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Special Section on The Opioid Crisis

Non-Opioid Neurotransmitter Systems that Contribute to the Opioid Withdrawal Syndrome: A Review of Preclinical and Human Evidence

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ABSTRACT

Opioid misuse and abuse is a major international public health issue. Opioid use disorder (OUD) is largely maintained by a desire to suppress aversive opioid withdrawal symptoms. Opioid withdrawal in patients seeking abstinence from illicit or prescribed opioids is often managed by provision of a μ-opioid agonist/partial agonist in combination with concomitant medications. Concomitant medications are administered based on their ability to treat specific symptoms rather than a mechanistic understanding of the opioid withdrawal syndrome; however, their use has not been statistically associated with improved treatment outcomes. Understanding the central and/or peripheral mechanisms that underlie individual withdrawal symptom expression in humans will help promote medication development for opioid withdrawal management. To support focused examination of mechanistically supported concomitant medications, this review summarizes evidence from preclinical ($N = 68$) and human ($N = 30$) studies that administered drugs acting on the dopamine, serotonin, cannabinoid, orexin/hypocretin, and glutamate systems and reported outcomes related to opioid withdrawal. These studies provide evidence that each of these systems contribute to opioid withdrawal severity. The Food and Drug Administration has approved medications acting on these respective systems for other indications and research in this area could support the repurposing of these medications to enhance opioid withdrawal treatment. These data support a focused examination of mechanistically informed concomitant medications to help reduce opioid withdrawal severity and enhance the continuum of care available for persons with OUD.

Introduction

The increased prevalence of opioid use disorder (OUD) and opioid-related morbidity and mortality is a national and international public health crisis. Continuous opioid exposure results in physiologic dependence and a prominent and aversive opioid withdrawal syndrome upon opioid discontinuation. As shown in Fig. 1, opioid withdrawal manifests as an acute syndrome that begins within hours of the final dose and can last for up to 14 days, and is followed by a protracted syndrome that can persist for several additional weeks (Martin and Jasinski, 1969; Jasinski, 1981). Opioid withdrawal symptoms vary in severity and expression across individuals and continued opioid use and opioid relapse in persons with OUD are driven, in part, by a goal of avoiding opioid withdrawal symptoms and associated cravings (Hutcheson et al., 2001; Negus and Banks, 2018). As a result, OUD pharmacotherapies frequently aim to suppress symptoms of acute opioid withdrawal, an approach first reported in 1949 (Powers, 1949) and validated in 1965 (Dole and Nyswander, 1965).

The current standard-of-care treatment of opioid withdrawal management is to administer methadone or buprenorphine, which act as full or partial agonists on the μ-opioid receptor, respectively (Gowing et al., 2016). Both medications suppress symptoms of withdrawal when administered chronically; however, symptoms reemerge when doses are tapered down, which occurs when patients are withdrawn from opioids they have been using illicitly or as prescribed to them for pain management (Farrell, 1994). Several concomitant medications are commonly administered to manage emergent symptoms of acute withdrawal (Hillhouse et al., 2010; Dunn et al., 2011; Schuckit, 2016). These include nonsteroidal anti-inflammatory

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ABBREVIATIONS: CB_1, cannabinoid type 1 receptor; DA, dopamine; FDA, Food and Drug Administration; 5-HT, serotonin; iGlu, ionotropic glutamate; mGlu, metabotropic glutamate; OUD, opioid use disorder; OX, orexin; THC, tetrahydrocannabinol.

