Addiction and withdrawal – current views

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The final common pathway of addiction (the dopamine hypothesis of reward) has recently been evolving, with the mesocorticolimbic dopaminergic system now seen as key to natural rewards and drug-seeking behaviour, though perhaps having less of a role in the maintenance of such behaviour. The perception of a common pathway has meant that treatments for one drug of addiction have 'crossed-over' and become possible treatments for other addictive drugs.

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Abbreviations

18-MC	18-methoxycoronaridine
GABA	γ-aminobutyric acid
KO	knockout
NMDA	*N*-methyl-D-aspartate
NOS	nitric oxide synthetase
RCT	randomised double-blind study
THC	delta-9-tetrahydrocannabinol

Introduction

Drug addiction, is one of the world's major health problems, with large direct health costs (psychiatric and physical) as well as massive indirect costs to society in terms of crime, loss of earnings and productivity, and social damage.

The addiction syndrome is remarkably similar between different drugs of abuse (see Table 1). The mesocorticolimbic dopaminergic system — the dopaminergic neurones in the ventral tegmental area (VTA) of the midbrain and their projections to the Nucleus Accumbens (part of the basal ganglia) and thence to the Prefrontal Cortex — has long been seen as a key component of the reward pathway. This has been extensively researched and a recent review [1] points to its role as a pathway in the learning process i.e. the mesolimbic dopaminergic system functions to enable an organism to learn by mediating the action of rewards. Addictive drugs such as opioids, alcohol, cocaine and amphetamines act by stimulating this system, which is more usually activated by natural rewards (food, water and sex). They do this in a variety of ways — for example, cocaine increases the amount of intra-synaptic dopamine by inhibiting the dopamine transporter (thus preventing dopamine's re-uptake from the synaptic cleft), whereas opioids act by inhibiting inhibitory γ-aminobutyric acid (GABA) interneurones in the ventral tegmental area to increase dopamine release. The above pathway is also thought to mediate a significant component of the positive reinforcement part of craving. This may be the main motivation for initial drug use, but does not account for all aspects of the pharmacology of drug addiction. In the long-term, there is a more complex interplay between this and the negative reinforcement/fear of withdrawal element of craving, which may arise partly because of neuro-adaptations to the drug [2]. This review will concentrate on recent work that is of interest from a neuropsychopharmacological perspective, both in clinical and preclinical areas.

Table 1

Common aspects of drug addiction.

Salience	Withdrawal
Mood modification	Craving
Tolerance	High relapse rate

Opioids

Recent work in this field has both expanded our understanding of the basic mechanisms of opioid addiction and explored potential new therapeutic avenues.

Basic mechanisms

The mechanism by which opioids are able to exert their rewarding properties has become more complicated by the demonstration that mice lacking the substance P NK_1-receptor do not appear to find opioids rewarding [3••] (see Figure 1). They do, however, still respond to cocaine and food rewards in a manner identical to wild types. Similar results have been reported with mice lacking the cannabinoid CB_1-receptor gene [4••]. The mutant strain is reported to show a reduction in the reinforcing effects of morphine and a reduction in the severity of naloxone-precipitatedopioid withdrawal, despite having no apparent change in the antinocioceptive effects of morphine or the development of tolerance.

There is increasing data on the role of receptor phosphorylation and endocytosis in the development of opioid tolerance. The ability of an opioid agonist to induce tolerance may be related to its ability to induce this process [5•]. It has also been shown that the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine, which blocks this process, was also able to block the development of morphine tolerance and reduced the effects of naloxone-induced morphine withdrawal in mice [6•].

Research continues into the role that the excitatory neurotransmitter glutamate plays in the mechanisms of tolerance, sensitisation and withdrawal, as well as into the possible usefulness of glutamatergic drugs as treatment agents. The drug LY235959 (a competitive glutamate antagonist at the *N*-methyl-D-aspartate [NMDA] receptor) has been shown

to block the development of morphine tolerance [7], an effect previously reported with the non-competitive blocker dizocilpine. Nitric oxide synthetase (NOS) is the main second-messenger system for the NMDA receptor. It has been shown that NOS expression is increased in morphine addiction and further increased in opioid withdrawal in areas such as the locus coeruleus, which is thought to mediate the noradrenergic component of the withdrawal syndrome [8]. Additionally, inhibition of the physiological target of NO (soluble guanylyl cyclase) blocked the behavioural expression of naloxone-precipitated withdrawals in morphine-dependent rats. This was mirrored by changes in excitatory amino acid levels in the locus coeruleus measured by *in vivo* microdialysis [9].

