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LEADING ARTICLE

Non-Opioid Treatments for Opioid Use Disorder: Rationales and Data to Date

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Abstract

Opioid use disorder (OUD) represents a major public health problem that affects millions of people in the USA and worldwide. The relapsing and recurring aspect of OUD, driven by lasting neurobiological adaptations at different reward centres in the brain, represents a major obstacle towards successful long-term remission from opioid use. Currently, three drugs that modulate the function of the opioidergic receptors, methadone, buprenorphine and naltrexone have been approved by the US Food and Drug Administration (FDA) to treat OUD. In this review, we discuss the limitations and challenges associated with the current maintenance and medication-assisted withdrawal strategies commonly used to treat OUD. We further explore the involvement of glutamatergic, endocannabinoid and orexin signaling systems in the development, maintenance and expression of addiction-like behaviours in animal models of opioid addiction, and as potential and novel targets to expand therapeutic options to treat OUD. Despite a growing preclinical literature highlighting the role of these potential targets in animal models of opioid addiction, clinical and translational studies for novel treatments of OUD remain limited and inconclusive. Further preclinical and clinical investigations are needed to expand the arsenal of primary treatment options and adjuncts to maximise efficacy and prevent relapse.

Key Points

Currently, treatment approaches for opioid use disorder (OUD), through modulators of mu-opioid receptors, have several limitations.

Substantial evidence from preclinical research suggests the involvement of glutamatergic, endocannabinoid, orexigenic and serotonergic systems in the development and maintenance of addiction.

Nonetheless, clinical trials investigating non-opioid treatments for OUD are scarce and inconclusive.

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1 Introduction

Opioid addiction can be defined as a chronically relapsing neuropsychiatric disorder characterised by dysregulation of the brain reward systems leading to uncontrollable motivation to obtain opioids, and an increased propensity to relapse despite extended periods of abstinence [1]. As defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), opioid use disorder (OUD) is characterised by the chronic and sustained manifestation of several symptoms within a 12-month period, including withdrawal symptoms, tolerance development, and an uncontrollable desire to seek and use drugs despite negative consequences on the patient's daily life [2]. The time course of this neuropsychiatric disorder is characterised by cycling periods of exacerbated use and abstinence over years, separated by periods of treatment and remission [3], during which the relapse vulnerability remains high due to sustained neuroadaptations to the brain's reward circuitry following chronic exposure to opioids [1].

Opioid addiction represents a major public health disorder in the United States (US) and globally. According to the 2018 National Survey on Drug Use and Health (NSDUH), more than 800,000 people in the US report using heroin during the last year [4]. Furthermore, epidemiological studies

with similar datasets indicate that almost 12.5 million Americans have misused prescription opioids over the past year [4, 5], drugs that are generally prescribed to control pain, diminish cough, or relieve diarrhoea [6]. Globally, the rate of extra-medical opioid use has been constantly increasing over the last 3 decades, despite medical and legal interventions aimed at limiting the supply of illicit drugs and the prescription opioid pain relievers [7].

Only a subset of the population that experiment with opioids develop OUD [8]. While the risk factors of developing dependence after exposure are often difficult to predict, they generally include a variety of factors, including sex (male > female), genetics [9], low educational attainment [10], family history of drug abuse, and adverse childhood events [11]. A meta-analysis of the NSDUH from 2002–2016 projects a 30% estimated risk of developing heroin dependence 1–12 months after first exposure to that drug [12]. Past or current opioid-use disorder is prevalent among more than 15 million people worldwide [6]. The increased prevalence of OUD is also accompanied by a subsequent increase in opioid overdose deaths [13], e.g. the rate of heroin overdose almost doubled in the US from 0.7 deaths per 100,000 in 1999 to 4.9 deaths per 100,000 in 2018 [14]. According to the Center for Disease Control and Prevention, opioid-related overdose deaths accounted for two-thirds of overall of drug-induced fatalities in the USA in 2017, at least half of which are attributed to synthetic opioids such as fentanyl [14, 15].

Three medications, methadone, buprenorphine and naltrexone are currently approved by the US Food and Drug Administration (FDA) as medications for opioid use disorder (MOUD). These drugs mainly target and modulate the activity of the endogenous opioid receptors in the brain, which provide different pharmacological strategies to treat OUD and the withdrawal syndromes that result from patient detoxification and rehabilitation. Clinically followed strategies include methadone/buprenorphine taper, naltrexone-assisted withdrawal, and opioid maintenance programmes [6, 16]. Despite the reasonable margin of success of such treatment programmes in controlling the negative affect that results from abrupt discontinuation of illicit opioid use, leading to decreased opioid-associated mortality and criminal behaviour [17], high attrition and relapse rates limit their efficacy and necessitate the need for novel therapies to complement the current approaches [18, 19].

The currently available drugs targeting the opioidergic receptors aim to control the withdrawal effects to help patients in maintaining a drug-free state. Nonetheless, patients with OUD frequently experience tolerance, escalated use, and increased craving, which make them prone to relapse despite extended drug-free periods. Thus, maintenance therapies need to be augmented with treatments employing a different neurobiological rationale to promote long-term remission and prevent recurrence. As previously mentioned, current MOUD strictly target the opioid reward system. However, ample imaging and preclinical studies suggest that several brain regions and other receptor systems are involved in the development and maintenance of drug addiction, as well as relapse. The diverse neurobiology and neuroadaptations that govern these areas may help in expanding the frontiers for discovering novel therapies to complement current MOUD.

In this review, we will discuss the current FDA-approved medications used to target the opioid system and highlight the challenges and limitations associated with their use. Then, we explore the rationale and potential of novel non-opioid-based treatments that target other brain systems, including the glutamatergic, endocannabinoid, the orexigenic and the serotonergic systems. These systems were selected based on the large existing literature that supports their involvement in the development and maintenance of OUD, and the translational potential that they show in preclinical and clinical levels, with potential drugs that are currently available or under investigation.

2 Targeting Opioid Receptors in OUD

There are currently three FDA-approved drugs to treat OUD: methadone, buprenorphine, and naltrexone [6, 16]. These drugs are modulators of the opioidergic receptors [16], and act through different mechanisms of action to minimize the physiological symptoms associated with the abrupt discontinuation of opioids after an extended period of illicit administration. Endogenous opioid receptors, notably mu-opioid receptors (MORs), play a key role in the neurobiology underlying opioid addiction, in both humans [20] and animal models [21]. MOR-knockout mice lack a pharmacological response to opioids, including opioid-induced drug self-administration (SA), conditioned place preference (CPP), and locomotion [21, 22]. As opposed to what is seen in chronic opioid users, imaging studies in previous opioid-dependent users during early abstinence show an increase in opioid receptor levels throughout the brain compared to control subjects [23], which results in decreased tolerance and the manifestation of withdrawal symptoms. Thus, the biological rationale for opioid-based therapies is to differentially modulate opioid receptors to offset the physiological effects of opioid receptor hypersensitivity.

2.1 Methadone

2.1.1 Overview

Methadone is a synthetic, long lasting MOR full agonist used to treat OUD and moderate-to-severe pain [6, 17, 24].

Methadone is used to control the euphoric effects induced by illicit and prescription opioids, to reduce craving, and to attenuate the withdrawal symptoms associated with the abrupt discontinuation of opioid use for at least 24 h after administration [16, 25]. This is achieved due to its long duration of action and slow elimination rates [24]. Methadone is an orally administered drug that has been used clinically since the 1960s [26] with substantial evidence supporting its safety and efficacy [16, 22], and remains the most widely employed drug in the management of OUD [16].

2.1.2 Methadone maintenance

Methadone maintenance, along with buprenorphine (see below), is widely considered as the gold standard for the pharmacological management of OUD [6, 16, 22, 27]. In these programmes, opioid-dependent patients, who are reluctant or unable to remain abstinent, receive a daily dose of methadone through dedicated methadone treatment centres [6, 16]. After stabilisation, patients require 80–120 mg maintenance dose [24], administered orally, which helps to blunt the reinforcing effects of needle injections that are previously associated with illicit drug use, and may therefore elicit craving, and trigger relapse [6]. Unlike short-acting opioids with high addiction potential such as heroin or morphine, methadone does not lead to the development of tolerance. As such, once a stabilising dose is reached by progressively increasing the amount given to reach a significant therapeutic effect, it is unlikely that it will need to be increased over the course of treatment [18]. Imaging studies of methadone-maintained patients show that almost 30% of MORs are occupied with methadone, suggesting that a significant number of MORs are spared to perform physiological functions [28]. Methadone maintenance therapy has been associated with decreased frequency of illicit drug use and associated criminal activities, as well as drug-associated hepatitis and HIV infections [17], improved social functioning and decreased overall mortality [6, 25].

2.1.3 Limitations and challenges

One of the main limitations of methadone-based programmes is the high attrition rates, where more than 40% of patients drop out within the first year [19, 29]. While predictors such as younger age, unemployment, self-pay (i.e. out-of-pocket payment) [29] and low satisfaction levels with treatment at 3 months [30] have been associated with early discharge, interventions to increase the response rate have been largely unsuccessful [31]. Methadone-based programmes are further limited by the need for daily commitment from patients and specialised clinicians, as well as the scarcity of opioid-treatment centres [24], resulting in significant logistic obstacles for the patients to reach such centres, especially seen in rural counties [32]. Notably, early dropout is associated with increased risk of death [33], mainly due to decreased tolerance and increased susceptibility to relapse. It is rather common for patients, in particular those on lower methadone dose and younger age, to continue the use of illicit drugs throughout their enrolment [34]. Importantly, virtually all patients in such programmes report high rates of relapse, shortly after discontinuation of methadone, despite successfully completing treatment [35].

As a full opioid agonist, methadone carries risks of abuse and overdose-death due to respiratory depression [27, 36]. The risk of methadone-related overdose is highest during induction, and requires higher levels of dosing supervision, as well as tight levels of medicolegal control [18]. At any point during treatment, patients are at increased risk of overdose in case of relapse to illicit opioids [18, 36] or multiple drug ingestion (mainly, benzodiazepines) with unknown drug–drug interactions [22, 37]. Similar to other opioids, methadone's side effects include, constipation [27], decrease in cognitive performance and erectile dysfunction [22], which would contribute to lower patient treatment-satisfaction levels and long-term compliance.

