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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 United States and worldwide. The relapsing and recurring aspect of OUD, driven by lasting neurobiological adaptations at different reward centers 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 behaviors 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 maximize efficacy and prevent relapse.

1. Introduction

Opioid addiction can be defined as a chronically relapsing neuropsychiatric disorder characterized 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 characterized by the chronic and sustained manifestation of several symptoms within a 12-months 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 characterized by cycling periods of exacerbated use and abstinence over years, separated by periods of treatment and remission [3], during which the

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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 [5, 4], drugs that are generally prescribed to control pain, diminish cough, or relieve diarrhea [6]. Globally, the rate of extra-medical opioid use has been constantly increasing over the last three 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 to develop 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 to 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 opioid-use disorder 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, opioid-related overdose deaths accounted for two thirds of overall of drug-induced fatalities in the US in 2017, at least half of which are attributed to synthetic opioids such as fentanyl [15, 14].

Three medications, methadone, buprenorphine, and naltrexone, are currently approved by the U.S. 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 programs [6, 16]. Despite the reasonable margin of success of such treatment programs in controlling the negative affect that results from abrupt discontinuation of illicit opioid use, leading to decreased opioid-associated mortality and criminal behavior [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 at controlling the withdrawal effects to facilitate 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 discussed, 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 MOUDs.

In this review, we will discuss the currently 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:

Overview.—Methadone is a synthetic, long lasting MOR full agonist, used to treat OUD and moderate to severe pain [17, 24, 6]. 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 hours after administration [25, 16]. 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 [22, 16], and remains the most widely employed drug in the management of OUD [16].

Methadone Maintenance.—Methadone maintenance, along with buprenorphine (see below), is widely considered as the gold standard for the pharmacological management of opioid-use disorder [6, 27, 22, 16]. In these programs, opioid-dependent patients, who are reluctant or unable to remain abstinent, receive a daily dose of methadone through dedicated methadone treatment centers [6, 16]. After stabilization, patients require 80–120 mg

maintenance dose [24], administered orally, which helps to blunt the reinforcing effects of needle injections, which 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 doesn't lead to the development of tolerance. As such, once a stabilizing 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 MOR are occupied with methadone, suggesting that a significant number of MOR 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].

Limitations and Challenges.—One of the main limitations of methadone-based programs is the high attrition rates, where more than 40% of patients drop out within the first year [29, 19]. 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 programs are further limited by the need for daily commitment from patients and specialized clinicians, as well as the scarcity of opioid-treatment centers [24], resulting in significant logistic obstacles for the patients to reach such centers, specially 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 enrollment [34]. Importantly, virtually all patients in such programs 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 [36, 27]. 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 [37, 22]. 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

Overview.—In contrast to the full agonist methadone, buprenorphine is a partial MOR agonist [38, 24, 39, 6] and a kappa-opioid receptor 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 centers, as well as specialized/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 programs. It is given as a sublingual tablet in conjugation 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].

Kappa-opioid receptor antagonism.—As opposed to the euphoric effects produced by activating MOR, Kappa-opioid receptors (KOR) are endogenously activated by dynorphin, producing a dysphoric effect in humans and animal models [45, 46]. It has been hypothesized 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 result in a compensatory increase of endogenous KOR activation, mediated by sustained release of dynorphins. The over-stimulated k-opioid receptor results in the generalized dysphoria associated with opioid withdrawal, precipitated by cessation of drug intake [47, 48]. As such, KOR antagonists have been hypothesized 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].

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 [36, 27]. 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 dose, 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 programs [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 occurs 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 to 24 hours after last administration of illicit opioids [6].

Limitations and Challenges.—Similarly to methadone treatment programs, 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 [24, 18, 58]. Although such incidents are more common when patients receive methadone treatment, fatalities have been reported following buprenorphine overdose, notably during the induction period [42, 18, 36], 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 [59, 38, 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

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 [18, 16]. 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 programs [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 programs, or risk missing multiple medication doses if registered in an opioid-maintenance program [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 doesn't carry any abuse potential, it has been preferred by law enforcement units, over other controlled medications such as methadone and buprenorphine [61].