These papers support the view that the locus coeruleus is a major site for determining withdrawal symptoms. This explains why drugs such as lofexidine and clonidine (α_2-agonists), which decrease firing in the noradrenergic neurons of this nucleus, work in withdrawal. Caillé *et al.* [10•] have demonstrated, however, that 94% ablation of the locus coeruleus with 6-OH-dopamine failed to attenuate naloxone-precipitated morphine withdrawal in rats as measured by conditioned place aversion or level of withdrawal symptoms. The lesioned rats also showed the same benefit from clonidine as sham-operated rats. This suggests that these drugs may be working at a 'downstream' post-synaptic site.

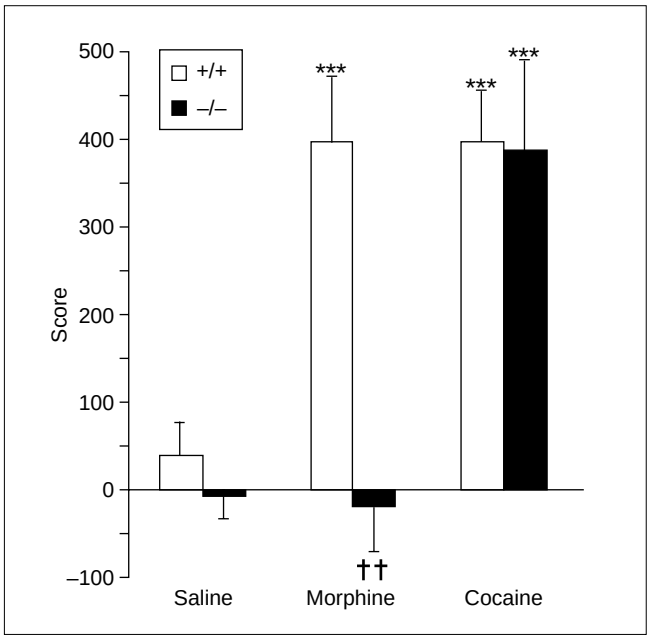
Treatments

The main-stay of the treatment of opioid withdrawal symptoms has been the α_2-adrenoceptor agonists lofexidine and clonidine. Standard treatment with lofexidine was compared to a naltrexone/lofexidine combination [11]. Contrary to expectations, the addition of naltrexone decreased the reported severity of withdrawal symptoms as well as having the expected effect of shortening the duration of the withdrawal syndrome. It has also been suggested that trazodone may be useful in treating opioid withdrawals because of its α_1-adrenoceptor antagonist action, but without the problem of hypotension associated with clonidine and lofexidine. In a clinical trial, trazodone showed slightly better efficacy in treating opioid withdrawals compared to clonidine and was equally well tolerated [12].

Substitute prescribing, typified by methadone, continues to be the main-stay of the pharmacological treatment of opioid addiction. However, researchers continue to look for newer and better substitutes as well as attempting to increase our understanding of methadone's effects.

Strain *et al.* [13] have reported that, in a randomised double-blind study (RCT) of outpatients, methadone doses of 80–100 mg were more effective at reducing use of illicit opioids than 40–50 mg doses, but gave no benefit in treatment retention rates. Another recent study has reported methadone's ability to induce its own metabolism, by cytochrome CYP3A4, so accelerating the speed of its clearance with chronic use [14].

Figure 1



Lack of conditioned place preference induced by morphine in substance P NK_1-receptor knockout mice (–/–) compared to wild-types (+/+). Scores are calculated as the difference between post-conditioning and pre-conditioning time (in seconds) spent in the compartment associated with the drugs. Morphine = 3 mg/kg subcutaneous injection; cocaine = 5 mg/kg intraperitoneal injection; saline was injected as a control. Values represent mean ± s.e.m.: ***P < 0.001; **P < 0.02 versus saline group with the same genotype; ††P < 0.02, versus wild-type group receiving the same treatment. Reproduced with permission from [3••].

