. Molecular changes that affect synaptic
connection strengths may occur both presynaptically and postsynaptically in the NAcc, and also in the PfCx itself, as reflected by changes in activity seen there in neuroimaging studies.

Pharmacotherapy in the clinic

N-acetylcysteine has shown some promise in the treatment of cocaine misuse. Aberrant glutamate levels have been restored by N-acetylcysteine in cocaine-treated rats, and it has also reduced cocaine cue-responses in human cocaine users. In addition, many of the anticonvulsants being investigated for relapse prevention will antagonize glutamatergic activity.

Acamprosate’s effectiveness in maintaining abstinence from alcohol is thought to be due to its antagonism of glutamatergic activity and enhancement GABA-ergic activity. The pharmacology of acamprosate is not fully determined but partial agonism at the NMDA receptor, activity at AMPA and mGLuR5 receptors have been demonstrated NAcc. Acamprosate reduced glutamate hyperactivity seen in withdrawal. It was therefore hypothesized that it would be particularly efficacious in those people who experience craving as a withdrawal-like state. Although some but not all studies reported acamprosate reduced ‘craving’, subsequent meta-analyses have not identified this or any other characteristics as predictors of efficacy.

Tolerance and withdrawal—two sides of the same coin

Tolerance in an individual is the process whereby increasing doses of a substance are required over time to give the same effect. It is mediated by a combination of post-synaptic receptor down-regulation and reduced receptor sensitivity. There may also be changes in pre-synaptic autoreceptors affecting tonic levels of dopamine. In addition there are often compensatory increases in opposing pharmacological systems to help maintain a homeostatic balance within brain neural circuits. A consequence of these processes of tolerance is that on abrupt cessation of taking an addictive substance, homeostasis is lost and the opponent processes dominate, giving rise to withdrawal symptoms. The neurotransmitter systems that are affected will vary from substance to substance. For instance, with opioids, reduced function of opioid receptors likely occurs through altered second messenger systems since few changes in receptor number have been found.

Tolerance to alcohol involves changes in two of its key targets, the inhibitory GABA-benzodiazepine and excitatory NMDA receptors. Alcohol acutely reduces activity in the brain by increasing GABA-ergic activity and antagonizing the NMDA receptor.
Alcohol alters the coupling between the benzodiazepine and GABA binding site to increase activation of this inhibitory receptor. Indeed many of the central effects of alcohol, such as ataxia, sedation and anxiolysis, are mediated through the GABA–benzodiazepine receptor. Chronic exposure to alcohol results in changes in the GABA-A receptor subunits making it less sensitive to alcohol, i.e. tolerance. At its extreme, this results in the ability of someone to drink large amounts of alcohol, e.g. a bottle of spirits/day, yet appear not intoxicated. In response to continued drinking and alcohol’s antagonism, the NMDA receptor number increases. In animal models, this has been shown to be associated with impaired long-term potentiation, a process involved in memory and therefore in man may underlie so-called ‘alcohol blackouts’.

Desensitization is particularly used to describe nicotinic receptor (nAChRs) sensitivity, which is rapidly reduced, i.e. desensitized after one cigarette with re-sensitization occurring over-night or within hours of not smoking. As with other substances of abuse, nicotine increases dopamine in the NAccs by stimulating nAChRs within the VTA, which in turn stimulate release of excitatory glutamate. Although nicotine also stimulates nAChRs on presynaptic GABA-releasing neurons that inhibit dopamine release, these are quickly desensitized resulting in a net increase in dopamine. Chronic nicotine use in animal models is associated with changes in glutamate and GABA transmission, which may increase withdrawal symptoms and craving for nicotine. However, experimenters have had difficulty in producing nicotine dependence and pharmacological reinforcement in animals. This highlights the importance of environmental cues in the acquisition and maintenance of nicotine dependence.

**Withdrawal**

While increases in phasic dopamine have a role in mediating initial pleasure, neuroadaptations occur in chronic use, resulting in a hypodopaminergic state. These changes, occurring in withdrawal and early abstinence, probably underlie symptoms such as dysphoria, anhedonia and irritability, and may contribute to craving and drug-seeking behaviour. For some substances, such as stimulants, such symptoms predominate with no or few physical symptoms. By contrast, for other substances of abuse such as opioids or alcohol, physical withdrawal symptoms can be prominent and contribute significantly to their dependency since drug use is to stave off or combat withdrawal. This is ‘negative reinforcement’, i.e. taking a drug to overcome an aversive state.
The signs and symptoms of alcohol withdrawal are thought to be primarily driven by the reduced inhibitory GABA-ergic and enhanced NMDA glutamatergic activity underpinning tolerance. A consequence of increased NMDA activity in the absence of alcohol is a greater influx of calcium into the cell through its ion channel aided by the absence of the ‘anticonvulsant’ Mg$^{2+}$ ions that usually sit in the NMDA channel but have been ‘flushed’ out. In addition, other voltage-dependent calcium channels open leading to toxicity resulting in neuronal excitability and seizures but also cell death and atrophy.

For opioids, a major contributor to withdrawal symptoms such as tachycardia, sweating, piloerection, rhinorrhoea and shivering is noradrenergic hyperactivity in the locus coeruleus or so-called ‘noradrenergic storm’. This arises because MOR are inhibitory, so to maintain noradrenergic homeostasis in the presence of continued opioid exposure, intracellular cAMP production is up-regulated to keep ascending noradrenergic pathways active.

