# PHARMACOTHERAPY OF ADDICTIONS

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Addiction to drugs, such as heroin, cocaine and alcohol, exacts great human and financial costs on society, but the development of pharmacotherapies for addiction has been largely neglected by the pharmaceutical industry. With advances in our understanding of the underlying biology of addictions now opening the door for the development of novel pharmacotherapies, it could be time for a reassessment of involvement in this increasingly important therapeutic area. Here, we summarize the current approved and implemented pharmacotherapeutic approaches to the treatment of addiction, and then highlight the most promising areas for future drug development from the perspective of our laboratory and our National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA) Research Center.

ADDICTION
Addictions have been defined by various scientific, national and international policy, and clinical groups. The most commonly used diagnostic criteria in the United States are those given by the Diagnostic and Statistical Manual IV (DSM-IV) for drug (or alcohol) abuse or drug (or alcohol) dependence.

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In 1964, studies were initiated by Dole, Nyswander and Kreek at The Rockefeller Institute for Medical Research and The Rockefeller Hospital that soon led to the development of methadone treatment, the first effective pharmacotherapy for the long-term management of a specific addictive disease — heroin addiction[1–8]. This work was based on the hypothesis that heroin addiction is a disease of the brain, with diverse physical and behavioural ramifications, and not simply due to criminal behaviour, a personality disorder or 'weak will'[1,2,7]. At the time, this hypothesis was a fundamental shift in thinking, but addictions are now increasingly accepted as disorders of the brain, with specific neurobiological, molecular and behavioural characteristics that have environmental, drug-induced and genetic determinants of vulnerability (FIG. 1).

ADDICTION can be defined as a compulsion to take a drug with loss of control over drug taking, despite adverse consequences. The initial events that lead to addiction involve acute effects at a specific site (or sites) of action of a drug of abuse — on its target protein and on neurons that express that protein (TABLE 1). These sites of action typically activate neural networks that are associated with POSITIVE REINFORCEMENT. Repeated 'on–off' exposure to a drug of abuse progressively leads to stable molecular and cellular changes in neurons, which alter the activity of neural networks that contain these neurons. This eventually results in complex physiological changes and related behaviours that characterize addiction, such as TOLERANCE, SENSITIZATION, DEPENDENCE, WITHDRAWAL, craving and stress-induced relapse (FIG. 2). These drug-induced changes are, in part, counteradaptive, and they contribute to dysphoria and dysfunction, which promotes continued drug use through negative-reinforcement mechanisms.

In the treatment of addiction, there are three main time points at which pharmacological interventions could be valuable (FIG. 2). First, would be during active use of the drug itself. Second, would be to facilitate and/or ameliorate the signs and symptoms of withdrawal, if 'detoxification' or achieving abstinence is considered to be the main initial goal. Third, would be 'relapse prevention' once a state of abstinence from the drug of abuse is reached, such as chronic maintenance or replacement treatment. In this review, which focuses on heroin, cocaine and alcohol addictions, we provide a brief overview of the underlying biology of addiction and the current pharmacotherapies, before highlighting the most promising targets for drug development for the treatment of addictions in the near future.

## Neurobiology of addiction: a brief overview

Technological advances in neurochemical techniques, molecular-biology approaches, behavioural-study

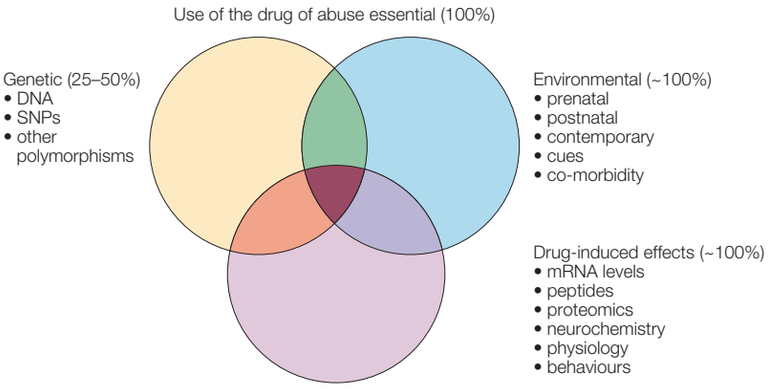


Figure 1 | **Factors involved in addiction.** Three domains of factors that contribute to vulnerability to developing a specific addiction can be delineated: drug-induced changes in the levels of messenger RNA (mRNA) and corresponding proteins and effects on the proteome in general; environmental influences, such as peer pressure, setting, stress (with an atypical response); and genetic factors. SNP, single-nucleotide polymorphism.

techniques and imaging technology, coupled with increasing interest in developing more appropriate animal models, have greatly increased our knowledge of the neurobiology of addiction over the past 15 years. A rapid overview can be gleaned by comparing the 1987 and 2002 editions of the *Third Generation of Progress* and *Fifth Generation of Progress* books of the American College of Neuropsychopharmacology[9,10]. Here, we provide a brief overview of some key findings to facilitate the discussion of potential therapeutic strategies; for a more comprehensive discussion, we refer the reader to REFS 11–15.

Although drugs of abuse have different initial targets and actions (TABLE 1), the resultant addictions share several key features owing to common effects on crucial neural circuits (FIG. 3). In particular, the release and/or increased levels of dopamine in crucial brain regions — particularly the nucleus accumbens, but also in related regions of the MESOLIMBIC–MESOCORTICAL DOPAMINERGIC SYSTEM — are important for the reinforcing effects of cocaine and other drugs of abuse, from alcohol and opiates to nicotine and cannabis. Cocaine acts primarily by blocking the presynaptic transporter for dopamine, but also the presynaptic transporters for serotonin and noradrenaline, thereby flooding the synapse with dopamine, serotonin and noradrenaline. Opiates inhibit γ-aminobutyric acid (GABA)ergic neurons that normally tonically inhibit the dopaminergic neurons in the ventral tegmental area, which leads to a surge of dopamine in the nucleus accumbens and other mesolimbic–mesocortical brain regions[16]. The mechanism by which alcohol enhances dopamine levels remains undefined.

Although dopamine has a key role in the reinforcing effects of drugs of abuse, particularly for cocaine, it is not the only determinant. For example, several groups have shown that mice with the dopamine transporter deleted will still self-administer cocaine, indicating the possible involvement of the serotonergic system[17–20]. Gene deletion of the μ-opioid receptor in mice attenuates or eliminates self-administration of heroin or morphine and attenuates or profoundly reduces drug-induced CONDITIONED PLACE PREFERENCE[21,22]. Furthermore, the analgesic effects of morphine and other μ-opioid-receptor compounds are eliminated in μ-opioid-receptor knockout mice[21,23]. Ablation of dopaminergic terminals in the nucleus accumbens does not stop heroin self-administration, whereas such a procedure does stop cocaine self-administration[24].

So, it has been proposed that dopamine is the main neurotransmitter involved in the rewarding properties of cocaine, as well as other stimulants, and that serotonin and noradrenaline might also be involved in those rewarding properties. By contrast, μ-opioid-receptor activation seems to be central to the rewarding properties of opiates, and dopamine has only a modest or secondary, non-obligatory role. Interestingly, alcohol self-administration is also significantly reduced in μ-opioid-receptor knockout mice (and, by contrast, is increased in δ-opioid-receptor knockout mice)[25,26]. In addition, reward as measured by conditioned place preference after cocaine administration is reduced in μ-opioid-receptor knockout mice[27]. So, μ-opioid-receptor activation seems to be of importance for self-administration of opiates, alcohol and cocaine.

Studies in animal models have also given insights into counter-regulatory mechanisms. The κ-opioid-receptor dynorphinergic system (which is discussed below as a possible therapeutic target) has been shown to be activated during chronic cocaine self-administration, as well as 'binge'-pattern cocaine administration, and also during intermittent morphine administration[28–35]. Various studies have indicated that dynorphin might function as a counter-regulatory neurotransmitter in modulating normal and frequent surges in dopamine tone[5,7]. During excessive stimulation, such as flooding of the synapses with dopamine during chronic cocaine administration, the level of expression of dynorphin and κ-opioid receptors is increased, which might act to counter-regulate the dopamine excess[35]. In addition, common polymorphisms of a putative promoter region of the human dynorphin gene might alter both initial and chronic responses of dynorphin, thereby changing this counter-modulatory response to the excessive extracellular flood of dopamine levels that is caused by cocaine and other stimulants[36,37].

Glutamate also has a role in this counter modulation, and it might be important for both CUE-INDUCED and drug-induced relapse[38–40]. GABAergic systems might also have an important role in the persistence of, or relapse to, chronic drug use[41–43]. Interestingly, the $GABA_B$-receptor agonist baclofen has been shown to produce a relatively selective reduction in cocaine self-administration[44,45]. A preliminary open-label study with baclofen indicated that this compound might be useful for the management of cocaine abuse[46]. Numerous studies over 30 years have shown the profound role of altered stress responsivity in the acquisition and persistence of addiction[47,48]. Specific components of the hypothalamic–pituitary–adrenal (HPA) axis, as well as other molecular and neurochemical components

POSITIVE REINFORCEMENT
Positive reinforcers (rewards) increase the frequency of behaviour that leads to their acquisition. Negative reinforcers (punishers) decrease the frequency of behaviour that leads to their encounter and increase the frequency of behaviour that leads to their avoidance, or alternatively might lead to an increase in the frequency of behaviour to offset the negative effects — for example, re-administration of an opiate to reverse or attenuate opiate-withdrawal signs and symptoms.