2.2 Buprenorphine

2.2.1 Overview

In contrast to the full agonist methadone, buprenorphine is a partial MOR agonist [6, 24, 38, 39] and a kappa-opioid receptor (KOR) antagonist [40]. Jasinski et al. first evaluated the use of buprenorphine to treat opioid dependence in 1978, noting its high efficacy, long duration of action, and low level of associated physical dependence [41]. It was later introduced to clinics in France in 1996 to be prescribed by all registered physicians to address the shortage in dedicated opioid-treatment centres, as well as specialised/licensed clinicians allowed to prescribe and administer methadone [42]. Similar to methadone, buprenorphine is generally used to treat withdrawal symptoms and prevent the negative affect that may trigger relapse in abstaining patients [6]; it is also used in medication-assisted management of withdrawal or in long-term maintenance programmes. It is given as a sublingual tablet in conjunction with naloxone, a short-acting full MOR antagonist with relatively poorer bioavailability, used intravenously to treat opioid overdose. In case of attempted diversion from treatment that would include intravenous use of this drug combination, naloxone blocks opioid receptors and precipitates withdrawal symptoms in OUD patients [27]. A new FDA-approved formulation of sustained-release buprenorphine that may be given as subcutaneous injection up to once monthly has also been shown to block the

reinforcing effects of opioids in OUD patients [43]. Clinical trials are currently being conducted to compare sublingual and extended-release forms on long-term abstinence [44].

2.2.2 Kappa-opioid receptor antagonism

As opposed to the euphoric effects produced by activating MOR, KORs are endogenously activated by dynorphin, producing a dysphoric effect in humans and animal models [45, 46]. It has been hypothesised that the dysphoric effect of KOR is necessary to maintain a homeostatic balance with MOR-induced euphoria. The chronic activation of MOR by continuous administration of illicit opioids results in a compensatory increase of endogenous KOR activation, mediated by sustained release of dynorphins. The over-stimulated KOR results in the generalised dysphoria associated with opioid withdrawal, precipitated by cessation of drug intake [47, 48]. As such, KOR antagonists have been hypothesised as a treatment strategy in OUD. The ability of selective KOR antagonists to successfully decrease morphine withdrawal in rats further support this hypothesis [49]. In particular, buprenorphine's antagonistic effects of KOR were shown to contribute to its efficacy as a treatment. When combined with naltrexone, a selective MOR antagonist aiming to block buprenorphine's partial agonist effects on MOR, buprenorphine performed better than naltrexone alone to increase retention in treatment and abstinence from illicit drug use [50].

2.2.3 Comparison to methadone

Due to its partial agonist function, buprenorphine is deemed generally safer than methadone. The ceiling effect of the partial agonist limits the risk of developing arrhythmias and respiratory failure [27, 36]. The longer duration of action and slower elimination rates account for larger intervals between drug administration in clinical settings; unlike methadone that must be administered daily, buprenorphine can be given every other day up to 3 times weekly [24]. Although such treatment regimens with less frequent dosing have shown similar efficacy and safety profiles [51], buprenorphine is most commonly given in daily doses. Studies that directly compare the use of buprenorphine to methadone for the treatment of OUD remain largely inconclusive. While some studies show that buprenorphine is associated with lower retention rates than high-dose methadone [52, 53], other studies suggest that buprenorphine, once given at high enough doses, provides similar efficacy profiles, with better safety margins [54, 55]. Evidence suggests that patients on buprenorphine are less likely to relapse to illicit drug use and have significantly lower levels of opioid-positive urines on regular tests compared to those in methadone maintenance programmes [53]. The lower levels of continuous opioid use during treatment may be associated with the unique ability of buprenorphine, as a partial opioid receptor agonist, to induce aversive withdrawal symptoms in patients actively using opioids. Withdrawal symptoms occur because buprenorphine has a high affinity to MOR, and will displace full agonist lower affinity opioids. Since treatment initiation can similarly precipitate withdrawal in current users, buprenorphine is given 16–24 h after last administration of illicit opioids [6].

2.2.4 Limitations and challenges

Similar to methadone treatment programmes, recent trials assessing the use of buprenorphine-based treatments have shown that up to 60% of patients relapse to opioid use within 3 months after initiating treatment [56, 57]. While methadone's effects can be enhanced through increasing the maintenance dose, the same strategy cannot be used effectively in buprenorphine, due to the ceiling effects of pharmacological partial agonists, which limits its use in severe forms of OUD [18, 24, 58]. Although such incidents are more common when patients receive methadone treatment, fatalities have been reported following buprenorphine overdose, notably during the induction period [18, 36, 42], or following concurrent use of benzodiazepines and antidepressants [22]. Similar to other MOR agonists, buprenorphine carries abuse liability, with several studies showing that it produces euphoric effects in recently-detoxified opioid users, notably when administered intravenously [38, 59, 60]. These results raised concerns over risk of diversion and intravenous use, which is alleviated by the addition of naloxone to the drug formulation. However, due to naloxone's poor absorption when administered sublingually, it induces MOR blockade exclusively when the combination is administered intravenously. Patients suffering from depression, pain, and withdrawal syndromes have reported illicit and illegal use of buprenorphine to treat their symptoms [36]. Epidemiological studies suggest IV use of buprenorphine is more common in countries with limited access to traditionally misused opioids, such as morphine [5, 16].

2.3 Naltrexone

2.3.1 Overview

Naltrexone is a high-affinity MOR antagonist [16] and is FDA-approved for the treatment of opioid and alcohol use disorders [6, 16]. Mechanistically, naltrexone acts by preventing illicit and prescription opioids from binding

to MORs, thereby blocking their euphoric and rewarding effects and likely decreasing further probability of abuse by eliminating conditioned responding [16, 18]. A rationale behind using antagonist treatment in selected patients is the ambition to overcome 'opioid dependence', including that to methadone or buprenorphine, rather than to solely reach the 'social rehabilitation' achieved in opioid agonists maintenance programmes [16]. Naltrexone has less pharmacokinetic interactions than methadone and buprenorphine [37], making it a convenient choice for patients on multiple medications [27]. It is also the drug of choice for patients who wish to remain in opioid-free programmes, or risk missing multiple medication doses if registered in an opioid-maintenance programme [24, 27]. Unlike prescription opioid receptor agonists, naltrexone has no potential of dependence, abuse or diversion of use [16], and can be safely administered by patients at home. Since naltrexone is not considered a controlled substance and does not carry any abuse potential, it has been preferred by law enforcement units over other controlled medications such as methadone and buprenorphine [61].

2.3.2 Challenges and limitations

Naltrexone must be given only to patients without physical dependence to opioids, as they will suffer from withdrawal symptoms shortly after the onset of antagonist effects otherwise [6, 16, 24]. Patients must therefore demonstrate opioid-withdrawal free state over multiple days before naltrexone initiation, pass an opioid-free urine test, or sustain naloxone-challenge without precipitation of withdrawal symptoms [6]; these conditions limit its use to highly motivated patients only. In fact, the main challenge facing naltrexone-based treatments is low retention levels and poor compliance rates [16, 18]: dropout rates from naltrexone-based treatment regimens are as high as 50% during the first 6 weeks [62], reaching up to 80% after 24 weeks [6, 27, 62]. Furthermore, patients on a naltrexone-based regimen show poor adherence to daily pill use; a limitation that can be partially circumvented by behavioural therapies or the use of extended-release formulations [63, 64]. Although extended-release naltrexone has been shown to have similar effects to buprenorphine treatment after treatment initiation on a per-protocol basis [57], multiple reports have shown significant challenges in initiating naltrexone treatment, likely due to precipitation of withdrawal symptoms [57, 63, 65].

The aforementioned limitations and challenges seen in traditional FDA-approved drugs to treat OUD highlight the need for novel treatment options that are not limited to target the endogenous opioidergic reward system, but extend to target other aspects of OUD including reward craving, cognitive control and relapse vulnerability [1, 66]. The overall limited effects of currently available medications accentuate the need to develop new therapies, notably to target patients unresponsive to traditional treatment approaches.

3 Potential Non-Opioid Treatments for OUD

Opioid-free treatments have been used in clinical settings to control withdrawal symptoms in abstaining patients [6]. It has been shown that alpha-adrenergic agonists, such as lofexidine [67], clonidine or tizanidine [68], are superior to placebo control to decrease anxiety and autonomic hyperactivity, but not as effective as opioid-based treatments in maintaining abstinence. Such agents are also used prudently as they might produce hypotension in these patients [6, 24, 68]. Anxiolytics, antiemetics, and anti-inflammatory drugs have been also evaluated in selected patients to treat withdrawal symptoms [6]. While such approaches may offer limited help in symptomatic relief, they do not address the neurobiological adaptations of drug addiction that control compulsive use and underlie relapse.

The following section will focus on other systems in the central nervous system that target different aspects of opioid addiction. An understanding of the neurobiology underlying OUD through the use of translational preclinical models and neuroimaging studies is fundamental towards a goal of identifying novel therapeutic targets. While non-contingent injections of substances of abuse help in the evaluation of their associated pharmacological effects and subsequent withdrawal consequences, preclinical behavioural models are used to model and investigate more complex aspects of opioid addiction, including models of CPP and SA. The former assesses the rewarding effects of the drugs by associating contextual cues to a specific drug, while modifications can be added to SA paradigms to mirror an array of addiction-associated behaviours such as contingent acquisition of drugs, escalation of intake, extinction of previously conditioned behaviours, responses to punished rewards, decision making, extinction responding and reinstatement of drug seeking.

3.1 Glutamatergic System

3.1.1 Rationale

Glutamate is the major excitatory neurotransmitter in the brain and plays an important role in the neurobiology of addiction [69–71]. Glutamate is the main neurotransmitter released by pyramidal neurons, the main projection neurons of the cerebral cortex, amygdala and hippocampus, all of which play key roles in the development, maintenance, and expression of the drug addiction [1]. While the rewarding

value of drugs is encoded by dopaminergic inputs from the ventral tegmental area (VTA) into the nucleus accumbens (NA), glutamatergic tone in the VTA is necessary for the opioid-dependent dopamine release [72]. In a heroin SA model, hippocampal glutamatergic projections to the NA [73] and the infralimbic cortex [74] in rats regulate context-induced reinstatement of heroin seeking after abstinence. Preclinical studies accentuate the role of glutamatergic projections from cortical and allocortical structures into the NA, a neural substrate for reward processing and motivational behaviour, on the acquisition and expression of opioid-conditioned behaviours, including relapse [75]. In fact, glutamate release from prelimbic cortical projection is necessary for the cue-induced reinstatement of heroin-seeking behaviour in previously extinguished rats [76]. Furthermore, cue- or drug prime- induced relapse to heroin use in rats depends on synaptic potentiation of glutamatergic inputs to the NA, seen as increases in surface expression of *N*-methyl-D-aspartate (NMDA) receptors containing the NR2B subunit [77, 78]. It has also been shown that chronic exposure to opioids upregulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the prefrontal cortex [79] and NA [80], which are necessary for the reinstatement of heroin-seeking behaviours.