**Pharmacotherapy in the clinic**
In alcohol withdrawal, pharmacotherapy can be needed to prevent significant and life-threatening complications such as seizures and delirium tremens. These adverse events arise due to the GABA-glutamate adaptations described above. GABA-ergic function is boosted by giving benzodiazepines such as diazepam or chlordiazepoxide, which are commonly used for alcohol detoxification. Glutamatergic antagonists and anticonvulsants can also effectively treat alcohol withdrawal. Preclinical data suggests that benzodiazepines can reduce symptoms of alcohol withdrawal but may not afford protection against the effects of glutamatergic hyperactivity such as development of seizures through kindling or cell death. Acamprosate reduces NMDA hyperactivity and can reduce glutamate levels and the morbidity associated with alcohol withdrawal. How acamprosate reduces NMDA activity is not fully determined but may be via partial agonism at the NMDA receptor, via AMPA or mGLuR5 receptors. Whether clinically acamprosate can have similar neuroprotective effect during detox is uncertain. Reducing glutamatergic activity does not negate the need to replenish nutritional deficiencies, particularly thiamine, that result in Wernicke’s encephalopathy acutely and if untreated, Korsakoff’s syndrome. Whilst clinicians may associate it with alcohol withdrawal, it can occur at any time and a high index of suspicion must be maintained.

Whilst withdrawal from opioids can be managed through gradual reduction in the substitute pharmacotherapy, an alternative is to calm the noradrenergic storm in the locus coeruleus with adrenergic alpha-2 receptor agonists such as clonidine or lofexidine. Hypotension is an
issue, but less so with lofexidine. However, other medication is required for symptoms not associated with noradrenergic hyperactivity, e.g. GI upset.

**Pharmacotherapeutic principles in substitution or maintenance treatment**

The principles of substitution pharmacotherapy are to give a substitute with a longer half-life to avoid the ‘highs and lows’ of shorter acting preparations, with slower onset kinetics so less likely to cause a ‘high’, at a dose that does not cause impairment and minimizes withdrawal. This approach can be applied for any substance of abuse but is not widely used in cocaine or amphetamine addiction. It is most commonly used to treat nicotine and opioid addiction.

In many clinical services for opioid addicts, substitution has become the mainstay of pharmacotherapy. The most commonly used substitute is methadone, which is clinically a full MOR agonist with a half-life of approximately 24 h. Whilst methadone causes reduced MOR function, a dose–occupancy relationship has not been well established with imaging, suggesting that at most 32% MOR receptors are occupied, although others have found minimal receptor binding. A newer substitute is buprenorphine, which acts as a partial agonist at the MOR and as an antagonist at the KOR. Its partial agonist properties mean that it produces less euphoria, sedation and positive reinforcement than full agonists as well as causing less respiratory depression. As a partial agonist with high affinity for the MOR, it can also act like an antagonist by preventing ‘on-top’ use of other opioids such as heroin having access to the receptor and therefore an effect. Consequently its use reduces the risk of unintentional overdose relative to full agonist medications, however the disadvantage is that its maximum efficacy is limited. The other major implication of its high affinity is that it will displace other opioids from the receptor when it is commenced as a treatment. Because it activates receptors less than a full agonist, there is a relative drop in receptor activation, which can lead to a degree of ‘precipitated opioid withdrawal’. This can be avoided if starting buprenorphine is delayed until the individual is in opioid withdrawal. Its antagonistic actions at the KOR may explain why buprenorphine produces less dysphoria than full agonists. To reduce its abuse potential, there is now a preparation containing the antagonist, naloxone, which is inactive if buprenorphine is taken orally but active if injected. Buprenorphine has a long half-life (>24 h) and although usually dispensed on a once daily basis, it can be dispensed
on alternate days. Unlike methadone, a clear dose–occupancy relationship has been shown with most MOR occupied at 16 mg.\textsuperscript{64}

For smokers there is a wide range of products available that can provide a constant plasma level of nicotine, e.g. patches as well as those that can give a ‘hit’ of nicotine, e.g. gum or inhalator.\textsuperscript{59} More recently a partial agonist at the alpha-4-beta-2 nicotinic acetylcholine receptor, varenicline has become available,\textsuperscript{65} varenicline results in partial stimulation of the NACHR with increases in dopamine, whilst blocking ‘on-top’ nicotine. In this way, it simultaneously treats symptoms of withdrawal and reduces reward from nicotine.

**Areas timely for developing research**

Pharmacogenetics is one area of research, which may bring specific benefits to the treatment of addiction, particularly through predicting response to treatment and so allowing optimal treatment matching. One good example of this is the A118G polymorphism of the MOR—the presence of which predicts a good response to naltrexone in the treatment of alcohol dependence.\textsuperscript{66}

Our increasing knowledge of the underlying neuropharmacology of addiction is informing appropriate application and development of medications to target specific mechanisms or stages of addiction. Moving beyond the reward pathways, targets involved in modulating stress and synaptic plasticity as well as those affecting learning, memory and impulsivity are all active areas of research that we hope soon translate into clinical practice to improve the range of therapeutic approaches.

**Conflicts of interest**

A.L.H. holds grants from NIHR, MRC and collaborations with GSK. A.L.H. is coordinating and A.R. contributed to update of clinical guidelines about management of substance misuse for British Association for Psychopharmacology, which received support from pharma. N.J.K. is supported by the Wellcome Trust and GSK. B.J.W. is supported by a grant from the MRC.

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