TOLERANCE
A progressive, reduced drug responsiveness with repeated exposure to a constant drug dose, therefore requiring an increase in dose to achieve the desired response.

SENSITIZATION
Enhanced drug responsiveness with repeated exposure to a constant drug dose; alternatively, a greater response on re-challenge with a lower dose of drug than used in the initial chronic-intermittent exposure.

DEPENDENCE
An altered physiological state that develops to compensate for persistent drug exposure, which could give rise to a withdrawal syndrome after drug use is stopped; also used by many to refer to psychological dependence that leads to compulsive drug use.

Table 1 | **Primary sites of action of major drugs of abuse**

| Drug | Effect | Sites of action |
|---|---|---|
| Heroin | Depressant | Acts primarily on endogenous opioid system; also affects dopaminergic system |
| Cocaine | Stimulant | Acts primarily on dopaminergic system, as well as on serotonergic and noradrenergic systems; also affects opioid system |
| Alcohol | Stimulant and depressant | Undefined primary site of action; affects dopaminergic, serotonergic and opioid systems |

of the stress-responsive system of the brain, including the amygdala, have also been shown to be involved, both during acute and chronic administration of a drug of abuse and during withdrawal[6–8,11,47,48]. Many studies have shown that stress or stressors seem to be the second most potent cause of relapse after drug PRIMING[48].

## Current treatments for addiction

Goals for the treatment of addiction include preventing withdrawal symptoms, reducing drug craving, normalizing any physiological functions that are disrupted by drug use and targeting the treatment agent to the specific site of action or physiological system that is affected by the drug of abuse. The optimal pharmacotherapeutic agent should be orally or transdermally effective, and have slow onset, long duration and slow termination of action.

In this section, we discuss the current treatments for three addictions with these goals in mind. Nicotine addiction is probably the most common and most costly addiction worldwide. Laboratory-based, neurobiological, molecular and behavioural studies, as well as clinical studies for the treatment of nicotine addiction, have been reviewed recently[49], and the approved pharmacotherapies for nicotine addiction are included in TABLE 2. However, because of constraints on length, there will be no further consideration of nicotine in this focus on new drug discovery. For the same reason, other than in ONLINE TABLE 3, we do not consider various stimulants or addictions to benzodiazepines, barbiturates or diverse plant products. This article is not a review of the many clinical trials that have led to the approval of medications in the United States or Europe, or the studies that have been carried out subsequently to further define the nuances of optimal patient selection for, and use of, existing pharmacotherapies. Also, it is not a thorough review of recent or continuing clinical trials of other medications (most of which are new uses for old medications that have been approved for other indications, but few of which are new; see TABLE 3, TABLE 4.)

*Heroin addiction.* At present, there are three effective pharmacotherapies for the long-term treatment of heroin addiction: two opioid agonists (methadone and levo-α-acetylmethadol, LAAM) and one partial agonist (buprenorphine combined with naloxone). Methadone and LAAM are approved for use in the United States (TABLE 2).

Methadone is an orally available synthetic opioid that is a full agonist of μ-opioid receptors. It was first tested as a treatment for heroin addicts in early 1964 at The Rockefeller University[1,7,8]. It was found that, by starting at moderate methadone doses that would not cause respiratory depression in a weakly tolerant or naive individual (20–40 mg per day if administered orally), followed by slow escalation up to a dose that was predicted to be maximally effective (80–120 mg per day taken orally), former heroin addicts experienced no opiate-like effects. At the same time, signs and symptoms of opiate withdrawal were completely prevented. Doses of 80 mg or more per day of methadone provided a 'blockade' against the effects of superimposed heroin through the mechanism of opioid tolerance and CROSS-TOLERANCE[1,7,8]. Furthermore, drug craving was markedly reduced or eliminated, and patients were able to focus on their concomitant counselling and behavioural treatment, and also on obtaining education and/or job skills to return to a normal lifestyle. This first set of studies (including all of the studies documenting the blockade of heroin effects by the mechanism of opioid cross-tolerance developed during high-dose methadone treatment) was completed in July 1964 and, after the addition of a few more patients at Rockefeller later in 1964, the clinical research was extended to Manhattan General Hospital in early 1965. Here, Nyswander, Dole and others documented effectiveness in a community-based, 'real world' setting, and also showed that six of the original patients who were studied at Rockefeller in 1964 were still in treatment after 10–15 months[50]. Methadone was approved by the FDA in 1973, and numerous studies since then have continued to show the high level of effectiveness of methadone treatment[51,52]. Studies showing the effectiveness of methadone maintenance treatment have stressed the importance of concomitant, usually on-site, behavioural treatment, including counselling, with or without group or individual therapy (for example, see REFS 1,2,50). One superb study has reported a rigorous assessment of the response to methadone maintenance treatment delivered with 'low,' 'medium' or 'high' doses of behavioural care, with clear evidence of a 'dose response'[53]. Approximately 179,000 former heroin addicts are now in methadone maintenance treatment in the United States, and around the same number are receiving treatment in Europe[52].

Recent studies have shown that in addition to being one of the most efficacious selective μ-opioid-receptor full agonists, methadone also has modest *N*-methyl-D-aspartate (NMDA) antagonist activity[54–56]. As NMDA antagonists have been shown to prevent or attenuate the development of tolerance to opiates, this modest NMDA antagonism might explain, in part, the apparent lack of development of progressive tolerance to methadone after stabilization on moderate to high doses. Patients have been maintained on steady doses, in the adequate dosage range of 80–150 mg per day, for more than 35 years with no need for an increase in dosage[56]. Another potentially interesting difference between methadone and natural plant-derived opiates, such as morphine, is the ability of methadone to cause

WITHDRAWAL
A collection of physiological signs and symptoms that appear after the sudden cessation of drug intake, which can include shaking, sweating and anxiety, depending on the drug.

MESOLIMBIC–MESOCORTICAL DOPAMINERGIC SYSTEM
This system is part of the motivational system that regulates responses to natural reinforcers, such as food, drink, social interaction and sex.

CONDITIONED PLACE PREFERENCE
The development in an experimental animal of a preference for a location that is repeatedly paired with a rewarding stimulus (for example, cocaine).

CUE-INDUCED RELAPSE
Relapse to drug taking ('reinstatement' in animal self-administration models) after a period of cessation can be induced by a drug-associated cue or specific environmental stimulus, such as a light or sound, which is not directly related to drug taking. Such a cue can elicit a neural response that leads to drug seeking or taking behaviours.

PRIMING
Re-administration of even a modest amount of the drug of abuse after chronic use, and then achievement of an abstinent state.

CROSS-TOLERANCE
The development of tolerance to the effects of a second drug, which results from the development of tolerance to a first drug after extended exposure to the first drug. For example, chronic treatment with methadone produces cross-tolerance to heroin.

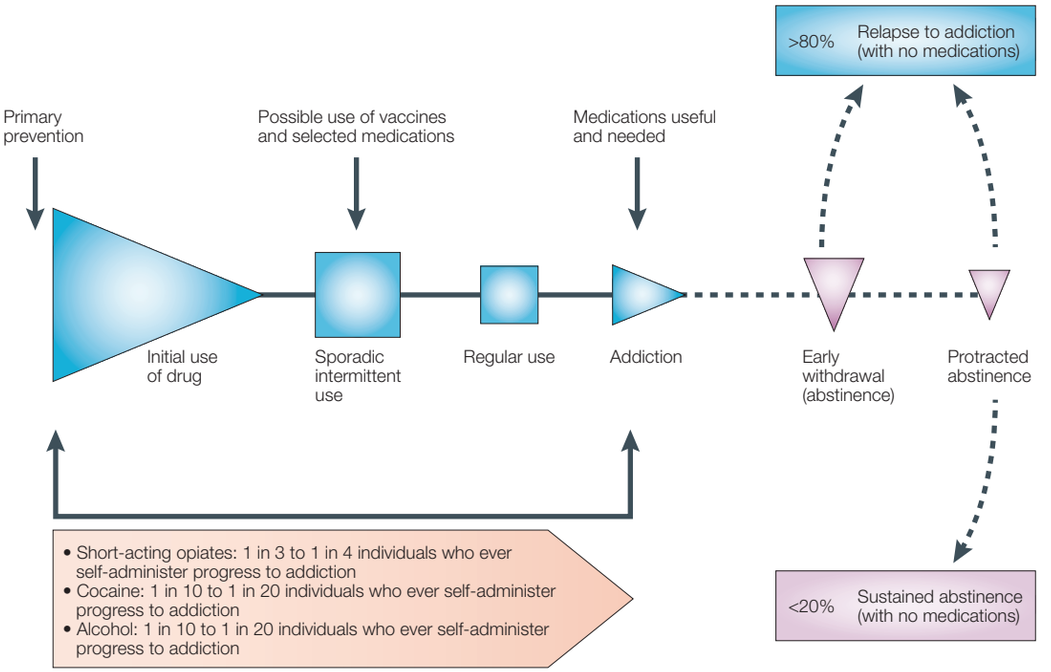


Figure 2 | **Time-course of addiction.**

rapid receptor internalization[57]. In addition, it has been shown that methadone causes greater agonist-induced μ-opioid-receptor desensitization, as measured *in vitro* using cyclic-AMP assays and inwardly rectifying potassium-channel currents[58].