One problem that has plagued the use of substitute medications is the risk of intravenous misuse of oral medications. As a possible counter-measure, the addition of naloxone to oral buprenorphine was tested in a group of intravenous opioid users [15]. Naloxone will provoke an unpleasant opioid withdrawal syndrome if the compound is injected, but will not adversely effect the correct oral usage of the preparation as naloxone has very poor oral bioavailability. In this RCT, a ratio of 2:1 or 4:1 (i.e. buprenorphine 2 mg and naloxone 1 mg or 0.5 mg) was found to produce consistent opioid withdrawal symptoms on all measures when administered parenterally without impinging on the efficacy of the buprenorphine when taken sublingually.

Buprenorphine has been shown to be as effective as methadone in a clinical outpatient setting [16]. Furthermore, less than once-daily dosing of buprenorphine has also been shown to be equally effective because of its pharmacodynamics and pharmacokinetics [17] (see Figure 2 for a comparison of buprenorphine with other opioids).

The opioid antagonist naltrexone has been used as an aid to maintaining abstinence in ex-users of opioids and alcohol. The new μ-opioid antagonist nalmefene was shown to

Figure 2

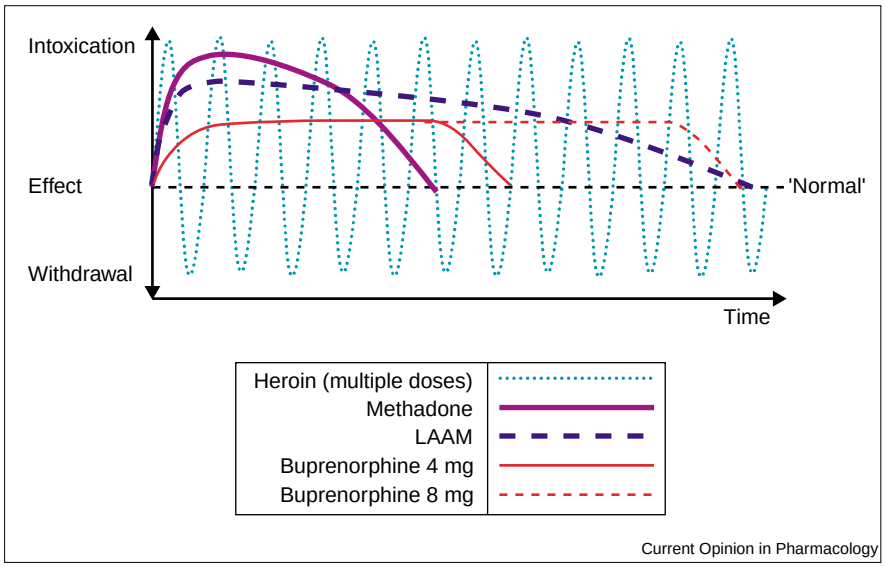


Diagram comparing the approximate duration of action of opioid substitute medications with heroin.

block the effects of morphine for up to 48 hours following a single oral dose of 50–100 mg [18], much longer than the duration of action of a single dose of naltrexone.

Two recent papers have examined the effects of the synthetic iboga congener 18-methoxycoronaridine (18-MC) on acute [19] and chronic [20] morphine in rats. In the acute study, pre-treatment with 18-MC inhibited dopamine release in the nucleus accumbens in response to morphine but did not inhibit the morphine-dependent increase in dopamine synthesis. 18-MC also blocked the effects of locomotor sensitisation to repeated doses of morphine. These reports, when combined with recent data on the use of ibogaine in animal models of cocaine addiction [21–23], may help to explain the anecdotal reports of ibogaine's value in detoxification.

Cocaine

Cocaine continues to be a serious public health problem, especially crack, which, in effect, is simply a more rapid means of delivering cocaine to the brain (faster pharmacokinetics equals increased addictive potential — see Figure 3). Recent work has attempted to tease out the nature of the profound craving experienced by cocaine users, to assess a variety of pharmacological 'cross-over' therapies and to look at immunological treatment.