The previously mentioned glutamatergic release at the level of the synapse is accentuated by long-lasting down-regulation of glutamate transporter 1 (GLT-1), a glial protein responsible for maintaining glutamate homeostasis [81]. Cue-induced extra-synaptic release of glutamate (glutamate spill-over) due to GLT-1-downregulation results in activation of extra-synaptic NMDA receptors that drive the reinstatement of heroin seeking in extinguished animals. On the other hand, acute withdrawal from morphine in morphine-dependent animals results in increase in GLT-1 expression in the hippocampus [82] and the locus coeruleus [83]. Deletion of mGluR2, a metabotropic glutamate receptor that decreases presynaptic glutamate release upon activation, potentiates heroin SA, and heightens withdrawal symptoms upon naloxone challenge in morphine-dependent rats [84]. Evidence from previous studies suggests that glutamatergic signalling is involved in both primary reward (learning/acquisition) and motivational (drug seeking/reinstatement) aspects of opioid addiction, which implies its importance in treating the multifaceted nature of OUD.

3.1.2 Preclinical evidence

Glutamate signalling can be modulated by a variety of mechanisms that may offer therapeutic targets for OUD, including presynaptic/postsynaptic metabotropic receptors, ionotropic receptors, and modulators of GLT-1 expression. Several studies have investigated the role of modulating metabotropic glutamatergic receptors on opioid-associated behaviours. Presynaptic mGluR2/3 agonists (such as *N*-acetyl-aspartyl-glutamate or LY379268) [85, 86] and post-synaptic mGluR5 antagonists [such as 2-methyl-6-phenylethynyl-pyridine (MPEP)] [87–89] attenuate morphine/heroin SA and block cue-induced reinstatement of seeking behaviour after extinction training. In addition, mGluR5 antagonists attenuate the expression of symptoms of opioid withdrawal in morphine-dependent rodents following naloxone challenge [90]. The NMDA receptor antagonists have been shown to reduce behavioural and physiological withdrawal symptoms in morphine-abstinent rats [91], and block the learning and expression of morphine-induced place preference in rodents [92]. Surprisingly, systemic injections of the NMDA receptor antagonist dizocilpine increased levels of heroin SA [93], which may be explained by decrease in opioid reward following NMDA receptor blockade [70]. Moreover, AMPA receptor blockade blocks cue-induced reinstatement of heroin seeking in extinguished rats [79]. These data provide preclinical evidence supporting the potential efficacy of modulators of glutamate receptors to help in treatment of OUD.

Glutamate homeostasis in the NA has been proposed to be involved in relapse to drug abuse after extended periods of abstinence and extinction [69, 71], and restoring GLT-1 function to prevent glutamate spill-over has been hypothesised as a potential therapeutic mechanism in OUD [94]. Systemic administration of *N*-acetylcysteine (NAC), a glutamatergic agent used in treatment of cystic fibrosis, restores GLT-1 expression in different brain regions of opioid-dependent animals, and effectively attenuates precipitation of withdrawal symptoms [83] and cue-induced reinstatement [81]. Ceftriaxone, a beta-lactam antibiotic and potent up-regulator of GLT-1 via unclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signalling, has been shown to block morphine-induced withdrawal effects [95] and inhibit the development of tolerance [96] despite chronic non-contingent morphine injections.

3.1.3 Clinical evidence

The clinical literature discussing the effects of manipulating the glutamatergic system in treatment of OUD is relatively limited. To date, despite its largely established safety and relative success in decreasing craving in cocaine-addicted individuals [94, 97], neither NAC nor other GLT-1-targeting drugs have been tested in clinical setting for treatment of opioid addiction. Clinical trials that assessed the effects of modulating glutamate receptors in OUD patients have yielded mixed results. Memantine is an orally administered non-competitive NMDA receptor antagonist that attenuates withdrawal symptoms and subjective ratings of heroin craving in addicted patients [98, 99], without affecting the

reinforcing effects of the drug that drive SA and relapse. Dextromethorphan, a non-competitive NMDA receptor antagonist, was shown to be ineffective as a primary treatment for opioid withdrawal [100]. Further studies are required to assess the potential role of glutamatergic modulators as adjunct treatments of OUD and define any safety concerns associated with such therapeutic interventions.

3.2 Endocannabinoid System

3.2.1 Overview

The endocannabinoid signalling system has been characterised by two main G-protein coupled receptors: cannabinoid receptors 1 and 2 (CB1R/CB2R). CB1 acts as the main endocannabinoid receptor and is widely expressed in the human adult brain, notably in reward-processing areas such as the ventral striatum, the amygdala, the VTA and the prefrontal cortex [101], while CB2 is expressed mainly on immune cells, epithelial lining of the brain and some neurons [102]. CB1 and CB2 are inhibitory receptors that block the release of Gamma aminobutyric acid (GABA), glutamate and acetylcholine when activated [102]; they are mainly stimulated by two endogenous ligands: anandamide (partial agonist) and 2-arachidonoylglycerol (2-AG, full agonist). The endocannabinoid system in the central nervous system is involved in different functions, including mood, appetite, pain regulation, sleep and neuronal development, [103], many of which are highly disturbed by OUD and the opioid withdrawal syndrome.

Multiple studies have shown the involvement of endocannabinoid systems in natural [104] and drug-associated [102, 105] reward processing, including opioids. CB1-knockout mice fail to SA morphine and do not develop CPP to morphine, despite unaffected morphine analgesic effects following acute injections [106]. Interestingly, pharmacological blockade of CB1 receptors induced similar decrease in levels of opioid intake without affecting morphine-dependent intra-accumbens dopamine release [107], supporting the hypothesis that CB1 receptors gate drug-dependent rewards through a dopamine-independent pathway. Furthermore, cue-induced reinstatement of heroin seeking can be reduced by systemic [108, 109] or intracranial injections of CB1 antagonist at the level of the prefrontal cortex or NA [108]. It is important to note that this effect is also seen with sucrose SA, during which pharmacological blockade of CB1 significantly decreased sucrose-seeking behaviour [110], suggesting a broader role of this receptor on reward-conditioned behaviours.

3.2.2 Preclinical evidence

The use of CB1 receptor agonists has been long hypothesised to decrease the severity of withdrawal symptoms of morphine and heroin dependence in rodent models [111]. Administration of Δ-(9)-tetrahydrocannabinol (Δ(9)-THC), a full CB1 agonist, attenuates tremors and headshakes seen in morphine-dependent mice following naloxone challenge [112]. Recent study has shown that vaporised Δ(9)-THC can reduce oxycodone SA in rats and enhance its antinociceptive effects [113]. Unfortunately, acute or chronic Δ(9)-THC injections were not sufficient to reduce rates of heroin SA in rhesus monkeys [114]. A more recent study by Ren et al. investigated the role of cannabidiol (CBD) as a treatment for opioid addiction, using a rat model of heroin SA and relapse. Acute CBD administration had no influence on levels of heroin SA, but significantly attenuated cue-induced, but not prime-induced, reinstatement of heroin-seeking behaviour in rats after a 2-week drug-free abstinence period in their home cage [115]. This cue-dependent effect of CBD makes it an optimal adjunct treatment to naltrexone, an opioid receptor antagonist, that would control for prime-induced reinstatement, and thereby simultaneously protect against relapse caused by opioid-associated cues or the drug itself [116]. Although CB1 receptor antagonists are unsuccessful in attenuating morphine withdrawal symptoms in mice [112], the neutral CB1 receptor antagonist, AM4113, and the CB1 inverse agonist, rimonabant (SR141716), have been shown to inhibit heroin SA in naïve [109] and opioid-dependent [117] animals, respectively.

3.2.3 Clinical evidence

Dronabinol, a CB1 receptor agonist, has been used in multiple clinical trials to assess its potential use in OUD patients [118–120]. In one of these trials, dronabinol was given to patients undergoing naltrexone-dependent management of withdrawal [118]. Dronabinol had no effect on treatment completion or rate of successful induction, but decreased patient-subjective rating of withdrawal symptoms when compared to placebo control. However, when compared to active treatment with opioid agonists (Oxycodone), low-dose dronabinol produced similar effects to placebo controls [120]. Whereas high doses of dronabinol were able to produce modest reductions on opioid withdrawal symptoms, they increased risks of serious side effects, such as tachycardia and cognitive impairment [119, 120]. On the other hand, the CB1 receptor antagonist, rimonabant, was shown to be a successful treatment regimen for obesity or smoking cessation [121], but has failed to survive in clinical trials due to development of serious side effects, such as anxiety,

depression, and suicidal ideations [109]. Since these side effects were attributed to the inverse agonist property of rimonabant, future strategies may employ neutral antagonists to avoid these undesirable consequences.

3.3 Orexigenic System

3.3.1 Rationale

Orexins A and B (or Hypocretin1/2) are peptide neurotransmitters released by a limited and specialised group of neurons in the lateral hypothalamus (LH). They act through two G-protein-coupled receptors, Orexin 1 and 2 receptors (Ox1R/2R) [122–124], and have been previously shown to be involved in feeding behaviour [123, 125], narcolepsy [126], pain regulation [127], and reward seeking [128]. Anterograde and retrograde labelling studies have shown that these neurons project to multiple reward-associated areas including the NA, the VTA, the amygdala, locus coeruleus, and the prefrontal cortex [122, 129], which implicates a potential role in reward processing and drug addiction. Georgescu et al. provided the first evidence of orexigenic involvement in opioid addiction, showing that following chronic morphine administration and withdrawal orexin-expressing neurons increase *fos* expression, an immediate early gene protein used as marker of neuronal activation [130]. Orexin neuronal activation was later shown to be correlated with amount of time spent in morphine-associated chamber in CPP paradigm [128]. In fact, chemical activation of orexigenic neurons was able to reinstate an extinguished morphine-seeking behaviour, an effect that was blocked by systemic injection of an Orexin A antagonist [128], indicating a causal role of the orexigenic system in the motivational aspect of opioid addiction. It is important to note that *fos* activation in these neurons was not restricted to drugs of abuse (cocaine and morphine), but was also seen with natural rewards (food and sucrose) [128, 131]. Neurotoxic lesion studies have shown that LH neurons are necessary for the association of morphine reward with contextual cues, as well as the retrieval and expression of this reward memory in CPP paradigms [132]. On the other hand, preclinical evidence suggests a role of the orexigenic projections from the LH to the locus coeruleus [133–135], midline thalamus [136], and shell sub-compartment of the NA [137] in the precipitation of withdrawal symptoms in morphine-dependent rodents.