Other medications that are opioid agonists or partial agonists have been developed for the treatment of opiate addiction. LAAM is an analogue of methadone, the development of which as a treatment for opiate addiction began in the 1970s, but which was approved to treat addiction only in the past decade[3,5,7,8,52]. Unfortunately, recent findings of the prolongation of QT intervals in the electrocardiograms of patients receiving LAAM treatment have stopped the use of this medication in many countries in Europe, and have reduced the number of new patients entering treatment in the United States[52]. Hopefully, rigorous studies will determine whether these QT intervals were actually spurious findings in the few patients that have been tested or whether they are, indeed, drug-related.

Buprenorphine is a partial agonist of μ-opioid receptors that has a slow onset and a long duration of action. Buprenorphine alone has been approved in most countries in Europe for the treatment of opiate addiction[4,5,8], and is also being tested in combination with the opioid antagonist naloxone to prevent abuse liability. As a partial agonist, buprenorphine has the advantage that it is more difficult to overdose unintentionally. However, the partial agonism also limits the maximum effectiveness, with 24 or 32 mg of sublingual buprenorphine being the maximum dose that achieves further agonist effects (a dose that is equivalent to 60 or 70 mg per day of methadone)[4]. As many heroin addicts require higher doses of methadone (80–150 mg per day), buprenorphine and buprenorphine–naloxone might emerge as valuable medications for initial treatment. Fortunately, direct conversion to methadone maintenance treatment if higher doses of opioid agonist are needed has been shown to be feasible. It is anticipated that buprenorphine and buprenorphine–naloxone will be approved by the FDA in late 2002.

Naltrexone, which directly blocks, by receptor occupancy, the effects of any exogenous (or endogenous) opioids (as contrasted with blockade through the mechanisms of tolerance and cross-tolerance, which pertains for methadone, LAAM and buprenorphine), has been studied since the late 1970s for the treatment of opiate addiction, and it has been approved by the FDA for that purpose[4,8]. However, numerous carefully controlled and conducted studies combining antagonist treatment with behavioural management have shown that this treatment approach results in less than 15% one-year retention of unselected heroin addicts. Therefore, it has limited effectiveness, although naltrexone treatment has been shown to be effective in populations in which specific state regulations have precluded access to methadone maintenance treatment, such as physicians and other health-care workers, and parolees[4]. Although some clinical researchers have proposed that compliance (adherence) is the main issue, other investigators suggest that there are other, more fundamental, reasons why naltrexone is not effective for the treatment of heroin addiction and, at the same time, why it might be (and has been) shown to be effective for the management of alcoholism (see below)[59–69].

However, there has never been a serious or rigorous trial of the use of opioid-receptor-antagonist treatment in those who do not fulfil the Federal Regulations

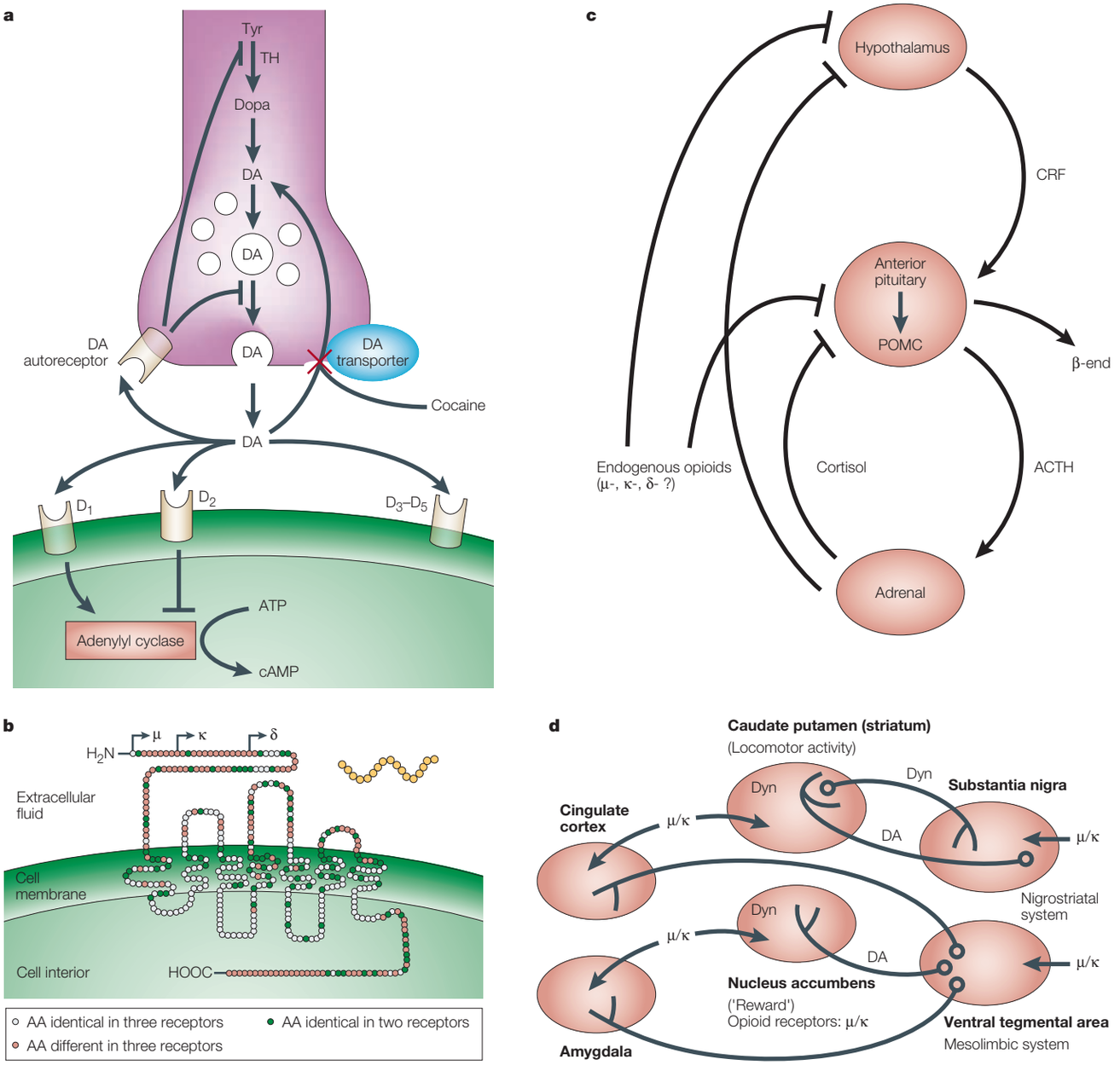


Figure 3 | **Potential targets for new medication development. a** | A dopamine (DA) synapse. Dopamine is biosynthesized from tyrosine (Tyr), with the rate-limiting step being catalysed by tyrosine hydroxylase (TH). Dopamine is packaged into synaptic vesicles and, on nerve firing, is released into the synaptic space, where it can activate postsynaptic dopamine receptors (types 1–5), as well as presynaptic dopamine autoreceptors. Dopamine receptors are G-protein-coupled receptors (GPCRs) that either increase ($D_1$, $D_5$), or inhibit ($D_2$, $D_3$, $D_4$) the activity of adenylyl cyclase. Cocaine blocks the reuptake of dopamine into presynaptic terminals by the dopamine transporter, thereby increasing synaptic dopamine levels. **b** | The human μ-, δ- and κ-opioid receptors are members of the GPCR superfamily. Agonist activation leads to inhibition of adenylyl cyclase, activation of postsynaptic G-protein-coupled, inwardly rectifying potassium channels and inhibition of presynaptic calcium channels. The μ-, δ- and κ-opioid receptors have substantial sequence homology. Amino-acid (AA) positions that are identical in all three receptors, identical in two of the three receptors or unique to each receptor are indicated. **c** | The hypothalamic–pituitary–adrenal (HPA) axis is a main component of the stress-responsive systems. Corticotropin-releasing factor (CRF) is released from the hypothalamus and stimulates the synthesis and release of the pituitary peptides β-endorphin (β-end; an opioid peptide) and adrenocorticotropin (ACTH), both of which are derived from the pro-hormone pro-opiomelanocortin (POMC). ACTH acts on the adrenal medulla to cause the release of the important stress hormone cortisol. Cortisol acts in a negative-feedback manner on both the hypothalamus and pituitary to inhibit the production and release of CRF, β-endorphin and ACTH. Endogenous opioid receptors (μ-, κ- and possibly δ-) also tonically inhibit this axis. **d** | Simplified schematic of projections of the nigrostriatal and mesocortolimbic dopaminergic systems, which are important in mediating both the reward and locomotor effects of addictive drugs. Components of the endogenous opioid system are also abundant in these regions; there is a high density of μ- and also κ-opioid receptors, which are involved in both reward and in countermodulatory mechanisms. Dynorphin (Dyn) and enkephalin peptides are also expressed and active here. Specific components of stress-responsive function are also present. The dopaminergic system here interacts with the stress-responsive HPA axis.