Pharmacological advances

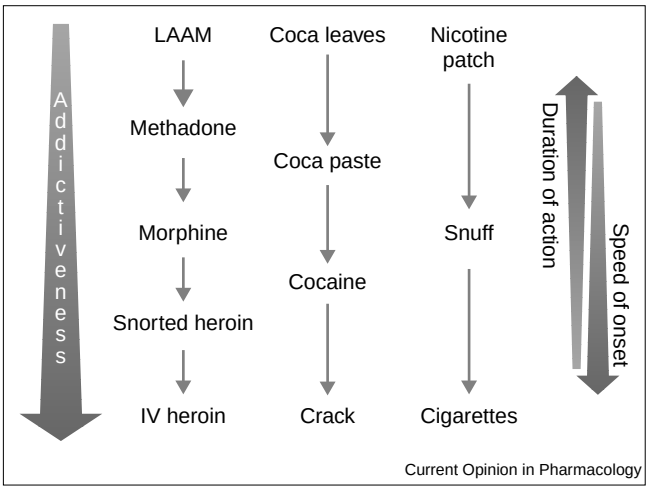
Recently, primate models have been developed to rapidly assess the actions of cocaine and related drugs [24]. The partial D_3-receptor agonist BP 897 was found to have no intrinsic reinforcing properties, but was able to significantly reduce cocaine-seeking behaviour [25••] (see Figure 4). This is an exciting finding, as, to date, drug treatment for cocaine has been bedevilled by the problem of finding a treatment that is effective but not excessively rewarding. Dopamine agonists can be rewarding in their own right, whereas D_2-receptor antagonists can produce unwanted side effects, such as dysphoria.

Other recent attempts at tackling cocaine craving have looked at other neurotransmitter systems that interact with the dopaminergic system. Preclinically, recent work in a variety of animal models shows that κ-opioid agonists can reduce cocaine self-administration [26]. A study in rats [27] assessing the actions of the noradrenergic α_2-agonists, lofexidine and clonidine, found them to be effective in attenuating the reinstatement of cocaine-seeking following a significant stressor (footshock). In one open-label out-patient study using phentermine (a dopamine releaser) and fenfluramine (a serotonin releaser), there was no improvement in abstinence from cocaine despite a reduction in the acute withdrawal symptoms [28]. Interestingly, a RCT of disulfiram [29] has shown a reduction in cocaine use in methadone- and cocaine-dependent individuals, as well as the expected reduction in alcohol use. It acts as a central inhibitor of dopamine β-hydroxylase, thus causing an excess of dopamine and decreased synthesis of noradrenaline. As a result, it may attenuate cocaine's 'high', causing a decreased desire to use more cocaine.

Cocaine immunopharmacology and cocaine-kindled seizures

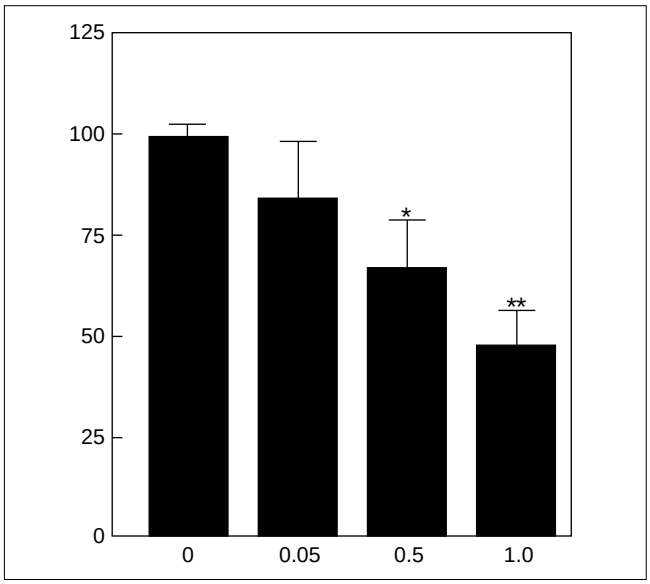
The hunt for novel therapies has also seen progress in the field of immunopharmacology. Cocaine vaccines, acting to prevent the entry of cocaine into the brain, have shown good initial promise in both rat and mouse models of cocaine addiction [30•,31,32]. Finally, progress has been made at developing an effective mouse model of cocaine-kindled seizures, which account for up to 10% of cocaine-intoxication related emergencies [33].

Figure 3



'Chasing the rush': showing the similarities in the pharmacokinetic changes between addictive substances.

Figure 4



The partial dopamine D_3 receptor agonist, BP 897, inhibits cue-controlled cocaine-seeking but has no reinforcing effects. Rats were trained to self-administer cocaine under a second-order schedule of reinforcement. The figure shows the dose-related effects of BP 897 (mg/kg), BP 897 decreased responding for cocaine (**P<0.01 and P>0.05) versus saline). Reproduced with permission from [25••].