3.3.2 Preclinical evidence

The effects of the orexigenic system on drug taking and drug seeking were further investigated using Ox1R and Ox2R modulators in animal models of addiction. Intracranial injections of OX1R antagonists directly into the NA [138], VTA [139], or CA1 area of the hippocampus [140, 141] inhibit the acquisition of morphine CPP and attenuate its expression on test day. Systemic injection of SB-334867, an OxR1 antagonist, attenuated heroin SA in adult rats and diminished cue-induced, but not prime-induced, reinstatement of heroin-seeking behaviour following extinction. Furthermore, systemic administration of OxR2 antagonists reduces escalated levels of heroin intake in long-access (12 h), but not short-access (2 h), SA paradigms [142]. Similarly, orexin receptor antagonists were also shown to attenuate withdrawal symptoms in morphine-dependent animals [143, 144]. Interestingly, OxR1 blockade in preclinical studies has been shown to be a valuable target for treatment of addiction across a variety of drugs including cocaine and psychostimulants [145], alcohol [146], nicotine and opioids [147]. Together, the preclinical data highlight the involvement of orexin receptors in the modulation of different addiction-like behaviours in rodents, and indicate that it may be a neurotransmitter system that can be modulated as an adjunct treatment of opioid addiction.

3.3.3 Clinical evidence

To date, no clinical study has directly studied the role of orexigenic blockade in OUD patients. Currently, the dual orexin receptor antagonist, Suvorexant, is FDA-approved for treatment of insomnia, mainly through its effects on OX2R. It has been preclinically tested for its utility and effect on cocaine-associated behaviours [148], and has been suggested for treatment of alcohol use disorder as well. Such a drug may be optimal to also target sleep disorders encountered in opioid users [149]. Nonetheless, Suvorexant is placed in Schedule IV-controlled substances in the USA due to data showing low level of abuse liability in preclinical models [150], which may limit its use in OUD patients.

3.4 Serotonergic System

3.4.1 Rationale

In the central nervous system, serotonin (5-hydroxytryptamine, 5-HT) is almost exclusively released by neurons forming the raphe nuclei in the brainstem [151, 152]. These neurons send ascending and descending projections, modulating a wide variety of human brain circuitries involved in different psychological and behavioural processes including mood, sleep, appetite, memory and reward [151], suggesting a pivotal role of the serotonergic system in drug addiction [153]. Notably, different symptoms of the opioid withdrawal syndrome, like depression, anxiety, weight loss, and tremors, are directly associated with behavioural systems and

neurological function partially controlled by serotonergic mechanisms in the central nervous system [153].

Different types of serotonin receptors are expressed pre-synaptically, post-synaptically, and extrasynaptically and along with the membrane serotonin transporter (SERT), contribute to serotonin release and turnover in the brain (for further information, check [152]). The variety of receptors provide multiple targets for drugs acting on the serotonergic system, many of which have been previously approved for a variety of conditions including eating and mood disorders; many with a reasonable margin of safety.

In rodents, opioid administration results in elevation of serotonin levels in the dorsal striatum [154], NA [154–156], central amygdala [157], and ventral hippocampus [157]. Chronic morphine administration over seven consecutive days results in significant decreases in basal serotonin levels in the prefrontal cortex, amygdala and hippocampus [158], which return to normal following 4 weeks of withdrawal. Nonetheless, serotonin levels in the dorsal nuclei of raphe decrease significantly after withdrawal, suggesting long-term changes in the serotonergic system after opioid administration [158].

3.4.2 Preclinical evidence

The 5-HT3 receptor antagonists [159] and 5-HT2C receptor agonists [160, 161] partially attenuate some aspects of naloxone-precipitated withdrawal in opioid-dependent rodents. Multiple studies investigated the role of different serotonergic modulators on morphine CPP. Pre-treatment of rats with ritanserin, a 5-HT2 receptor blocker, attenuated the acquisition of morphine CPP in a dose-dependent manner, strongly hinting towards a role of serotonin in reward processing of morphine [162, 163]. This is likely due to the 5-HT3 receptor-dependent decrease in dopamine release in freely behaving rats receiving non-contingent injections of morphine [155]. Similarly, 5-HT3 receptor antagonists, administered 15 min before the test, block the expression of morphine-induced CPP [164–166] However, 5-HT3 receptor antagonists have inconsistent ability to inhibit morphine SA in rats [167, 168]. Dexfenfluramine, a serotonin reuptake inhibitor approved to treat obesity, significantly decreases heroin SA and heroin preference in rats [168, 169]. Similarly, lorcaserin, a 5-HT2C receptor agonist that is FDA-approved for weight loss, successfully inhibits opioid SA in rats [170] and non-human primates [171]. Importantly, lorcaserin was shown to dose-dependently inhibit cue-induced reinstatement of oxycodone-seeking behaviour in rats [170], and heroin-induced reinstatement of heroin-seeking behaviour in rhesus monkeys [171], suggesting an important role of 5-HT2C receptors in relapse vulnerability.

3.4.3 Clinical evidence

Despite the availability of different FDA-approved serotonergic modulators, with a reasonable margin of safety, few studies assessed the effects of such drugs in patients with OUD, likely due to the lack of any promising results. One study assessed the effect of sertraline, a selective serotonin reuptake inhibitor approved for treatment of major depression, on OUD treated with naltrexone [172], showing a negative effect on increasing treatment retention by the end of the study. Another study showed no effect of ondansetron, a 5-HT3 receptor antagonist, on withdrawal syndrome in opioid-dependent patients [173].

4 Discussion

One of the major aspects of OUD is the sustained propensity to relapse, despite extended period of abstinence, largely associated with long-term neurobiological adaptations in the brain [174]. The challenges associated with treating OUD patients stem from the complex symptom profile of this neuropsychiatric disorder with continued drug use. For example, the OUD may begin with uncontrolled reward-seeking behaviours (binge/intoxication) that can shift to avoiding withdrawal and negative effects associated with the drug's absence, and ultimately keep brain circuits pre-occupied to seek these drug [1]. While the main goal of the treatment is to reach abstinence from illicit drug use, efforts of current treatment strategies are directed solely towards minimising the negative effects of the opioid withdrawal syndrome.

This review discusses the preclinical and clinical data to date on a variety of systems that may be used as targets to supplement currently available treatments and expand their therapeutic effects by targeting circuitry involved in other aspects of drug addiction. Despite promising results of such targets in rodents and non-human primates, the translational potential of such strategies remains modest, with the effects of new drugs under investigation providing largely inconsistent data in clinical studies. One important factor behind marginal clinical efficacy is the lack of personalizing treatment in OUD. The heterogeneity of OUD stems from, but is not restricted to, the presence of different stages that contain different, even competing behavioural symptoms, the different genetic and epigenetic backgrounds of the patients, and the role of societal, cultural, and religious backgrounds that can cofound any treatment approach. It is important to note that despite tightly controlled environments and genetic backgrounds, such heterogeneity is also often seen in animal models of drug addiction.

The heterogeneity of OUD across patients is a primary rationale to evolve pharmacotherapy towards personalizing

the treatment [175]. While it is largely accepted that different neurotransmitter systems and brain circuits are associated in the development, maintenance and manifestation of OUD, inter-subject variability of the influence of these systems and circuits must be closely assessed. Patients may therefore be treated according to selective symptoms, manifestations or involvement of one neurotransmitter system over the other. Final outcomes of treatments, currently unified into abstinence from drug use, can also be personalized to individual patients. Furthermore, different neurotransmitter systems are likely associated with different underlying symptoms in OUD patients. Advances in analysing individual baseline state circuit strength using functional magnetic resonance imaging show promise for providing evidence of individual circuit profiles corresponding to individual differences in the balance of OUD symptoms [176]. Similarly, preclinical studies should incorporate, rather than ignore, individual differences manifested by heterogenous responses in different models of opioid withdrawal, SA, and CPP. In addition, more effort is needed towards understanding mechanisms to prevent developing OUD, permitting prophylactic treatments and allowing safer use of opioids in medical settings.

Finally, the low rate of translating potential treatments from animal models of OUD to humans is alarming. Moving forward in treatment translation is to increase the studies in non-human primates, as they may show more complex behaviour and might offer a better translational model. Adding genetic variability may also reconcile the gap between the results seen in the laboratories and those seen in clinical trials. Another way to move forward is to develop symptom-specific models with higher construct validity. Such approach, akin to that used in anxiety or schizophrenia, may involve multi-drug therapies providing clinicians with a symptom-by-symptom arsenal of drugs that can be used to personalize therapies.

5 Conclusion

The currently rising opioid crisis requires urgent measures and increasing efforts to develop novel pharmacological therapeutics that will help expand the current scope of mechanisms available for treating OUD. These efforts should run in parallel at a preclinical and clinical level, to expand the potential targets for treatment and develop safe alternatives or adjuncts for currently approved medications. The expanding preclinical literature reveals that opioid use elicits novel neurobiological adaptations in glutamatergic, endocannabinoid, orexigenic and serotonergic neurotransmission that control the development, maintenance and expression of opioid dependence in different animal models of addiction. Even though such efforts have yielded key targets and potential pharmacological treatments, translational efforts have not revealed strong therapeutically beneficial effects in human OUD patients. Clinical experiences with non-opioid treatments for opioid withdrawal syndrome, such as glutamatergic modulators and dronabinol, have been inconclusive. It is equally important to further diversify the endpoints to treatments under investigation, such as dronabinol, to include other aspects of OUD such as propensity to

Table 1 Clinical studies using non-opioid based treatments to treat opioid use disorder

Drug	Target	Endpoint	Results	References
Memantine	NMDA receptor antagonist	Opioid withdrawal symptoms	Attenuation of withdrawal symptoms after naloxone challenge	[98]
Memantine	NMDA receptor antagonist	Preference to drug	Modest reductions in subjective ratings of drug qualities and craving for heroin	[99]
		Reinforcing effects of heroin	Minimal changes vs control group	
Dronabinol	CB1 receptor partial agonist	Withdrawal symptoms	Attenuation of withdrawal symptoms	[118]
		Rates of naltrexone induction	No changes compared to the control group	
Dronabinol	CB1 receptor partial agonist	Safety profile in OUD patients	Increase in heart rate compared to placebo group	[119]
Dronabinol	CB1 receptor partial agonist	Withdrawal symptoms	Modest attenuation of withdrawal symptoms at high doses (> 20 mg), compared to placebo, but not compared to oxycodone maintenance	[120]
		Safety profile	Cognitive impairment, tachycardia and sedation compared to placebo	[120]
Sertraline	Selective serotonin reuptake inhibitor	Retention in naltrexone treatment programmes	No significant effect compared to placebo by the end of the study	[172]
Ondansetron	5HT-3 receptor antagonist	Opioid withdrawal symptoms	No effect compared to placebo control	[173]

5HT 5-hydroxytryptamine, *CB1* cannabinoid receptor 1, *NMDA* N-methyl-D-aspartate, *OUD* opioid use disorder

relapse, cue reactivity, craving, and escalated consumption. Although different non-opioid-based targets and strategies, as discussed in this review, have not been assessed clinically and may offer promising results, personalized multi-target treatment strategies at a single-patient level should be advanced to optimise outcomes.