Table 2 | **Pharmacotherapies for specific addictive diseases**

| Addiction | Pharmacotherapy | Mode of action |
|---|---|---|
| Opiates (primarily heroin) | Methadone* | μ-Opioid-receptor agonist |
| | LAAM* | μ-Opioid-receptor agonist |
| | Buprenorphine and naloxone* | Partial μ-opioid-receptor agonist and non-orally bioavailable μ-opioid-receptor antagonist |
| | Naltrexone‡ | μ-Opioid-receptor antagonist |
| Alcoholism | Naltrexone§ | μ-Opioid- and κ-opioid-receptor antagonist |
| | Nalmefene§ | μ-Opioid- and κ-opioid-receptor antagonist |
| | Acamprosate§ | NMDA antagonist |
| Cocaine, amphetamines and other stimulants | None | |
| Nicotine | Nicotine replacement§ | |
| | Bupropion§ | SSRI/noradrenaline inhibitor |

*Effective in >50% of unselected persons (high). ‡Effective in <15% of unselected persons (low). §Effective in 20–50% of unselected persons (moderate). LAAM, levo-α-acetylmethadol; NMDA, *N*-methyl-D-aspartate; SSRI, selective serotonin-reuptake inhibitor.

inclusion criteria for agonist pharmacotherapy[4,51]. Voluntary use of an extended-release preparation of naltrexone or nalmefene (another opioid antagonist, see below) should, therefore, be studied, and could be found to be helpful, as those who have not yet developed 'addiction' probably do not have the associated drug-induced changes in the brain, although they might have genetic alterations of the stress-responsivity mechanisms[6,70–73].

***Cocaine and related stimulant addiction.*** There are no pharmacotherapies that are effective in unselected groups of cocaine addicts, and so an emphasis is placed on this need in this article. Any medications that are shown to be effective for cocaine addiction might or might not be effective for amphetamine or other stimulant addictions. Each of these other classes of compounds not only enhances the level of dopamine and other neurotransmitters by blockade of the respective monoaminergic transporters, but also leads to an enhancement of neurotransmitter release through action on the vesicles that presynaptically store the neurotransmitters. Profound neurotoxicity has also been found for both methamphetamine and MDMA (3,4-methylenedioxy-*N*-methylamphetamine; also known as ecstasy). Further studies might identify targets for more specifically directed treatments for these other stimulant drugs of abuse. Particular medications might be beneficial at specific stages of therapy. For example, the β-adrenoceptor antagonist propranolol can lower cocaine-withdrawal symptoms. This could produce a clinically significant benefit in patients who experience severe withdrawal symptoms that could trigger relapse[74]. Recent studies have also shown that disulfiram (possibly by virtue of its dopamine β-hydroxylase inhibition) might be beneficial for the treatment of cocaine dependence in patients with co-morbid alcoholism or opiate abuse[75–80].

***Alcoholism.*** Three medications have been shown to be effective in 20–50% of unselected alcoholics — the opioid-receptor antagonists naltrexone and nalmefene (which have been shown to be effective except in severely long-term-impaired alcoholics) and acamprosate, which probably acts as an NMDA-receptor antagonist[59–66,68,69,81–87]. The proposed methods of action of the opioid-receptor antagonists will be discussed below, and are thought to be related to endogenous opioid-receptor blockade and, possibly, activation of the stress-responsive axis[69]. Naltrexone has been approved for the treatment of alcoholism in the United States and most countries in Europe[60,61,63,65,67]. Nalmefene has yet to be presented to the FDA in the United States, and is under study, although not yet approved for use, in Europe[62,66]. Acamprosate has been approved for the treatment of alcoholism in most countries in Europe, and is under an FDA Investigational New Drug (IND)-status study in the United States, both for use alone and in combination with naltrexone[67,81–87]. As for methadone maintenance and any other μ-opioid-receptor agonist or partial-agonist treatment, the pharmacotherapeutic management of alcoholism has been shown to be most effective when combined with behavioural treatment — specifically manual-driven cognitive-behavioural therapy. Several sustained-release preparations of naltrexone have been developed, and a recent report shows that one of these preparations maintains effective plasma levels of naltrexone for 3–5 weeks[88].

### Examples of medications under study

A partial list of compounds that are under study at present for the management of one or more specific addictive diseases and one or more phases thereof, such as active addiction, detoxification, withdrawal and relapse prevention, is provided in TABLE 3, TABLE 4 and ONLINE TABLE 3. Some of these have been shown to be effective only when there is a co-morbid condition, such as depression or attention-deficit hyperactivity disorder (ADHD). Others have been shown to be potentially effective for the conditioned-cue component of relapse only. Yet others could be important for ameliorating stress-induced relapse, and still others might reduce the rewarding effects of a drug when self-administered, either on a chronic basis or during a post-abstinence 'priming' or attempt at renewed use, and so might be useful for relapse prevention.

### Potential therapeutic targets

The addictions to be considered in this review for potential new pharmacotherapeutic agents have been limited to heroin addiction, cocaine (and possibly other stimulant) addiction and alcoholism. It is probable that agonists or partial agonists will be the most effective medications for the treatment of any addiction. Profound changes in the brain are caused by chronic exposure to a short-acting drug of abuse, and they result in changes in perception. The changes occur due to the intrinsic neuroplasticity of the brain, and they are persistent and, at best, slowly reversible. It is, therefore, unlikely that an antagonist, which would prevent even endogenous compounds from having their normal physiological activity, would become the treatment of choice for any addiction. However, such an antagonist, simply by blocking the effects of the drug of abuse, might be effective as an intervention early on during drug abuse, before

Table 3 | **Medications in development for cocaine addiction*: part 1**

| Generic, chemical or code name | US trade name | Primary site of action and action |
|---|---|---|
| Abecarnil | | Benzodiazepine partial agonist |
| Amantadine | Symmetrel (Endo Pharmaceuticals) | DA agonist |
| Amantadine + baclofen | N/A | DA agonist/$GABA_B$ receptor |
| Amantadine + propanolol | N/A | DA agonist + β-adrenoceptor blocker |
| Amlodipine | Lotrel (Novartis), Norvasc (Pfizer) | Calcium-channel blocker |
| Baclofen | (Watson Pharmaceuticals) | $GABA_A$ receptor |
| Baclofen + oxazepam | | $GABA_B$/$GABA_A$ receptor |
| Butorphanol | Stadol NS (Bristol-Myers Squibb) | Mixed agonist/antagonist and μ-opioid-receptor partial agonist |
| Captopril | (Mylan Laboratories, Endo Pharmaceuticals, Geneva Pharmaceuticals, Novopharm, Watson Pharmaceuticals) | ACE inhibitor |
| Cabergoline | Dostinex (Pharmacia & Upjohn) | DA $D_2$-receptor agonist |
| Celecoxib | Celebrex | COX-2 inhibitor |
| Coenzyme Q | (Vitaline, Major Pharmaceutical Laboratories, Carlson) | Oxidative phosphorylation/some involvement in fatty-acid storage |
| Coenzyme Q + carnitine | | |
| Cyclazocine | | μ- + κ-opioid-receptor mixed agonist/antagonist |
| D-Amphetamine | Am-Dex (Superior Pharmaceutical) | DA/NE/5-HT indirect agonist |
| (Unnamed) | | DA $D_3$-receptor agonist |
| DAS-431 Clin Pharm | (DrugAbuse Sciences) | DA $D_1$-receptor agonist |
| DAS-431CD1 | (DrugAbuse Sciences) | DA $D_1$-receptor agonist |
| Desipramine | Norpramin (Hoechst-Marion-Roussel) | NE/5-HT/DA-reuptake prohibitor |
| Dexamethasone | Numerous | Glucocorticoid receptor |
| Dextromethorphan | Numerous | NMDA antagonist |
| Dehydroepiandrosterone | Vitamist (Major Pharmaceutical Laboratories) | |
| Disulfiram | Antabuse (Wyeth-Ayerst) | ALDH2/DA antagonist |
| Donepezil | Aricept (Eisai, Pfizer) | ACE inhibitor |
| Disulfiram + naltrexone | | ALDH2 + opioid |
| Ergoloid mesylates | Hydergine (Novartis) | Unknown; DA directed (?) |
| Fluoxetine | Prozac (Eli Lilly, Dista, Geneva Generics, Par Pharmaceutical, Mylan Pharmaceuticals) | SSRI |
| Flupenthixol | | DA antagonist/$D_2$-receptor blockade |
| Gabapentin | Neurontin (Parke-Davis) | GABA; NMDA antagonist |
| GBR 12909 | | DAT inhibitor |
| Ginko biloba | Numerous | Unknown: lowers flavinoids, MAO inhibitor |