Alcohol and benzodiazepines

Neurobiological advances

The effects of alcohol have, in the past, been shown to spread far beyond the $GABA_A$-receptor, with treatments acting on, for example, the serotonergic or opioid systems. A recent review has also focussed on preclinical work showing the possible benefits of using NMDA-receptor antagonists [34]. Recently, Löw *et al.* [35] have shown, using point mutations in mice, that the $GABA_A$-receptor α_2-subtype (which predominate in the limbic system) mediate anxiety, whereas the sedative and amnestic effects of benzodiazepines are mediated by the $GABA_A$ receptor α_1-subtype. This, in the future, may allow for the precise targeting of drug development to minimise the addictive nature of the benzodiazepines.

γ-Hydroxybutyric acid (GHB), which is an endogenous neurotransmitter structurally similar to GABA, has multiple effects. It has recently been shown to be of benefit in small trials of both acute alcohol withdrawal and in longer term abstinence, probably because of cross-tolerance [36,37]. Unfortunately, GHB itself is a drug of abuse, which probably means that, unless a longer-acting and safer analogue can be found, it will not be clinically useful.

Pharmacological advances

The most exciting advance in the past year has been the large RCT of ondansetron, a $5HT_3$-receptor antagonist [38•]. $5HT_3$ receptors have been shown to regulate the mesocorticolimbic system. This study showed a reduction in self-reported drinking measures among those with early-onset alcoholism (Type II/B), which is consistent with the knowledge that this group have a serotonergic dysfunction [39]. Unexpectedly, a recent study with a selective serotonin reuptake inhibitor (SSRI), sertraline, showed that it was more effective in the late-onset alcoholics (Type I/A) compared to the early onset group [40]. Taken together, it clearly indicates that future therapy needs to consider subtyping of alcoholics for treatment.

Naltrexone has recently been shown to be no more effective than placebo (or nefazodone, a serotonergic antidepressant) in a large RCT of alcohol addiction [41], in contrast with earlier, smaller studies. This may be because of problems with its tolerability in this population. When combined with cognitive behavioural therapy or ondansetron, however, it seemed to have a synergistic effect on reducing relapse [38•], as well as reducing cue-induced craving [42].

Cannabis

Neurobiological advances

The use of gene knockout (KO) mice continues to provide us with valuable knowledge. Ledent *et al.* [4••] have shown, using a CB_1 cannabinoid receptor KO mouse, that the CB_1 receptor has a key role in the mediation of the cannabinoid drugs (as expected). There is now much evidence that the endocannabinoids and their G-protein-coupled receptors are involved in the neuromodulation of, for example, the control of movement, cognition, learning and memory, and brain development [43–46]. A recent study by Welch and Eads [47] hypothesises the existence of subtypes of the CB_1 cannabinoid receptor to explain the differing antinocioceptive actions of a variety of cannabinoid ligands, which could, therefore, have an impact on future drug development in this area.

A study by Tanda *et al.* [48] has finally found an animal model for cannabis use — intravenous self-administration of the active component, delta-9-tetrahydrocannabinol (THC), by squirrel monkeys. They demonstrate reliable self-administration behaviour of THC, indicating that it has abuse potential. Similarly, they also report [49] that rats, when given THC intraperitoneally, had measurable dopamine changes in the Nucleus Accumbens, as well as a physical abstinence syndrome when given a cannabinoid antagonist. A mild withdrawal syndrome associated with heavy cannabis use has now been proven in humans, including in placebo-controlled single-blind trials [50•,51•].

However, these results must be interpreted with caution. Some of the authors suggest that cannabis has as much potential for abuse as drugs such as cocaine and heroin. Clinically, this is clearly not the case (see [52,53] for a review on the current consensus).

Nicotine

Neurobiological advances

Evidence has been accumulating, both preclinically in rats [54] and clinically, using a naloxone challenge in human smokers [55], that chronic nicotine exposure causes alterations in the endogenous opioid system, including an up-regulation of μ-opioid receptors. Also, in the field of immunopharmacology, nicotine antibodies have been shown to be effective in reducing some of nicotine's actions in the rat, with the possibility, therefore, of novel treatment options in the future [56].

The link between nicotine's actions and the mesocorticolimbic dopaminergic system has been known for some time in animal models. The link has been shown in humans for the first time in a study by Salokangas *et al.* [57]. They measured striatal dopamine activity using position emission tomography (PET) scanning with ^{18}F-DOPA and showed that nicotine addiction was associated with an increase in dopamine activity in the basal ganglia.