Declarations

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References

1. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016;3(8):760–73. https://doi.org/10.1016/S2215-0366(16)00104-8.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington: American Pyschiatric Publishing; 2013.
3. Hser Y-I, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry. 2001;58(5):503–8. https://doi.org/10.1001/archpsyc.58.5.503.
4. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. NSDUH Series H-54. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2019.
5. Brady KT, McCauley JL, Back SE. Prescription opioid misuse, abuse, and treatment in the United States: an update. Am J Psychiatry. 2016;173(1):18–26. https://doi.org/10.1176/appi.ajp.2015.15020262.
6. Schuckit MA. Treatment of opioid-use disorders. N Engl J Med. 2016;375(4):357–68. https://doi.org/10.1056/NEJMra1604339.
7. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet. 2019;394(10208):1560–79. https://doi.org/10.1016/S0140-6736(19)32229-9.
8. Sweeting MJ, De Angelis D, Ades AE, Hickman M. Estimating the prevalence of ex-injecting drug use in the population. Stat Methods Med Res. 2008;18(4):381–95. https://doi.org/10.1177/0962280208094704.
9. Berrettini W. A brief review of the genetics and pharmacogenetics of opioid use disorders. Dialogues Clin Neurosci. 2017;19(3):229–36.
10. Townsend L, Flisher AJ, King G. A systematic review of the relationship between high school dropout and substance use. Clin Child Fam Psychol Rev. 2007;10(4):295–317. https://doi.org/10.1007/s10567-007-0023-7.
11. Conroy E, Degenhardt L, Mattick RP, Nelson EC. Child maltreatment as a risk factor for opioid dependence: comparison of family characteristics and type and severity of child maltreatment with a matched control group. Child Abuse Negl. 2009;33(6):343–52. https://doi.org/10.1016/j.chiabu.2008.09.009.
12. Santiago Rivera OJ, Havens JR, Parker MA, Anthony JC. Risk of heroin dependence in newly incident heroin users. JAMA Psychiatry. 2018;75(8):863–4. https://doi.org/10.1001/jamapsychiatry.2018.1214.
13. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Annu Rev Public Health. 2015;36(1):559–74. https://doi.org/10.1146/annurev-publhealth-031914-122957.
14. Hedegaard H, Minino AM, Warner M. Drug Overdose Deaths in the United States, 1999–2018 Hyattsville, MD: National Center for Health Statistics 2020 Contract No.: No. 356.
15. Wilson N, Kariisa M, Seth P, Davis NL. Drug and opioid-involved overdose deaths—United States, 2017–2018. MMWR Morb Mortal Wkly Rep. 2020;2020(69):290–7. https://doi.org/10.15585/mmwr.mm6911a4.
16. Oesterle TS, Thusius NJ, Rummans TA, Gold MS. Medication-assisted treatment for opioid-use disorder. Mayo Clin Proc. 2019;94(10):2072–86. https://doi.org/10.1016/j.mayocp.2019.03.029.
17. Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. Addiction. 1998;93(4):515–32. https://doi.org/10.1046/j.1360-0443.1998.9345157.x.
18. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. J Addict Dis. 2012;31(3):207–25. https://doi.org/10.1080/10550887.2012.694598.
19. Jensen KP, DeVito EE, Yip S, Carroll KM, Sofuoglu M. The cholinergic system as a treatment target for opioid use disorder. CNS Drugs. 2018;32(11):981–96. https://doi.org/10.1007/s40263-018-0572-y.
20. Listos J, Lupina M, Talarek S, Mazur A, Orzelska-Gorka J, Kotlinska J. The mechanisms involved in morphine addiction: an overview. Int J Mol Sci. 2019. https://doi.org/10.3390/ijms20174302.
21. Charbogne P, Kieffer BL, Befort K. 15 years of genetic approaches in vivo for addiction research: opioid receptor and peptide gene knockout in mouse models of drug abuse. Neuropharmacology. 2014;76:204–17. https://doi.org/10.1016/j.neuropharm.2013.08.028.
22. Noble F, Marie N. Management of opioid addiction with opioid substitution treatments: beyond methadone and buprenorphine. Front Psychiatry. 2019. https://doi.org/10.3389/fpsyt.2018.00742.
23. Williams TM, Daglish MR, Lingford-Hughes A, Taylor LG, Hammers A, Brooks DJ, et al. Brain opioid receptor binding in early abstinence from opioid dependence: positron emission tomography study. Br J Psychiatry J Ment Sci. 2007;191:63–9. https://doi.org/10.1192/bjp.bp.106.031120.
24. Gonzalez G, Oliveto A, Kosten TR. Treatment of heroin (Diamorphine) addiction. Drugs. 2002;62(9):1331–433. https://doi.org/10.2165/00003495-200262090-00004.
25. Farrell M, Ward J, Mattick R, Hall W, Stimson GV, des Jarlais D, et al. Fortnightly review: methadone maintenance treatment in opiate dependence: a review. BMJ. 1994;309(6960):997–1001. https://doi.org/10.1136/bmj.309.6960.997.
26. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (Heroin) addiction: a clinical trial with methadone hydrochloride. JAMA. 1965;193(8):646–50. https://doi.org/10.1001/jama.1965.03090080008002.
27. Koehl JL, Zimmerman DE, Bridgeman PJ. Medications for management of opioid use disorder. Am J Health Syst Pharm. 2019;76(15):1097–103. https://doi.org/10.1093/ajhp/zxz105.
28. Kling MA, Carson RE, Borg L, Zametkin A, Matochik JA, Schluger J, et al. Opioid receptor imaging with positron emission tomography and [¹⁸F]Cyclofoxy in long-term, methadone-treated former heroin addicts. J Pharmacol Exp Ther. 2000;295(3):1070–6.

29. Proctor SL, Copeland AL, Kopak AM, Hoffmann NG, Herschman PL, Polukhina N. Predictors of patient retention in methadone maintenance treatment. Psychol Addict Behav. 2015;29(4):906–17. https://doi.org/10.1037/adb0000090.
30. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: a survival analysis. Drug Alcohol Depend. 2011;117(2–3):170–5. https://doi.org/10.1016/j.drugalcdep.2011.01.008.
31. Belding MA, McLellan AT, Zanis DA, Incmikoski R. Characterizing, "nonresponsive" methadone patients. J Subst Abuse Treat. 1998;15(6):485–92. https://doi.org/10.1016/s0740-5472(97)00292-4.
32. Joudrey PJ, Edelman EJ, Wang EA. Drive times to opioid treatment programs in urban and rural counties in 5 US States. JAMA. 2019;322(13):1310–2. https://doi.org/10.1001/jama.2019.12562.
33. Caplehorn JRM, Dalton MSYN, Cluff MC, Petrenas A-M. Retention in methadone maintenance and heroin addicts'risk of death. Addiction. 1994;89(2):203–7. https://doi.org/10.1111/j.1360-0443.1994.tb00879.x.
34. Davstad I, Stenbacka M, Leifman A, Beck O, Korkmaz S, Romelsjö A. Patterns of illicit drug use and retention in a methadone program: a longitudinal study. J Opioid Manag. 2007;3(1):27–34. https://doi.org/10.5055/jom.2007.0036.
35. Magura S, Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. Mt Sinai J Med N Y. 2001;68(1):62–74.
36. Modesto-Lowe V, Swiezbin K, Chaplin M, Hoefer G. Use and misuse of opioid agonists in opioid addiction. Clevel Clin J Med. 2017;84(5):377–84. https://doi.org/10.3949/ccjm.84a.16091.
37. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4–16. https://doi.org/10.1111/j.1521-0391.2009.00005.x.
38. Comer SD, Collins ED. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. J Pharmacol Exp Ther. 2002;303(2):695–703. https://doi.org/10.1124/jpet.102.038141.
39. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev. 2011;4(1):28–41. https://doi.org/10.2174/1874473711104010028.
40. Leander JD. Buprenorphine has potent kappa opioid receptor antagonist activity. Neuropharmacology. 1987;26(9):1445–7. https://doi.org/10.1016/0028-3908(87)90112-2.
41. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry. 1978;35(4):501–16. https://doi.org/10.1001/archpsyc.1978.01770280111012.
42. Auriacombe M, Fatséas M, Dubernet J, Daulouède J-P, Tignol J. French field experience with buprenorphine. Am J Addict. 2004;13(S1):S17–S28. https://doi.org/10.1080/10550490490440780.
43. Nasser AF, Greenwald MK, Vince B, Fudala PJ, Twumasi-Ankrah P, Liu Y, et al. Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. J Clin Psychopharmacol. 2016;36(1):18–26. https://doi.org/10.1097/jcp.0000000000000434.
44. Extended-Release Buprenorphine vs. Sublingual Buprenorphine for the Treatment of Opioid Use Disorder. https://ClinicalTrials.gov/show/NCT04352166.
45. Mysels D, Sullivan MA. The kappa-opiate receptor impacts the pathophysiology and behavior of substance use. Am J Addict. 2009;18(4):272–6. https://doi.org/10.1080/10550490902925862.
46. Carlezon WA Jr, Krystal AD. Kappa-opioid antagonists for psychiatric disorders: from bench to clinical trials. Depress Anxiety. 2016;33(10):895–906. https://doi.org/10.1002/da.22500.
47. Rothman RB, Gorelick DA, Heishman SJ, Eichmiller PR, Hill BH, Norbeck J, et al. An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. J Subst Abuse Treat. 2000;18(3):277–81. https://doi.org/10.1016/s0740-5472(99)00074-4.
48. Helal MA, Habib ES, Chittiboyina AG. Selective kappa opioid antagonists for treatment of addiction, are we there yet? Eur J Med Chem. 2017;141:632–47. https://doi.org/10.1016/j.ejmech.2017.10.012.
49. Kelsey JE, Verhaak AM, Schierberl KC. The kappa-opioid receptor antagonist, nor-binaltorphimine (nor-BNI), decreases morphine withdrawal and the consequent conditioned place aversion in rats. Behav Brain Res. 2015;283:16–211. https://doi.org/10.1016/j.bbr.2015.01.008.
50. Rothman RB, Gorelick DA, Heishman SJ, Eichmiller PR, Hill BH, Norbeck J, et al. An open-label study of a functional opioid κ antagonist in the treatment of opioid dependence. J Subst Abuse Treat. 2000;18(3):277–81. https://doi.org/10.1016/S0740-5472(99)00074-4.
51. Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-weekly versus daily buprenorphine maintenance. Biol Psychiatry. 2000;47(12):1072–9. https://doi.org/10.1016/s0006-3223(99)00270-x.
52. Gryczynski J, Mitchell SG, Jaffe JH, Kelly SM, Myers CP, O'Grady KE, et al. Retention in methadone and buprenorphine treatment among African Americans. J Subst Abuse Treat. 2013;45(3):287–92. https://doi.org/10.1016/j.jsat.2013.02.008.
53. Hser Y-I, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109(1):79–877. https://doi.org/10.1111/add.12333.
54. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2002. https://doi.org/10.1002/14651858.Cd002207.
55. Gerra G, Borella F, Zaimovic A, Moi G, Bussandri M, Bubici C, et al. Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. Drug Alcohol Depend. 2004;75(1):37–45. https://doi.org/10.1016/j.drugalcdep.2003.11.017.
56. Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(12):1947–54. https://doi.org/10.1001/jamainternmed.2014.5302.
57. Lee JD, Nunes EV, Novo P, Bachrach K, Bailey GL, Bhatt S, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2018;391(10118):309–18. https://doi.org/10.1016/S0140-6736(17)32812-X.
58. Li X, Shorter D, Kosten TR. Buprenorphine in the treatment of opioid addiction: opportunities, challenges and strategies. Expert Opin Pharmacother. 2014;15(15):2263–75. https://doi.org/10.1517/14656566.2014.955469.
59. Pickworth WB, Johnson RE, Holicky BA, Cone EJ. Subjective and physiologic effects of intravenous buprenorphine in humans. Clin Pharmacol Ther. 1993;53(5):570–6. https://doi.org/10.1038/clpt.1993.72.
60. Comer SD, Sullivan MA, Walker EA. Comparison of intravenous buprenorphine and methadone self-administration by recently