*Approved for use in humans in the United States. ACE, angiotensin-converting enzyme; ALDH2, acetaldehyde dehydrogenase 2; COX-2, cyclooxygenase-2; DA, dopamine; DAT, dopamine transporter; GABA, γ-aminobutyric acid; MAO, monoamine oxidase; NE, noradrenaline; NMDA, *N*-methyl-D-aspartate; 5-HT, 5-hydroxytryptamine, serotonin; SSRI, selective serotonin-reuptake inhibitor. Modified from F. Vocci (personal communication) and the Division of Treatment Research, National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA).

the development of brain changes. Furthermore, other agents, such as vaccines, which slow the kinetics of entry of a drug of abuse into the brain, might also be useful for early intervention. In this discussion, no approved (for example, methadone and clonidine) or under-study (buprenorphine and lofexidine) medications to prevent or ameliorate signs and symptoms of opiate withdrawal, or any medications that are used during detoxification from any other addictive drug, will be considered. Unfortunately, after any type of detoxification, relapse rates in individuals who do not receive targeted medications, such as methadone, LAAM or buprenorphine for opiate-addicted patients, or individuals for whom no medications are available, such as individuals with cocaine addiction, have been shown to be more than 80% (within one year and usually much sooner; see FIG. 2).

There have been many other exciting molecular, peptide, receptor, neurobiological, signal-transduction and other neurochemical and integrated neurobiological studies, as well as physiological and behavioural studies, related to the specific effects of drugs of abuse and the neurobiology of addictions. All of these studies teach us about the neuroplasticity of the brain, which responds to the insults of a drug of abuse by excessive use or misuse of existing neuropathways. Toxicity, destruction of previously formed synapses, formation of new synapses, enhancement or reduction of cognition and the development of specific memories of the drug of abuse, which are coupled with the conditioned cues for enhancing relapse to drug use, might have a role in the addictions. Each of these provides numerous potential targets for pharmacotherapies for the future. However, the temporal dynamics of the changes have yet to be fully worked out in many cases. Many of the systems that are involved in the addictive-disease process are also important general systems in the body. Therefore, unless specific regions of the brain could be targeted with a therapeutic agent (or with gene therapy), it is unlikely that such an intervention would be feasible and effective.

For the purpose of this discussion, and to focus on approaches that might be immediately applicable for developing medications, four groups of target will be considered: the μ-opioid receptor and its endogenous ligands β-endorphin and the enkephalin peptides; the stress-responsive axis; the components of the dopaminergic system; and the κ-opioid receptor and dynorphin peptides.

### μ-Opioid receptor and endogenous ligands

The μ-opioid receptor has already been well targeted with effective medications. In fact, with one exception (acamprosate), every medication that has general effectiveness for the treatment of any of these addictions is an agonist, partial agonist or antagonist of the μ-opioid-receptor system.

Nonetheless, a few modest changes in terms of medication development might still be of help. For instance, if a sustained-release form of methadone could be developed, which would allow once-per-week dosing, this might be effective in managing those individuals who do not meet the criteria for one-week, take-home medication (now defined in the Federal Regulations), but who would clearly benefit overall from agonist pharmacotherapy[51]. Such a formulation, however, might not be as effective as daily dosing. After each daily dose of methadone, there is a modest peak, which is barely a doubling of the nadir (that is, lowest daily levels) plasma concentration (and, presumably, brain concentration), and then resumption of a steady-state plasma level over a 24-hour dosing period. In such a 'steady state', we have recently reported, using positron emission tomography (PET), that there is approximately a 20–30% occupancy of μ-opioid receptors in all brain regions[89]. However, peak plasma levels of methadone, when methadone acts as a full agonist at the μ-opioid receptor, might be important for entraining hormones of the HPA axis. The HPA axis is under essentially equal tonic inhibition by the μ- (and also, possibly, the κ-) opioid-receptor system, and by the well-established, long-appreciated, negative-feedback control of the adrenal glucocorticoid cortisol. Cortisol levels have a circadian rhythm — levels are highest in the morning after peak levels of adrenocorticotropin (ACTH) and β-endorphin and lower in the evening, which allows a rise in corticotropin-releasing factor (CRF). Studies in healthy humans by our group have shown that the κ-opioid-receptor system, as well as the μ-opioid-receptor system, participates in this tonic inhibition of the HPA axis by the endogenous opioids, at both hypothalamic and pituitary sites[90]. So, ideally, a sustained-release formulation of methadone would have a modest surge, or peak, every 24 hours, in the morning.

In most studies, buprenorphine and buprenorphine–naloxone have been used on a daily basis. It has been shown that the occupancy of μ-opioid receptors by buprenorphine is very prolonged. Therefore, buprenorphine or buprenorphine–naloxone could be given every other day. However, this does not provide a sustained plasma level. Therefore, as with methadone, a formulation of buprenorphine or buprenorphine–naloxone that would provide a sustained plasma level for up to one week, possibly with a modest peak plasma level on a daily basis, would also be advantageous.

It is striking that, whereas numerous studies have shown that 70–90% of heroin addicts who undertake opioid-receptor-agonist pharmacotherapy with methadone are also cocaine dependent, this number drops to around 30% who have continuous cocaine abuse or addiction after one year or more of adequate-dose methadone treatment[91]. In our laboratory-based studies, we have found that μ-opioid-receptor density is significantly increased after 14 days of binge-pattern cocaine administration, specifically in those brain regions that contain abundant terminals of the mesolimbic–mesocortical dopaminergic system, including the nucleus accumbens, amygdala and anterior cingulate, and also the nigrostriatal system, including the caudate putamen[32,92]. An upregulation of μ-opioid receptors in similar brain regions has also been shown in recently abstinent chronic cocaine addicts[93]. This upregulation of μ-opioid receptors in rodents has been shown to be preceded by an increase

in μ-opioid-receptor messenger RNA levels[94,95]. Therefore, it is possible that, if we continue to be unsuccessful in developing a putatively more-specific medication for cocaine dependency, we should address the μ-opioid-receptor system for this indication.

We have recently shown that there is a relative endorphin deficiency in cocaine addicts and also in chronically cocaine-abusing, methadone-maintained former heroin addicts, just as we showed years ago that there is a persistent endorphin deficiency in medication-free, illicit-heroin-free, former heroin addicts[5–7,96–99]. A sustained-release preparation of buprenorphine, which would provide a steady state, and the use of modest doses for those with 'pure' cocaine dependency or cocaine dependency complicated by alcohol, but not opiate dependency (because, in this case, methadone maintenance or buprenorphine maintenance could be attempted), would be of interest as a possible medication[91,100]. However, it should be noted that 30% of people continue with some cocaine abuse or addiction even

Table 4 | **Medications in development for cocaine addiction*: part 2**

| Generic, chemical or code name | US trade name | Primary site of action and action |
|---|---|---|
| Hypericum | Bio St. John's (Pharmanex), Vitamist, VitaZac (Major Pharmaceutical Laboratories) | 5-HT, minor MAO inhibitor |
| Isradipine | DynaCirc (Novartis) | Calcium-channel blocker |
| Ketoconazole | Nizoral (Janssen Pharmaceutica) | 17α-hydroxylase inhibitor |
| Labetalol | Normodyne (Schering-Plough/Key Pharmaceuticals),Trandate (Glaxo Wellcome) | β-adrenoceptor antagonist |
| Lamotrigine | Lamictal (Glaxo Wellcome) | GABA; NMDA antagonist |
| Levo-Dopa/carbidopa | Sinemet (Merck) | |
| Mecamylamine | Inversine (Merck) | Nicotine antagonist |
| Memantine | | NMDA antagonist |
| Methylphenidate | Ritalin (Novartis) | DA/NE |
| Metyrapone | Metopirone (Novartis) | 11β-hydroxylase inhibitor |
| Modafinil | Provigil (Cephalon) | Orexin |
| Naltrexone | ReVia (DuPont Pharmaceuticals) | μ- (κ)-opioid-receptor antagonist |
| Nefazodone | Serzone (Bristol-Myers Squibb) | 5-HT/NE |
| NS 2359 | | Dopamine enhancer |
| Paroxetine | Paxil (GlaxoSmithKline) | SSRI/NE |
| Pemoline | Cylert (Abbott) | Psychostimulant/DA/NE |
| Pentoxifylline | Trental (Aventis Pharmaceuticals) | ATP or cAMP directed |
| Pergolide | Permax (Athena) | $D_2$-like agonist |
| Piracetam | Nootropil (UCB Pharma) | Unknown; ATP directed (?) |
| Pramipexole | Mirapex (Pharmacia) | $D_2$-like agonist/ $D_3$ agonist |
| Propranolol | Numerous | β-adrenoceptor antagonist |
| Reserpine | Diupres (Merck), Hydropres (Merck), Diutensen-R (Wallace) | Monoamine depleter |
| Riluzole | Rilutek (Aventis Pharmaceuticals) | Inhibitor of glutamate release |
| Risperidone | Risperdol (Janssen Pharmaceutica) | DA/5-HT |
| Selegiline | Carbex (Endo Pharmaceuticals), Atapryl (Athena Neurosciences) | MAO inhibitor |
| Sertraline | Zoloft (Pfizer) | SSRI |
| Sibutramine | Meridia (Knoll) | 5-HT/NE |
| Taurine | | Glutamate |
| Tiagabine | Gabitril Film Tab (Abbott Laboratories) | GABA/NMDA |
| Tolcapone | Tasmar (Roche Laboratories) | COMT inhibitor |
| Tryptophan | | Serotonin |
| Valproate | Depacon, Depakote (Abbott Laboratories) | GABA enhancer |
| Venlafaxine | Effexor (Wyeth-Ayerst) | SSRI/NE |
| Venlafaxine + bupropion | | 5-HT/NE/DA |