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 [24, 6, 16]. 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 [18, 16]: 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 [62, 6, 27]. Furthermore, patients on a naltrexone-based regimen show poor adherence to daily pill use; a limitation that can be partially circumvented by behavioral 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 traditionally 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]. Alpha-adrenergic agonists, such as lofexidine [67], clonidine or tizanidine [68], have been shown to be 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 [24, 68, 6]. 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 behavioral 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 behaviors such as contingent acquisition of drugs, escalation of intake,

extinction of previously conditioned behaviors, responses to punished rewards, decision making, extinction responding and reinstatement of drug seeking.

3.1. Glutamatergic System

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 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 behavior, on the acquisition and expression of opioid-conditioned behaviors, including relapse [75]. In fact, glutamate release from prelimbic cortical projection is necessary for the cue-induced reinstatement of heroin-seeking behavior 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 behaviors.

The previously mentioned glutamatergic release at the level of the synapse is accentuated by long-lasting downregulation of Glutamate Transporter 1 (GLT1), a glial protein responsible for maintaining glutamate homeostasis [81]. Cue-induced extrasynaptic release of glutamate (glutamate spillover) due to GLT1-downregulation results in activation of extrasynaptic 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 suggest that glutamatergic signaling 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.

Preclinical Evidence.—Glutamate signaling 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 GLT1 expression. Several studies have investigated the role of modulating metabotropic glutamatergic receptors on opioid-associated behaviors. Presynaptic mGluR2/3 agonists (such as N-

acetylaspartylglutamate 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 behavior 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 behavioral 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 [71, 69], and restoring GLT-1 function to prevent glutamate spillover has been hypothesized 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- κ B) signaling, has been shown to block morphine-induced withdrawal effects [95] and inhibit the development of tolerance [96] despite chronic non-contingent morphine injections.

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 [97, 94], 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

Overview.—The endocannabinoid signaling system has been characterized 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 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 [105, 102] 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 behavior [110], suggesting a broader role of this receptor on reward-conditioned behaviors.

Preclinical Evidence.—The use of CB1 receptor agonists has been long hypothesized to decrease the severity of withdrawal symptoms in rodent models of morphine and heroin dependence [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 vaporized 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 behavior 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, opioid receptor antagonist, that would control for prime-induced reinstatement, and thereby simultaneously protect against relapsed 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.

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

Rationale.—Orexins A and B (or Hypocretin1/2) are peptide neurotransmitters released by a limited and specialized 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 behavior [123, 125], narcolepsy [126], pain regulation [127], and reward seeking [128]. Anterograde and retrograde labeling 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 behavior, 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.

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 behavior following extinction. Furthermore, systemic administration of OxR2 antagonists reduces escalated levels of heroin intake in long-access (12 hours), but not short-access (2 hours), 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 behaviors in rodents, and indicate that it may be a neurotransmitter system that can be modulated as an adjunct treatment of opioid addiction.

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 behaviors [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 US due to data showing low level of abuse liability in preclinical models [150], which may limit its use in OUD patients.

3.4. Serotonin System

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 behavioral 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 behavioral 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 [155, 156, 154], 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 go back 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].

Preclinical Evidence.—The 5-HT₃ receptor antagonists [159] and 5-HT_{2C} 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. Pretreatment 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 minutes 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 [169, 168]. Similarly, lorcaserin, a 5-HT_{2C} 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 behavior in rats [170], and heroin-induced reinstatement of heroin seeking behavior in rhesus monkeys [171], suggesting an important role of 5-HT_{2C} receptors in relapse vulnerability.

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 behaviors (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 minimizing 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 different stages that contain different, even competing behavioral symptoms, the different genetic and epigenetic backgrounds of the patients, and the role of societal, cultural, and religious backgrounds that can confound 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 analyzing individual baseline state circuit strength using functional magnetic resonance imaging shows 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 heterogeneous 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.

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 behavior 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 on 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 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 optimize outcomes.

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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.

Table 1.

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

Drug	Target	Endpoint	Result	Reference
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 (>20mg), 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 Programs	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]