detoxified heroin-dependent individuals. J Pharmacol Exp Ther. 2005;315(3):1320–30. https://doi.org/10.1124/jpet.105.090423.
61. Andraka-Christou B, Gabriel M, Madeira J, Silverman RD. Court personnel attitudes towards medication-assisted treatment: A state-wide survey. J Subst Abuse Treat. 2019;104:72–82. https://doi.org/10.1016/j.jsat.2019.06.011.
62. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. Addiction. 2006;101(4):491–503. https://doi.org/10.1111/j.1360-0443.2006.01369.x.
63. Sullivan MA, Bisaga A, Glass A, Mishlen K, Pavlicova M, Carpenter KM, et al. Opioid use and dropout in patients receiving oral naltrexone with or without single administration of injection naltrexone. Drug Alcohol Depend. 2015;147:122–9. https://doi.org/10.1016/j.drugalcdep.2014.11.028.
64. Sullivan MA, Bisaga A, Pavlicova M, Carpenter KM, Choi CJ, Mishlen K, et al. A randomized trial comparing extended-release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder. A J Psychiatry. 2019;176(2):129–37. https://doi.org/10.1176/appi.ajp.2018.17070732.
65. Jarvis BP, Holtyn AF, Subramaniam S, Tompkins DA, Oga EA, Bigelow GE, et al. Extended-release injectable naltrexone for opioid use disorder: a systematic review. Addiction. 2018;113(7):1188–209. https://doi.org/10.1111/add.14180.
66. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid use disorder. Nat Rev Dis Prim. 2020;6(1):3. https://doi.org/10.1038/s41572-019-0137-5.
67. Rehman SU, Maqsood MH, Bajwa H, Tameez UDA, Malik MN. Clinical efficacy and safety profile of lofexidine hydrochloride in treating opioid withdrawal symptoms: a review of literature. Cureus. 2019;11(6):e4827. https://doi.org/10.7759/cureus.4827.
68. Stotts AL, Dodrill CL, Kosten TR. Opioid dependence treatment: options in pharmacotherapy. Expert Opin Pharmacother. 2009;10(11):1727–40. https://doi.org/10.1517/14656560903037168.
69. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci. 2009;10:561. https://doi.org/10.1038/nrn2515.
70. Peters J, De Vries TJ. Glutamate mechanisms underlying opiate memories. Cold Spring Harbor Perspect Med. 2012;2(9):a012088. https://doi.org/10.1101/cshperspect.a012088.
71. Kruyer A, Chioma VC, Kalivas PW. The opioid-addicted tetrapartite synapse. Biol Psychiatry. 2020. https://doi.org/10.1016/j.biopsych.2019.05.025.
72. Jalabert M, Bourdy R, Courtin J, Veinante P, Manzoni OJ, Barrot M, et al. Neuronal circuits underlying acute morphine action on dopamine neurons. Proc Natl Acad Sci. 2011;108(39):16446–50. https://doi.org/10.1073/pnas.1105418108.
73. Bossert JM, Adhikary S, St Laurent R, Marchant NJ, Wang HL, Morales M, et al. Role of projections from ventral subiculum to nucleus accumbens shell in context-induced reinstatement of heroin seeking in rats. Psychopharmacology. 2016;233(10):1991–2004. https://doi.org/10.1007/s00213-015-4060-5.
74. Wang N, Ge F, Cui C, Li Y, Sun X, Sun L, et al. Role of glutamatergic projections from the ventral CA1 to infralimbic cortex in context-induced reinstatement of heroin seeking. Neuropsychopharmacology. 2018;43(6):1373–84. https://doi.org/10.1038/npp.2017.279.
75. Kalivas PW, Volkow ND. New medications for drug addiction hiding in glutamatergic neuroplasticity. Mol Psychiatry. 2011;16(10):974–86. https://doi.org/10.1038/mp.2011.46.
76. LaLumiere RT, Kalivas PW. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. J Neurosci. 2008;28(12):3170–7. https://doi.org/10.1523/jneurosci.5129-07.2008.
77. Shen H, Moussawi K, Zhou W, Toda S, Kalivas PW. Heroin relapse requires long-term potentiation-like plasticity mediated by NMDA2b-containing receptors. Proc Natl Acad Sci. 2011;108(48):19407–12. https://doi.org/10.1073/pnas.1112052108.
78. Ma YY, Chu NN, Guo CY, Han JS, Cui CL. NR2B-containing NMDA receptor is required for morphine-but not stress-induced reinstatement. Exp Neurol. 2007;203(2):309–19. https://doi.org/10.1016/j.expneurol.2006.08.014.
79. Van den Oever MC, Goriounova NA, Wan Li K, Van der Schors RC, Binnekade R, Schoffelmeer ANM, et al. Prefrontal cortex AMPA receptor plasticity is crucial for cue-induced relapse to heroin-seeking. Nat Neurosci. 2008;11(9):1053–8. https://doi.org/10.1038/nn.2165.
80. Russell SE, Puttick DJ, Sawyer AM, Potter DN, Mague S, Carlezon WA Jr, et al. Nucleus accumbens AMPA receptors are necessary for morphine-withdrawal-induced negative-affective states in rats. J Neurosci Off J Soc Neurosci. 2016;36(21):5748–62. https://doi.org/10.1523/jneurosci.2875-12.2016.
81. Shen H-W, Scofield MD, Boger H, Hensley M, Kalivas PW. Synaptic glutamate spillover due to impaired glutamate uptake mediates heroin relapse. J Neurosci. 2014;34(16):5649–57. https://doi.org/10.1523/jneurosci.4564-13.2014.
82. Xu NJ, Bao L, Fan HP, Bao GB, Pu L, Lu YJ, et al. Morphine withdrawal increases glutamate uptake and surface expression of glutamate transporter GLT1 at hippocampal synapses. J Neurosci Off J Soc Neurosci. 2003;23(11):4775–844.
83. Ozawa T, Nakagawa T, Sekiya Y, Minami M, Satoh M. Effect of gene transfer of GLT-1, a glutamate transporter, into the locus coeruleus by recombinant adenoviruses on morphine physical dependence in rats. Eur J Neurosci. 2004;19(1):221–6. https://doi.org/10.1111/j.1460-9568.2004.03101.x.
84. Gao JT, Jordan CJ, Bi GH, He Y, Yang HJ, Gardner EL, et al. Deletion of the type 2 metabotropic glutamate receptor increases heroin abuse vulnerability in transgenic rats. Neuropsychopharmacology. 2018;43(13):2615–26. https://doi.org/10.1038/s41386-018-0231-5.
85. Zhu H, Lai M, Chen W, Mei D, Zhang F, Liu H, et al. N-acetylaspartylglutamate inhibits heroin self-administration and heroin-seeking behaviors induced by cue or priming in rats. Neuroscience bulletin. 2017;33(4):396–404. https://doi.org/10.1007/s12264-017-0140-3.
86. Bossert JM, Liu SY, Lu L, Shaham Y. A role of ventral tegmental area glutamate in contextual cue-induced relapse to heroin seeking. J Neurosci. 2004;24(47):10726–30. https://doi.org/10.1523/jneurosci.3207-04.2004.
87. Brown RM, Stagnitti MR, Duncan JR, Lawrence AJ. The mGlu5 receptor antagonist MTEP attenuates opiate self-administration and cue-induced opiate-seeking behaviour in mice. Drug Alcohol Depend. 2012;123(1–3):264–8. https://doi.org/10.1016/j.drugalcdep.2011.11.002.
88. Lou ZZ, Chen LH, Liu HF, Ruan LM, Zhou WH. Blockade of mGluR5 in the nucleus accumbens shell but not core attenuates heroin seeking behavior in rats. Acta Pharmacol Sin. 2014;35(12):1485–92. https://doi.org/10.1038/aps.2014.93.
89. van der Kam EL, de Vry J, Tzschentke TM. Effect of 2-methyl-6-(phenylethynyl) pyridine on intravenous self-administration of ketamine and heroin in the rat. Behav Pharmacol. 2007;18(8):717–24. https://doi.org/10.1097/FBP.0b013e3282f18d58.
90. Palucha-Poniewiera A, Novak K, Pilc A. Group III mGlu receptor agonist, ACPT-I, attenuates morphine-withdrawal symptoms after peripheral administration in mice. Prog