*Approved for used in humans in the United States. cAMP, cyclic AMP; COMT, catechol-*O*-methyltransferase; DA, dopamine; DAT, dopamine transporter; GABA, γ-aminobutyric acid; MAO, monoamine oxidase; NE, noradrenaline; NMDA, *N*-methyl-D-aspartate; 5-HT, 5-hydroxytryptamine, serotonin; SSRI, selective serotonin-reuptake inhibitor. Modified from F. Vocci (personal communication) and the Division of Treatment Research, National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA).

after adequate-dose methadone or buprenorphine treatment, and these individuals therefore need an alternative treatment approach.

### Components of the stress-responsive system

In the late 1960s, we proposed that an atypical responsivity to stress and stressors might contribute to the persistence of, and relapse to, an addictive disease — specifically, opiate addiction. So, we included specific laboratory tests in our initial prospective studies that examined the stress-responsive HPA axis. Notably, we found derangements of the endogenous opioid system[3,6–8,47,101,102] (FIG. 3; TABLE 4). We have continued to show that an atypical responsivity to stress and stressors results from chronic administration of a short-acting drug of abuse, including opiates, cocaine and alcohol, when administered in animal models in a pattern that mimics the respective human patterns of abuse — that is, intermittent administration (short-acting opiates), binge-pattern administration (short-acting stimulants, such as cocaine) and oral binge-pattern administration (alcohol)[103–105].

In human heroin addicts, we have found that there is a blunting of the components of the HPA axis, with reduced plasma levels and flattened circadian rhythm of both ACTH and cortisol. During steady-state, long-term, moderate-to-high-dose methadone maintenance treatment, normalization of all of these aspects of the HPA axis occurs[5–8,47]. We have also found that the response to metyrapone challenge — a challenge that blocks the final step of cortisol synthesis for a few hours and thereby results in increased levels of CRF and pro-opiomelanocortin, with resultant increases in plasma levels of ACTH and β-endorphin (which can be measured peripherally) — is blunted during cycles of heroin addiction. However, in stabilized methadone-maintained patients, this returns to normal[47,96,99,101,102]. Also, no disruption of this axis occurs when rats are administered methadone by pump in a steady-state chronic model[106]. Interestingly, we have found that there is hyperresponsivity to this chemically induced stressor in medication-free, drug-free former heroin addicts[97]. So, there is a relative endorphin deficiency in both medication-free, drug-free former heroin addicts and in recently abstinent cocaine addicts.

Extensive interviews with heroin addicts have elicited a history of a desire to be detached from the worries of life and to be delivered into a quiet state. This is achieved with the euphoria and 'rush' that occurs after self-administering heroin or other short-acting opiates, which is followed by a relatively 'dulled' or sleeping period. In sharp contrast, cocaine addicts usually give a history of a desire to become stimulated, to increase alertness and mental acuity, and to feel exhilarated.

Many studies have shown activation of the HPA axis during acute cocaine administration in humans and in animal models. Provocatively, findings from our laboratory again showed activation of the HPA axis with resultant increases in CRF mRNA levels in the hypothalamus, as well as increases in ACTH and corticosterone levels after acute binge-pattern cocaine administration in the rodent[104]. However, after sub-acute binge-pattern cocaine administration, CRF mRNA levels in the hypothalamus returned to normal, whereas the hormones continued to show evidence of activation. After 14 days of binge-pattern cocaine administration, CRF mRNA levels were significantly lower than control levels and, although the ACTH and β-endorphin levels were still elevated, they were significantly attenuated compared with those during acute and sub-acute cocaine administration[104].

By contrast, only transient increases in CRF mRNA levels were found after acute (one day) or sub-acute (two or three day) binge-pattern cocaine administration in other regions of the brain that are involved in the CRF-related stress-responsive function, including the frontal cortex, amygdala and olfactory bulb[104]. No changes in CRF mRNA levels were found in any of these other brain regions after 14 days of binge-pattern cocaine administration. Furthermore, no significant changes were found in any of the CRF-related stress-responsive brain regions after ten days of withdrawal from binge-pattern cocaine administration[104]. However, one group has found increases in CRF peptide levels in microdialysates from the amygdala of rats after acute withdrawal from chronic administration of cocaine, alcohol and other substances[12,15].

In other studies in rats and mice, we found that administration of both dopamine $D_1$- and $D_2$-receptor antagonists, and also gene deletion of *DARPP32*, a central component of the main signal-transduction pathway from $D_1$ receptors, attenuates cocaine-mediated activation of the HPA axis, as shown by the attenuation of plasma ACTH and corticosterone levels[107,108]. Furthermore, in recent studies, we have found that both $D_1$- and $D_2$-receptor antagonists can modestly, but significantly, alter the response of CRF mRNA levels to binge-pattern cocaine administration on a sub-acute basis (three days) in the hypothalamus, and also in the frontal cortex. However, they do not affect CRF mRNA levels in the amygdala or the olfactory bulb[109]. These studies, together with studies of mice in which *Darpp32* is deleted, have all documented a direct relationship between the effect of cocaine on the $D_1$- and $D_2$-dopaminergic-receptor systems and the stress-responsive HPA axis. At present, there are no parallel studies in humans to show a direct relationship between the effect of cocaine on the dopaminergic system and the HPA stress-responsive axis.

So, in both humans and rodents, there are dynamic changes in the state of activation of the HPA axis over time, and in the progressive attenuation of activation of that axis after chronic binge-pattern cocaine administration. Similarly, whereas intermittent cocaine abusers have a rapid response to administered cocaine with respect to a rise in hormones of the HPA axis, long-term cocaine addicts have a much more attenuated response[110].

Activation of the HPA axis after alcohol administration has been shown in both animal models and in humans. Again, we have found attenuation of the response after chronic binge-pattern alcohol administration by the oral route[105]. Recent clinical studies support our hypothesis that alcoholics, similar to cocaine addicts, might be seeking activation of the HPA axis[69].

In other studies, it has been shown that opiate withdrawal after chronic use activates the HPA axis. This activation is associated with the signs and symptoms of opiate withdrawal, and is considered by the heroin addict to be aversive. So, for opiate addiction, suppression of the HPA axis is considered to be desirable or 'rewarding', whereas the counter-adaptive development of tolerance and physical dependence, which leads to activation of this axis after abrupt or gradual opiate withdrawal, is considered by the opiate addict to be aversive, and might serve as a negative reinforcer, leading to the persistence of, or relapse to, opiate use. Cues, whether physiological or environmental, which are reminiscent of that activation, such as occur during metyrapone tests, when levels of both CRF and ACTH surge, are interpreted as aversive and might lead to 'drug hunger' or craving and the desire to self-administer a drug of abuse[111]. Intriguingly, activation of the HPA axis, including elevation of the levels of ACTH, β-endorphin and cortisol, is an early event that occurs near the beginning of opiate withdrawal or abstinence, and actually precedes the appearance of any objective signs and symptoms of opiate withdrawal[112–114]. So, counter to the earlier concepts, activation of the HPA axis in humans might actually drive the signs and symptoms, and therefore the stress, of withdrawal, rather than simply resulting from the stress of the withdrawal[111–114].

Opioid-receptor antagonists have been shown to activate the HPA axis in humans. Building on the very earliest findings of Volavka, our group and others have studied the effects of opioid-receptor antagonists in healthy humans, as well as those who have defined conditions[115–117]. Naloxone, naltrexone and nalmefene all activate the HPA-axis hormones in humans, and this activation is persistent[118–120]. However, this activation does not occur during steady-state administration of these antagonists[117–119]. So, in both healthy volunteers and those who have an addictive disease, opioid-receptor antagonists will activate this axis. Activation is greater with an antagonist that targets both μ- and κ-opioid receptors, such as nalmefene, than it is with a more μ-opioid-receptor-selective antagonist, such as naloxone[90]. Again, this is the basis on which we propose that opioid-receptor antagonists might, in part, be effective for the treatment of alcoholism, which has been shown to be the case by Volpicelli, O'Brien, O'Malley and others[60–66,68,69]. By contrast, we have proposed that opioid-receptor antagonists would be perceived as unpleasant in abstinent opiate addicts, which has, indeed, been found to be the case in all studies of unselected, non-coerced heroin addicts[4].