Pharmacological advances

Bupropion (amfebutamone) is used as an aid to stopping smoking. Originally developed as an antidepressant, its mechanism of action is thought to be through dopamine and noradrenaline re-uptake inhibition. A large RCT [58•] shows that it is much more effective than either placebo or nicotine patches alone. Recent work has extended our knowledge in this area [59], showing that during withdrawal it seems to act primarily to improve affect, with smaller effects on craving than previously thought.

Amphetamines and ecstasy

Neurobiological advances

A preclinical study by DeSousa *et al.* [60] has, in a rat model, shown that intravenous amphetamine consumption can be predicted by differences in sucrose feeding (rats that were high sucrose feeders beforehand consumed greater amounts of amphetamine). Sucrose feeding can be thought of as a natural dopaminergic-mesocorticolimbic-mediated rewarding behaviour. It emphasised the need for future research to consider individual variability in responses to the reinforcing and rewarding aspects of drugs and natural rewards.

3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy') has, in recent human studies, been shown to mediate its physiological effects via serotonin and noradrenaline, whereas its euphoriant effects seem to be partly mediated via dopamine [61•].

Despite extensive research, as a recent review [62] has shown, there is still little evidence or knowledge of the potential long-term effects of MDMA in humans, though it does seem clear that it is far less dangerous than drugs such as heroin and cocaine [53].

Conclusion

The field of addiction pharmacology continues its impressive recent progress in both the preclinical and clinical fields, which hopefully reflects the growing realisation of the health and social costs of the human addiction problem. There has been significant progress in understanding the molecular basis of addiction with further insights into the role of opioid and glutamatergic receptor processes, including NOS, in addiction. Several new therapeutic lines have emerged from this, such as drugs that can interfere with receptor internalisation and guanylyl cyclase activation. There is growing clinical evidence for the utility of opioid partial agonists such as buprenorphine and the discovery of BP 897, a D3 partial agonist that is not self administered yet blocks the use of cocaine, offers a similar hope for stimulant abuse. It seems plausible that the revelation that subtypes of the benzodiazepine receptor mediate differing actions of these drugs could lead to similar selective agents for benzodiazepine and alcohol abuse. Finally, it is important to emphasise the growing evidence for cross-talk between receptor systems for the various drugs of abuse, as demonstrated by the substance P (NK_1) and cannabis (CB_1) KO mice showing reduced opioid reinforcement.

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- •• of outstanding interest

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Mice lacking the NK1 receptor for substance P are shown not to respond to morphine as rewarding. They demonstrated no conditioned place preference to a morphine-paired environment and less conditioned place aversion to a

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This elegant study used mutant mice that had had the gene for the central cannabinoid receptor (CB1) invalidated. The mice did not respond to cannabinoid drugs and, in a variety of models of behaviour, the authors were thus able to show that the CB1 receptor has a key role in mediating aspects of analgesia, reinforcement, hypothermia, locomotion, and hypotension. They also looked at the interaction of this system with the opioid system and clearly demonstrated the role CB1 plays in both the withdrawal syndrome and in the reinforcing properties of opiates. They suggest, therefore, that CB1 antagonists may well have a future role in the treatment of opiate addiction.

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This paper opens up a potentially new avenue for reducing drug craving. The authors looked at BP 897, the first D3-receptor-selective partial agonist, in rats. They found that it reduced cocaine-seeking in the presence of cocaine cues, though was not, in itself, rewarding. They hypothesised that this partial agonism allowed it to act both to antagonise the actions of cocaine and maintain, as an agonist, a moderate degree of D3-receptor stimulation. Given the probability that the D3-receptors may also mediate some of the craving effects of other drugs of abuse, BP 897 or similar compounds could have a much wider use.

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This large study, involving 271 patients, clearly showed that ondansetron, a 5-HT3-receptor antagonist, was an effective means of reducing alcohol consumption in early-onset, but not late-onset, alcoholics. A 4 μg/kg twice daily dose, for example, significantly increased abstinent days (70.1% versus 50.2% in the control group; P = 0.02) in the early-onset group. 5HT-3 receptors are thought to regulate dopamine release in the mesocorticolimbic rewarding pathway and alcohol, in part, acts by enhancing this effect. The study shows the importance of being aware of the clinical subtypes of dependence based on specific biological differences (here, serotonergic dysfunction). It also increases the small number of drugs known to be effective in the treatment of alcoholism.

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