Neuropsychopharmacol Biol Psychiatry. 2009;33(8):1454–7. https://doi.org/10.1016/j.pnpbp.2009.07.029.
91. Kolik LG, Konstantinopolsky MA. Comparative assessment of the effectiveness of noncompetitive NMDA receptor antagonists amantadine and hemantane in morphine withdrawal syndrome model. Bull Exp Biol Med. 2019;166(6):739–43. https://doi.org/10.1007/s10517-019-04430-2.
92. Ma YY, Yu P, Guo CY, Cui CL. Effects of ifenprodil on morphine-induced conditioned place preference and spatial learning and memory in rats. Neurochem Res. 2011;36(3):383–91. https://doi.org/10.1007/s11064-010-0342-9.
93. Xi ZX, Stein EA. Blockade of ionotropic glutamatergic transmission in the ventral tegmental area reduces heroin reinforcement in rat. Psychopharmacology. 2002;164(2):144–50. https://doi.org/10.1007/s00213-002-1190-3.
94. Douglas JR-W, Peter WK. Glutamate transporter GLT-1 as a therapeutic target for substance use disorders. CNS & neurological disorders. Drug Targets. 2015;14(6):745–56. https://doi.org/10.2174/1871527314666150529144655.
95. Rawls SM, Baron DA, Kim J. Beta-Lactam antibiotic inhibits development of morphine physical dependence in rats. Behav Pharmacol. 2010;21(2):161–4. https://doi.org/10.1097/FBP.0b013e328337be10.
96. Rawls SM, Zielinski M, Patel H, Sacavage S, Baron DA, Patel D. Beta-lactam antibiotic reduces morphine analgesic tolerance in rats through GLT-1 transporter activation. Drug Alcohol Depend. 2010;107(2–3):261–3. https://doi.org/10.1016/j.drugalcdep.2009.10.010.
97. McClure EA, Gipson CD, Malcolm RJ, Kalivas PW, Gray KM. Potential role of *N*-acetylcysteine in the management of substance use disorders. CNS Drugs. 2014;28(2):95–106. https://doi.org/10.1007/s40263-014-0142-x.
98. Bisaga A, Comer SD, Ward AS, Popik P, Kleber HD, Fischman MW. The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. Psychopharmacology. 2001;157(1):1–10. https://doi.org/10.1007/s002130100739.
99. Comer SD, Sullivan MA. Memantine produces modest reductions in heroin-induced subjective responses in human research volunteers. Psychopharmacology. 2007;193(2):235–45. https://doi.org/10.1007/s00213-007-0775-2.
100. Akerele E, Bisaga A, Sullivan MA, Garawi F, Comer SD, Thomas AA, et al. Dextromethorphan and quinidine combination for heroin detoxification. Am J Addict. 2008;17(3):176–80. https://doi.org/10.1080/10550490802019543.
101. Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience. 1997;77(2):299–318. https://doi.org/10.1016/s0306-4522(96)00428-9.
102. Parsons LH, Hurd YL. Endocannabinoid signalling in reward and addiction. Nat Rev Neurosci. 2015;16:579. https://doi.org/10.1038/nrn4004.
103. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci. 2018. https://doi.org/10.3390/ijms19030833.
104. Wenzel JM, Cheer JF. Endocannabinoid regulation of reward and reinforcement through interaction with dopamine and endogenous opioid signaling. Neuropsychopharmacology. 2018;43(1):103–15. https://doi.org/10.1038/npp.2017.126.
105. Fattore L, Deiana S, Spano SM, Cossu G, Fadda P, Scherma M, et al. Endocannabinoid system and opioid addiction: behavioural aspects. Pharmacol Biochem Behav. 2005;81(2):343–59. https://doi.org/10.1016/j.pbb.2005.01.031.
106. Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science. 1999;283(5400):401–4. https://doi.org/10.1126/science.283.5400.401.
107. Caille S, Parsons LH. Cannabinoid modulation of opiate reinforcement through the ventral striatopallidal pathway. Neuropsychopharmacology. 2006;31(4):804–13. https://doi.org/10.1038/sj.npp.1300848.
108. Alvarez-Jaimes L, Polis I, Parsons LH. Attenuation of cue-induced heroin-seeking behavior by cannabinoid CB1 antagonist infusions into the nucleus accumbens core and prefrontal cortex, but not basolateral amygdala. Neuropsychopharmacology. 2008;33(10):2483–93. https://doi.org/10.1038/sj.npp.1301630.
109. He XH, Jordan CJ, Vemuri K, Bi GH, Zhan J, Gardner EL, et al. Cannabinoid CB1 receptor neutral antagonist AM4113 inhibits heroin self-administration without depressive side effects in rats. Acta Pharmacol Sin. 2019;40(3):365–73. https://doi.org/10.1038/s41401-018-0059-x.
110. De Vries TJ, de Vries W, Janssen MC, Schoffelmeer AN. Suppression of conditioned nicotine and sucrose seeking by the cannabinoid-1 receptor antagonist SR141716A. Behav Brain Res. 2005;161(1):164–8. https://doi.org/10.1016/j.bbr.2005.02.021.
111. Bhargava HN. Effect of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice. Psychopharmacology. 1976;49(3):267–70. https://doi.org/10.1007/bf00426828.
112. Lichtman AH, Sheikh SM, Loh HH, Martin BR. Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice. J Pharmacol Exp Ther. 2001;298(3):1007–144.
113. Nguyen JD, Grant Y, Creehan KM, Hwang CS, Vandewater SA, Janda KD, et al. Δ(9)-tetrahydrocannabinol attenuates oxycodone self-administration under extended access conditions. Neuropharmacology. 2019;151:127–35. https://doi.org/10.1016/j.neuropharm.2019.04.010.
114. Maguire DR, France CP. Effects of daily delta-9-tetrahydrocannabinol treatment on heroin self-administration in rhesus monkeys. Behav Pharmacol. 2016;27(2–3 Spec Issue):249–57. https://doi.org/10.1097/fbp.0000000000000192.
115. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci. 2009;29(47):14764–9. https://doi.org/10.1523/jneurosci.4291-09.2009.
116. Sloan ME, Gowin JL, Ramchandani VA, Hurd YL, Le Foll B. The endocannabinoid system as a target for addiction treatment: trials and tribulations. Neuropharmacology. 2017;124:73–83. https://doi.org/10.1016/j.neuropharm.2017.05.031.
117. Navarro M, Carrera MRA, del Arco I, Trigo JM, Koob GF, de Fonseca FR. Cannabinoid receptor antagonist reduces heroin self-administration only in dependent rats. Eur J Pharmacol. 2004;501(1):235–7. https://doi.org/10.1016/j.ejphar.2004.08.022.
118. Bisaga A, Sullivan MA, Glass A, Mishlen K, Pavlicova M, Haney M, et al. The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. Drug Alcohol Depend. 2015;154:38–45. https://doi.org/10.1016/j.drugalcdep.2015.05.013.
119. Jicha CJ, Lofwall MR, Nuzzo PA, Babalonis S, Elayi SC, Walsh SL. Safety of oral dronabinol during opioid withdrawal in humans. Drug Alcohol Depend. 2015;157:179–83. https://doi.org/10.1016/j.drugalcdep.2015.09.031.
120. Lofwall MR, Babalonis S, Nuzzo PA, Elayi SC, Walsh SL. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. Drug Alcohol Depend. 2016;164:143–50. https://doi.org/10.1016/j.drugalcdep.2016.05.002.
121. Nguyen T, Thomas BF, Zhang Y. Overcoming the psychiatric side effects of the cannabinoid CB1 receptor antagonists: current

approaches for therapeutics development. Curr Top Med Chem. 2019;19(16):1418–35. https://doi.org/10.2174/1568026619666190708164841.
122. Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (Orexin) project to multiple neuronal systems. J Neurosci. 1998;18(23):9996–10015. https://doi.org/10.1523/jneurosci.18-23-09996.1998.
123. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998;92(4):573–85. https://doi.org/10.1016/s0092-8674(00)80949-6.
124. DiLeone RJ, Georgescu D, Nestler EJ. Lateral hypothalamic neuropeptides in reward and drug addiction. Life Sci. 2003;73(6):759–68. https://doi.org/10.1016/S0024-3205(03)00408-9.
125. Ho CY, Berridge KC. An orexin hotspot in ventral pallidum amplifies hedonic 'liking' for sweetness. Neuropsychopharmacology. 2013;38(9):1655–64. https://doi.org/10.1038/npp.2013.62.
126. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet. 2000;355(9197):39–40. https://doi.org/10.1016/s0140-6736(99)05582-8.
127. Chiou LC, Lee HJ, Ho YC, Chen SP, Liao YY, Ma CH, et al. Orexins/hypocretins: pain regulation and cellular actions. Curr Pharm Des. 2010;16(28):3089–100. https://doi.org/10.2174/138161210793292483.
128. Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature. 2005;437(7058):556–9. https://doi.org/10.1038/nature04071.
129. Fadel J, Deutch AY. Anatomical substrates of orexin–dopamine interactions: lateral hypothalamic projections to the ventral tegmental area. Neuroscience. 2002;111(2):379–87. https://doi.org/10.1016/S0306-4522(02)00017-9.
130. Georgescu D, Zachariou V, Barrot M, Mieda M, Willie JT, Eisch AJ, et al. Involvement of the lateral hypothalamic peptide orexin in morphine dependence and withdrawal. J Neurosci Off J Soc Neurosci. 2003;23(8):3106–11.
131. James MH, Mahler SV, Moorman DE, Aston-Jones G. A decade of orexin/hypocretin and addiction: where are we now? Curr Top Behav Neurosci. 2017;33:247–81. https://doi.org/10.1007/7854_2016_57.
132. Harris GC, Wimmer M, Randall-Thompson JF, Aston-Jones G. Lateral hypothalamic orexin neurons are critically involved in learning to associate an environment with morphine reward. Behav Brain Res. 2007;183(1):43–51. https://doi.org/10.1016/j.bbr.2007.05.025.
133. Ghaemi-Jandabi M, Azizi H, Ahmadi-Soleimani SM, Semnanian S. Intracoerulear microinjection of orexin-A induces morphine withdrawal-like signs in rats. Brain Res Bull. 2017;130:107–11. https://doi.org/10.1016/j.brainresbull.2017.01.010.
134. Hooshmand B, Azizi H, Javan M, Semnanian S. Intra-LC microinjection of orexin type-1 receptor antagonist SB-334867 attenuates the expression of glutamate-induced opiate withdrawal like signs during the active phase in rats. Neurosci Lett. 2017;636:276–81. https://doi.org/10.1016/j.neulet.2016.10.051.
135. Davoudi M, Azizi H, Mirnajafi-Zadeh J, Semnanian S. Decrease of inhibitory synaptic currents of locus coeruleus neurons via orexin type 1 receptors in the context of naloxone-induced morphine withdrawal. J Physiol Sci JPS. 2019;69(2):281–93. https://doi.org/10.1007/s12576-018-0645-1.
136. Li Y, Wang H, Qi K, Chen X, Li S, Sui N, et al. Orexins in the midline thalamus are involved in the expression of conditioned place aversion to morphine withdrawal. Physiol Behav. 2011;102(1):42–50. https://doi.org/10.1016/j.physbeh.2010.10.006.
137. Sharf R, Sarhan M, DiLeone RJ. Orexin mediates the expression of precipitated morphine withdrawal and concurrent activation of the nucleus accumbens shell. Biol Psychiatr. 2008;64(3):175–83. https://doi.org/10.1016/j.biopsych.2008.03.006.
138. Sahafzadeh M, Karimi-Haghighi S, Mousavi Z, Haghparast A. Role of the orexin receptors within the nucleus accumbens in the drug priming-induced reinstatement of morphine seeking in the food deprived rats. Brain Res Bull. 2018;137:217–24. https://doi.org/10.1016/j.brainresbull.2017.12.008.
139. Farahimanesh S, Zarrabian S, Haghparast A. Role of orexin receptors in the ventral tegmental area on acquisition and expression of morphine-induced conditioned place preference in the rats. Neuropeptides. 2017;66:45–51. https://doi.org/10.1016/j.npep.2017.08.003.
140. Alizamini MM, Kavianpour M, Karimi-Haghighi S, Fatahi Z, Haghparast A. Intra-hippocampal administration of orexin receptor antagonists dose-dependently attenuates reinstatement of morphine seeking behavior in extinguished rats. Peptides. 2018;110:40–6. https://doi.org/10.1016/j.peptides.2018.10.011.
141. Edalat P, Kavianpour M, Zarrabian S, Haghparast A. Role of orexin-1 and orexin-2 receptors in the CA1 region of hippocampus in the forced swim stress- and food deprivation-induced reinstatement of morphine seeking behaviors in rats. Brain Res Bull. 2018;142:25–322. https://doi.org/10.1016/j.brainresbull.2018.06.016.
142. Schmeichel BE, Barbier E, Misra KK, Contet C, Schlosburg JE, Grigoriadis D, et al. Hypocretin receptor 2 antagonism dose-dependently reduces escalated heroin self-administration in rats. Neuropsychopharmacology. 2015;40(5):1123–9. https://doi.org/10.1038/npp.2014.293.
143. Azizi H, Mirnajafi-Zadeh J, Rohampour K, Semnanian S. Antagonism of orexin type 1 receptors in the locus coeruleus attenuates signs of naloxone-precipitated morphine withdrawal in rats. Neurosci Lett. 2010;482(3):255–9. https://doi.org/10.1016/j.neulet.2010.07.050.
144. Laorden ML, Ferenczi S, Pinter-Kubler B, Gonzalez-Martin LL, Lasheras MC, Kovacs KJ, et al. Hypothalamic orexin–a neurons are involved in the response of the brain stress system to morphine withdrawal. PLoS ONE. 2012;7(5):e36871. https://doi.org/10.1371/journal.pone.0036871.
145. Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G. Role of orexin/hypocretin in reward-seeking and addiction: Implications for obesity. Physiol Behav. 2010;100(5):419–28. https://doi.org/10.1016/j.physbeh.2010.03.009.
146. Campbell EJ, Marchant NJ, Lawrence AJ. A sleeping giant: Suvorexant for the treatment of alcohol use disorder? Brain Res. 2018. https://doi.org/10.1016/j.brainres.2018.08.005.
147. Zarrabian S, Riahi E, Karimi S, Razavi Y, Haghparast A. The potential role of the orexin reward system in future treatments for opioid drug abuse. Brain Res. 2018. https://doi.org/10.1016/j.brainres.2018.11.023.
148. Simmons SJ, Gentile TA. Cocaine abuse and midbrain circuits: Functional anatomy of hypocretin/orexin transmission and therapeutic prospect. Brain Res. 2019. https://doi.org/10.1016/j.brainres.2019.02.026.
149. James MH, Fragale JE, Aurora RN, Cooperman NA, Langleben DD, Aston-Jones G. Repurposing the dual orexin receptor antagonist suvorexant for the treatment of opioid use disorder: why sleep on this any longer? Neuropsychopharmacology. 2020. https://doi.org/10.1038/s41386-020-0619-x.
150. Born S, Gauvin DV, Mukherjee S, Briscoe R. Preclinical assessment of the abuse potential of the orexin receptor antagonist,