There has been much activity recently by several pharmaceutical companies in developing a CRF-receptor antagonist, primarily for the treatment of depression. Many researchers in the field of addictive diseases have proposed that such an antagonist could be effective for the treatment of several different addictions, especially as stress is second only to drug priming in precipitating relapse to drug self-administration for various drugs. Furthermore, microdialysis studies have shown the appearance of CRF in limbic regions of the brain after withdrawal from self-administration of various drugs of abuse[11,12,15]. We suggest, on the basis of all these findings, that a CRF-receptor antagonist might be effective for relapse prevention in a medication-free, drug-free former heroin abuser. It might also be helpful in the small group of former heroin addicts on methadone, LAAM or buprenorphine maintenance (agonist or partial-agonist pharmacotherapy) who show some continued use of illicit heroin or other short-acting opiates after stabilization for six months or more on adequate doses of long-acting opioid-receptor agonist.

It would be intriguing, however, to consider the possible much greater effectiveness of a CRF-receptor partial agonist for the treatment of cocaine and other stimulant dependency, and also for the management of alcoholism. It seems that the counter-regulatory effect that pertains in cocaine and alcohol chronic exposure is a reduction or attenuation of the basal activation state of the HPA axis, rather than a hyperactivation, which occurs in the setting of relative or absolute opiate withdrawal. It also seems that many cocaine addicts and alcoholics are, in fact, seeking a modest stimulation of this axis (although it is quite clear that overstimulation becomes aversive). Therefore, a CRF-receptor partial agonist might be extremely effective in managing these disorders. It is of interest that a recent report of cocaine self-administration in CRF receptor 1 (*Crfr1*) knockout mice (potentially equivalent to the administration of a life-long CRF-receptor antagonist) showed increased cocaine self-administration when the mice were placed under intermittent stress[121]. This study supports the possible lack of clinical effectiveness of a CRF-receptor antagonist and would support the effectiveness of a CRF-receptor partial agonist.

### Components of the dopaminergic system

As discussed above, dopamine is a key neurotransmitter for the acute rewarding effects of drugs of abuse[17,122–124]. This is true not only for cocaine, but also other stimulants. Much attention has been, and will continue to be, directed at targeting therapeutic agents to specific components of the dopaminergic system.

***Dopamine-receptor antagonists.*** Antagonists of dopamine receptors (both $D_1$- and $D_2$-like) can block the reinforcing effects of cocaine, amphetamine and other reinforcing drugs in experimental animals under various conditions[125]. Clinically available dopamine-receptor antagonists (principally in use as anti-psychotic medications) can block behavioural and reinforcing effects of drugs of abuse in experimental animals[125–127]. However, there might be a limited margin of selectivity in blocking psychostimulant-induced effects compared with non-drug-induced behaviours[127]. In humans, experiments with haloperidol and flupenthixol indicate that these compounds might not fully block the subjective effect of cocaine (for example, the initial 'rush' after intravenous administration). Given the potential undesirable effects (such as tardive dyskinesia), chronic therapy with the $D_2$-receptor antagonists that are available

at present is not considered to be a practical alternative in patients without co-morbid psychiatric symptoms[128–130]. A recent study examined the effect of repeated (five-day) dosing with a selective $D_1$-receptor antagonist (ecopipam) in non-treatment-seeking cocaine users[131]. Under the study conditions, ecopipam enhanced the subjective effects of cocaine and its self-administration. Therefore, these data do not support the pharmacotherapeutic potential of a chronic $D_1$-receptor antagonist in cocaine abuse.

***Partial agonists.*** Compounds that have intermediate efficacy at $D_1$ and $D_2$/$D_3$ dopamine receptors (partial agonists; for example, BP 897) have also been evaluated for their ability to modulate psychostimulant self-administration in experimental animals[132–134]. Such compounds, if able to produce a selective reduction in psychostimulant-induced reinforcement, might be of value in preventing sudden changes in dopaminergic tone as a result of psychostimulant application. So, dopamine partial agonists might minimize the subjective/reinforcing effects of psychostimulants and, potentially, the dysphoric/withdrawal effects, thereby preventing relapse or repeated use. It would be highly desirable to have a selective $D_1$-receptor partial agonist with no significant other actions for use in human studies as a potential therapeutic agent for cocaine addiction. Until such a selective $D_1$-receptor partial agonist is approved for at least experimental studies in humans, it will be impossible to further assess the potential value of such a medication target (that is, desired effects, as well as potential problems). However, most studies in primates continue to suggest potential effectiveness, and modest augmentation of dynorphin tone would be expected with such compounds (see section on κ-opioid receptors below).

***High-efficacy agonists.*** Several compounds that have high efficacy at $D_1$ and $D_2$ receptors have been studied for their ability to modulate psychostimulant self-administration and behavioural effects in experimental animals[135–137]. Representative compounds from both receptor classes are self-administered by animals, but sufficiently high doses can also modulate cocaine self-administration behaviour. Several $D_2$-like agonists (or non-selective dopamine-receptor agonists), such as pergolide and bromocriptine, are in clinical use for other indications, and their effectiveness in treating psychostimulant addiction has not been shown[138–140]. A clinical study has been completed recently with a $D_1$-receptor-like agonist (ABT 431, now DAS 431) in active cocaine-base smokers[141]. Acutely administered ABT 431 did not decrease cocaine self-administration in this non-treatment-seeking subject group; however, ABT 431 did decrease cocaine-induced subjective effects and craving under some conditions. So, it might be of value to study the clinical potential of repeated treatment with $D_1$-receptor-like agonists in a treatment-seeking clinical-subject group, particularly in relapse prevention in patients who have achieved a period of abstinence.

***Monoamine-reuptake inhibitors.*** Many orally active monoamine-reuptake inhibitors are clinically available as one of the main modalities for antidepressant treatment. This class of compounds is of interest because of their ability to produce a long-lasting inhibition of one, two or three of the transporters for the monoamines dopamine, serotonin and noradrenaline (DAT, SERT and NET, respectively), which are the main sites for the acute effects of cocaine[142]. As such, this pharmacological class can produce a stable pharmacological effect that might 'mask' the immediate and subsequent effects of cocaine during a cycle of abuse (for example, rush, withdrawal or relapse). Several clinically available monoamine-reuptake inhibitors, acting on one or more of the monoamine transporters (for example, bupropion, imipramine, desipramine and fluoxetine), have been tested for their effectiveness in psychostimulant abuse (see REFS 143–147 for examples). So far, robust therapeutic effects have not been reported, although future studies in genetically or psychiatrically defined populations might identify particularly sensitive populations. Methylphenidate, which also inhibits dopamine reuptake, has also been studied as a treatment in cocaine abusers, or abusers with co-morbid ADHD, with some positive results, particularly in the co-morbid group[148,149]. More selective, long-lasting dopamine-reuptake inhibitors, such as GBR12909 (vanoxerine), are also undergoing preclinical and initial clinical studies (see REFS 150–153 for examples). Although these compounds have reinforcing effects in experimental animals, their long duration of action might provide an effective therapeutic approach to limit psychostimulant abuse in human populations.

### κ-Opioid receptor and dynorphin peptides

The κ-opioid system has been implicated in the reinforcing effects of several drugs of abuse, on the basis of neurobiological and behavioural studies in various species. κ-Opioid receptors are widely distributed in the mammalian central nervous system (CNS), and are activated by opioid neuropeptides, including those derived from the pre-prodynorphin gene (for example, dynorphin $A_{1–17}$ or dynorphin B). With particular relevance to their effects on drug-induced reinforcement and addiction, κ-opioid receptors are localized in several areas of the dopaminergic nigrostriatal and mesolimbic–mesocortical system. So, it has been found that synthetic κ-opioid-receptor agonists and dynorphin peptides decrease dopaminergic overflow in the terminal areas of the above pathways, after either local, systemic or intracerebroventricular (ICV) administration[154–156]. This effect of κ-opioid-receptor agonists is opposite to that observed with μ-opioid-receptor agonists, such as β-endorphin or heroin, and drugs of abuse, such as alcohol, cocaine or amphetamine[154]. Consistent with these divergent effects, animal models have shown that selective, non-peptidic κ-opioid-receptor agonists do not have abuse potential and are, in fact, aversive at high enough doses[157,158]. The κ-opioid-receptor–dynorphin system might therefore be considered to be a part of the counter-regulatory mechanisms

of the brain after direct or indirect dopaminergic stimulation[28–35]. The behavioural effects of selective κ-opioid-receptor ligands might be expected to differ as a function of their efficacy on κ-opioid receptors.

***κ-Opioid-receptor antagonists.*** Clinically available opioid-receptor antagonists, such as naloxone, naltrexone or nalmefene, have highest affinity for μ-opioid receptors. However, they also have affinity for κ-opioid receptors[159,160], and both naltrexone and nalmefene can exert potent κ-opioid-receptor antagonist effects *in vivo* at high enough doses[90,161,162]. To our knowledge, there are no available data in humans on the effects of a selective κ-opioid-receptor antagonist, as none has been studied adequately in preclinical tests to determine human safety. Administration of the selective κ-opioid-receptor antagonist nor-binaltorphimine (nor-BNI) does not influence ongoing cocaine self-administration behaviour in rodents or primates[158,163]. However, nor-BNI decreased the acquisition of cocaine self-administration behaviour in rodents[164]. So, κ-opioid-receptor antagonists could have pharmacotherapeutic potential in blocking the acquisition of cocaine self-administration or its re-acquisition (for example, relapse). Of note, however, κ-opioid-receptor full agonists also block cocaine self-administration (see below). Also, κ-opioid-receptor antagonism would be expected to prevent the usual dynorphin-peptide counter-regulation of dopamine tone, an action that is mediated by the κ-opioid receptor. From a drug discovery perspective, it should be noted that nor-BNI and a more recently discovered κ-opioid-receptor antagonist, 5′-guanidino naltrindole (GNTI), have a long duration of action (that is, from several days to several weeks) when administered systemically in rodents or primates[165–168]. This long duration of action might be desirable from the pharmacotherapeutic perspective of preventing acquisition or relapse (that is, not requiring daily treatment). However, this does complicate the design of clinical, as well as laboratory-based experiments, and the design of experiments requiring 'within-subject' designs (for example, in non-human primates), which would be needed to define potential clinical usefulness.

***Partial κ-opioid-receptor agonists.*** Partial κ-opioid-receptor agonists could have potential advantages as pharmacotherapeutic tools for psychostimulant abuse. First, they might be expected to produce less-severe undesirable effects compared with high efficacy κ-opioid-receptor agonists (for example, less-severe maximal sedation or dysphoria; see below). Second, partial κ-opioid-receptor agonists might be of potential value in minimizing the effects of sudden changes (either decreases or increases) in dynorphin release or κ-opioid-receptor availability that might occur at different times during a cycle of psychostimulant administration or abuse[28–30,33,100]. From a drug discovery perspective, there are few examples of selective, partial κ-opioid-receptor agonists at present (that is, those that are not also antagonists or partial agonists at μ-opioid receptors), which complicates the investigation of the pharmacotherapeutic potential of this class[169, 170]. For example, the prototypical partial κ-opioid-receptor agonist nalorphine has μ-opioid-receptor antagonist effects *in vivo* and *in vitro*[170–172]. Another prototypical partial κ-opioid-receptor agonist, cyclazocine, also has antagonist effects at μ-opioid receptors, and it decreases cocaine self-administration in rats[173,174]. Butorphanol and nalbuphine, opioid analgesics that are in clinical use, have affinity for both κ-opioid- and μ-opioid-receptors, and might have partial-agonist effects on either receptor *in vivo*, depending on the experimental conditions[54,160,171,172,175–177].

***High-efficacy, selective κ-opioid-receptor agonists.*** As mentioned above, κ-opioid-receptor agonists can block cocaine-induced increases in dopamine overflow in dopaminergic terminal fields. Consistent with this, high-efficacy, selective κ-opioid-receptor agonists also block cocaine self-administration, cocaine-induced place preference and cocaine-induced locomotor stimulant effects in several species[158,179–181]. However, in some cases in primates, a small degree of selectivity was observed in the potency of these agonists in blocking cocaine-reinforced responding compared with food-reinforced responding (a high degree of selectivity for the former effect would be considered more promising for a pharmacotherapeutic agent). Furthermore, selective, high-efficacy κ-opioid-receptor agonists have undesirable effects at relatively high doses in non-human primates (for example, sedation or emesis)[182,183] and humans (for example, sedation and dysphoria, and occasionally psychotomimesis)[176,183,184]. These undesirable effects of high-efficacy κ-opioid-receptor agonists are dose dependent and reversible; a degree of tolerance to these undesirable effects, but also dependence, has been observed after their repeated administration in primates[181, 185].

In a laboratory study in non-treatment-seeking humans, the high-efficacy κ-opioid-receptor agonist enadoline decreased some subjective effects of cocaine[176], but did not decrease cocaine self-administration (at the highest acute enadoline dose that did not produce unacceptable side effects). It is unknown at present whether a high-efficacy κ-opioid-receptor agonist would modulate cocaine self-administration behaviour in a treatment-seeking population at chronic doses that would not also cause unacceptable side-effects.

The natural sequence but shortened dynorphin $A_{1–13}$ has been shown to reduce tuberoinfundibular dopaminergic tone, as reflected by a dose-dependent increase in serum prolactin levels in healthy human volunteers[186]. In humans, prolactin release is under tonic inhibition by dopamine. No dysphoric or psycho-to-mimetic effects were found in humans receiving dynorphin $A_{1–13}$ (REF. 187).

Peptidic κ-opioid-receptor agonists (for example, dynorphin analogues) could be investigated for their therapeutic value, if their *in vivo* stability, pharmacokinetics and ability to cross the blood–brain barrier are suitable. For example, the stable dynorphin $A_{1–8}$ analogue E-2078 is a high-efficacy κ-opioid-receptor agonist *in vitro* and *in vivo*, but causes limited sedation in primates[188–191]. This compound has been administered to humans for other

indications, and, similar to dynorphin $A_{1–13}$, neither sedation nor dysphoria were reported[191]. This compound might serve as a prototype (or be the actual agent) to be developed as a systemically bioavailable peptide ligand for the κ-opioid receptor for use in humans as a possible therapeutic agent for cocaine addiction (as well as an adjunctive agent in pain management).

## Polymorphisms

Recently, several studies have provided evidence that polymorphisms in genes of the endogenous opioid system might affect cellular functioning and have consequent effects on endogenous physiology, which might have importance for various physiological responses to drugs of abuse. As a brief illustration, one such key example is the A118G polymorphism of the μ-opioid receptor, which has allelic frequencies that range from 2% to nearly 50%, depending on the ethnic population that is studied[70–72,192]. This polymorphism (A118G) has been shown in Han Chinese living in Hong Kong to have a positive association with heroin addiction[193]. We proposed, and recently it has been shown, that humans who have one copy of this variant have altered stress responsivity, as objectively measured by opioid-antagonist challenge, making the A118G polymorphism an extremely attractive target for future medication[70,71,73]. For further discussion of polymorphisms that have relevance to addiction, we refer the reader to REFS 71,72.

## Conclusion

Many advances in our understanding of the underlying biology of addiction are opening the door to the development of novel pharmacotherapies, which are in great demand, owing to the massive financial and human costs of addiction, as well as the negative effects on personal and public health. The cost-effectiveness of the treatment of addiction has been well established; for example, estimates of the economic impact of heroin addiction in the United States in 1996 were that US $5.0 billion was required for extra medical care for untreated heroin addicts, US $5.2 billion was incurred due to criminal activity and an estimated US $11 billion was incurred because of loss of productivity[194]. Moreover, it should be kept in mind that any medication that is developed for the treatment of addiction might also be an effective medication for some other disorders. For example, the μ-opioid-receptor system has an important role in modulating not only the stress-responsive axis, but also the gonadal axis (through inhibition of luteinizing hormone), immune function, gastrointestinal function and cardiovascular function. The dopaminergic system is directly involved in several diseases, including Parkinson's disease. However, the involvement of pharmaceutical companies in the development of pharmacotherapies for addiction has been limited for two main reasons. The first is stigma, including stigma about the subjects or potential patients who have addictive diseases, as well as, unfortunately, treatment providers and the treatments themselves. The second is the more valid concerns about the potential complex nature of the people who suffer from each of these diseases or disorders who would have to become participants in clinical trials and possibly present major problems from both medical and legal stand points, and for the regulatory-affairs review of such trials. But, as the development of successful treatments, such as methadone, buprenorphine and naltrexone, has shown, these problems can and should be overcome.


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## Online links

### DATABASES

**The following terms in this article are linked online to:**

**LocusLink:** http://www.ncbi.nlm.nih.gov/LocusLink/
ACE | ALDH2 | COX-2 | CRF | $D_1$ receptor | $D_2$ receptor | $D_3$ receptor | *DARRP32* | dopamine β-hydroxylase | β-endorphin | enkephalin | $GABA_A$ receptor | $GABA_B$ receptor | 11β-hydroxylase | 17α-hydroxylase | luteinizing hormone | MAO | δ-opioid receptor | κ-opioid receptor | μ-opioid receptor | prolactin

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amantadine | amlodipine | D-amphetamine | baclofen | buprenorphine | bupropion | butorphanol | cabergoline | captopril | carnitine | celecoxib | clonidine | coenzyme Q | desipramine | dexamethasone | dextromethorphan | disulfiram | donepezil hydrochloride | fluoxetine | gabapentin | haloperidol | hydergine | hypericum | imipramine | isradipine | ketoconazole | labetalol | lamotrigine | Levo-Dopa | mecamylamine | methadone | methylphenidate | metyrapone | modafinil | morphine | nalbuphine | nalmefene | naloxone | naltrexone | nefazodone | oxazepam | paroxetine | pemoline | pentoxifylline | pergolide | pramipexole | propanolol | reserpine | riluzole | risperidone | selegiline | sertraline | sibutramine | taurine | tiagabine | tolcapone | tryptophan | valproate | venlafaxine

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