suvorexant. Regul Toxicol Pharmacol RTP. 2017;86:181–92. https://doi.org/10.1016/j.yrtph.2017.03.006.
151. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu Rev Med. 2009;60:355–66. https://doi.org/10.1146/annurev.med.60.042307.110802.
152. Müller CP, Homberg JR. The role of serotonin in drug use and addiction. Behav Brain Res. 2015;277:146–92. https://doi.org/10.1016/j.bbr.2014.04.007.
153. Dunn KE, Huhn AS, Bergeria CL, Gipson CD, Weerts EM. Non-opioid neurotransmitter systems that contribute to the opioid withdrawal syndrome: a review of preclinical and human evidence. J Pharmacol Exp Ther. 2019;371(2):422–52. https://doi.org/10.1124/jpet.119.258004.
154. Fadda P, Scherma M, Fresu A, Collu M, Fratta W. Dopamine and serotonin release in dorsal striatum and nucleus accumbens is differentially modulated by morphine in DBA/2J and C57BL/6J mice. Synapse (New York, NY). 2005;56(1):29–38. https://doi.org/10.1002/syn.20122.
155. Imperato A, Angelucci L. 5-HT3 receptors control dopamine release in the nucleus accumbens of freely moving rats. Neurosci Lett. 1989;101(2):214–7. https://doi.org/10.1016/0304-3940(89)90533-8.
156. Bland ST, Twining C, Schmid MJ, Der-Avakian A, Watkins LR, Maier SF. Stress potentiation of morphine-induced dopamine efflux in the nucleus accumbens shell is dependent upon stressor uncontrollability and is mediated by the dorsal raphe nucleus. Neuroscience. 2004;126(3):705–15. https://doi.org/10.1016/j.neuroscience.2004.04.025.
157. Tao R, Auerbach SB. Increased extracellular serotonin in rat brain after systemic or intraraphe administration of morphine. J Neurochem. 1994;63(2):517–24. https://doi.org/10.1046/j.1471-4159.1994.63020517.x.
158. Goeldner C, Lutz PE, Darcq E, Halter T, Clesse D, Ouagazzal AM, et al. Impaired emotional-like behavior and serotonergic function during protracted abstinence from chronic morphine. Biol Psychiatry. 2011;69(3):236–44. https://doi.org/10.1016/j.biopsych.2010.08.021.
159. Higgins GA, Nguyen P, Joharchi N, Sellers EM. Effects of 5-HT3 receptor antagonists on behavioural measures of naloxone-precipitated opioid withdrawal. Psychopharmacology. 1991;105(3):322–8. https://doi.org/10.1007/bf02244425.
160. Wu X, Pang G, Zhang YM, Li G, Xu S, Dong L, et al. Activation of serotonin 5-HT(2C) receptor suppresses behavioral sensitization and naloxone-precipitated withdrawal symptoms in heroin-treated mice. Neurosci Lett. 2015;607:23–8. https://doi.org/10.1016/j.neulet.2015.09.013.
161. Zhang G, Wu X, Zhang YM, Liu H, Jiang Q, Pang G, et al. Activation of serotonin 5-HT(2C) receptor suppresses behavioral sensitization and naloxone-precipitated withdrawal symptoms in morphine-dependent mice. Neuropharmacology. 2016;101:246–54. https://doi.org/10.1016/j.neuropharm.2015.09.031.
162. Nomikos GG, Spyraki C. Effects of ritanserin on the rewarding properties of d-amphetamine, morphine and diazepam revealed by conditioned place preference in rats. Pharmacol Biochem Behav. 1988;30(4):853–8. https://doi.org/10.1016/0091-3057(88)90110-4.
163. Carboni E, Acquas E, Leone P, Di Chiara G. 5HT3 receptor antagonists block morphine- and nicotine-but not amphetamine-induced reward. Psychopharmacology. 1989;97(2):175–8. https://doi.org/10.1007/bf00442245.
164. Acquas E, Carboni E, Leone P, Di Chiara G. 5-HT3 receptors antagonists block morphine- and nicotine-but not amphetamine-induced place-preference conditioning. Pharmacol Res Commun. 1988;20(12):1113–4. https://doi.org/10.1016/s0031-6989(88)80752-5.
165. Carboni E, Acquas E, Leone P, Perezzani L, Di Chiara G. 5-HT3 receptor antagonists block morphine- and nicotine-induced place-preference conditioning. Eur J Pharmacol. 1988;151(1):159–60. https://doi.org/10.1016/0014-2999(88)90710-8.
166. Higgins GA, Joharchi N, Nguyen P, Sellers EM. Effect of the 5-HT3 receptor antagonists, MDL72222 and ondansetron on morphine place conditioning. Psychopharmacology. 1992;106(3):315–20. https://doi.org/10.1007/bf02245411.
167. Hui SC, Sevilla EL, Ogle CW. 5-HT3 antagonists reduce morphine self-administration in rats. Br J Pharmacol. 1993;110(4):1341–6. https://doi.org/10.1111/j.1476-5381.1993.tb13966.x.
168. Higgins GA, Wang Y, Corrigall WA, Sellers EM. Influence of 5-HT3 receptor antagonists and the indirect 5-HT agonist, dexfenfluramine, on heroin self-administration in rats. Psychopharmacology. 1994;114(4):611–9. https://doi.org/10.1007/bf02244992.
169. Higgins GA, Wang Y, Sellers EM. Preliminary findings with the indirect 5-HT agonist dexfenfluramine on heroin discrimination and self-administration in rats. Pharmacol Biochem Behav. 1993;45(4):963–6. https://doi.org/10.1016/0091-3057(93)90148-m.
170. Neelakantan H, Holliday ED, Fox RG, Stutz SJ, Comer SD, Haney M, et al. Lorcaserin suppresses oxycodone self-administration and relapse vulnerability in rats. ACS Chem Neurosci. 2017;8(5):1065–73. https://doi.org/10.1021/acschemneuro.6b00413.
171. Gerak LR, Collins GT, Maguire DR, France CP. Effects of lorcaserin on reinstatement of responding previously maintained by cocaine or remifentanil in rhesus monkeys. Exp Clin Psychopharmacol. 2019;27(1):78–86. https://doi.org/10.1037/pha0000234.
172. Farren CK, O'Malley S. A pilot double blind placebo controlled trial of sertraline with naltrexone in the treatment of opiate dependence. Am J Addict. 2002;11(3):228–34. https://doi.org/10.1080/10550490290088009.
173. Chu LF, Sun J, Clemenson A, Erlendson MJ, Rico T, Cornell E, et al. Ondansetron does not reduce withdrawal in patients with physical dependence on chronic opioid therapy. J Addict Med. 2017;11(5):342–9. https://doi.org/10.1097/adm.0000000000000321.
174. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2009;35:217. https://doi.org/10.1038/npp.2009.110.
175. Nora D, Volkow MD. Personalizing the treatment of substance use disorders. Am J Psychiatry. 2020;177(2):113–6. https://doi.org/10.1176/appi.ajp.2019.19121284.
176. Stewart JL, May AC, Aupperle RL, Bodurka J. Forging neuroimaging targets for recovery in opioid use disorder. Front Psychiatry. 2019. https://doi.org/10.3389/fpsyt.2019.00117.