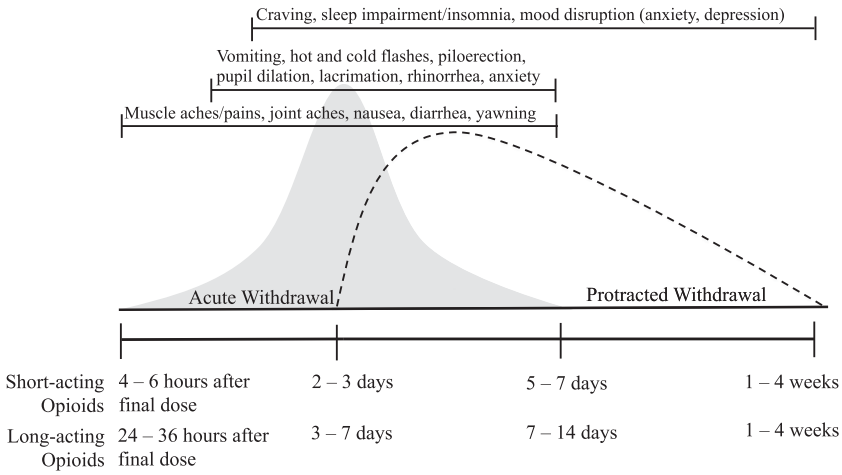

Fig. 1. Schematic of the human opioid withdrawal syndrome. The prototypical human opioid withdrawal curve is shown here for both the acute (gray) and protracted (dashed line) phases. Although the specific duration and magnitude of withdrawal varies across individuals, the acute withdrawal syndrome generally begins 4–6 (short acting) and 24–36 (long acting) hours after opioid discontinuation, peaks within 2 to 3 (short acting) and 3–7 (long acting) days, and ends within 5–7 (short acting) and 7–14 (long acting) days, as indicated by the vertical lines. Although specific symptoms emerge at different times for different individuals, an expected symptom progression is indicated in the brackets across the top of the figure; the ends of the brackets signify when the clusters of specific symptoms generally emerge and dissipate. Protracted withdrawal is hypothesized to extend for an additional 1–4 weeks following resolution of the acute withdrawal syndrome. Note: additional symptoms may exist that are not included here.

drugs for muscle aches and pains, promethazine for nausea/vomiting, loperamide for diarrhea, and klonipin or trazodone for sleep disturbance. The use of these medications is based on their perceived effectiveness for individual symptoms rather than a mechanistic understanding of the opioid withdrawal syndrome or empirical evidence of their efficacy in reducing opioid withdrawal severity. The only retrospective evaluation conducted on this topic reported no significant association between these medications and opioid withdrawal outcomes (Hillhouse et al., 2010).

The exceptions to this are two adrenergic agonists. The first is clonidine, which is prescribed off-label (Gold et al., 1978), and the second is lofexidine (Lucemyra), which was approved by the Food and Drug Administration (FDA) for opioid withdrawal in 2018 (Gorodetzky et al., 2017). Administration of clonidine and lofexidine is premised upon a mechanistic understanding that the adrenergic system modulates some opioid withdrawal symptoms through locus coeruleus–mediated noradrenergic hyperactivity (Gold et al., 1979; van Dongen, 1981). The majority of research examining adrenergic agonist withdrawal suppression has focused on clonidine, and there is strong evidence that clonidine reliably suppresses some symptoms of opioid withdrawal while concurrently increasing the severity of other symptoms (Gianutsos et al., 1976; Schulz and Herz, 1977; Bednarczyk and Vetulani, 1978). The net result is that clonidine produces mild-to-moderate opioid withdrawal suppression (Gowing et al., 2016), the degree to which varies across individuals (Dunn et al., 2018b).

Despite the fact that OUD treatment is largely organized around the provision of pharmacotherapy to manage opioid withdrawal, concomitant medications are not selected based on a mechanistic understanding of the central and/or peripheral systems underlying individual opioid withdrawal symptom expression in humans. This review summarizes preclinical animal and human evidence that the dopamine (DA), serotonin (5-HT), cannabinoid, orexin/hypocretin, and glutamate neurotransmitter systems directly contribute to the expression and/or severity of specific opioid withdrawal symptoms. These systems were selected for review because of the body of literature supporting their pivotal involvement in the opioid withdrawal syndrome and the fact that several FDA-approved or investigational medications that act on these systems exist and could be evaluated and ultimately repurposed for an opioid withdrawal indication. The expectation is not that these medications would be used in lieu of opioid agonists but that they would be administered in combination with opioid agonist therapy to replace the aforementioned symptomatic medications and improve opioid withdrawal management. The norepinephrine system is not discussed here because lofexidine has gained recent FDA approval and the GABA system was omitted because the majority of FDA-approved medications acting on that system have prominent abuse liability profiles that limit their adoption in OUD treatment settings. The overarching goal of this review is to provide a resource to support the prospective examination of candidate concomitant medications for opioid withdrawal symptom management.

Materials and Methods

This review reports the results of studies that described opioid withdrawal symptom incidence and/or severity following exposure to agents acting on the aforementioned systems. As shown in Table 1, there is generally good concordance for a number of opioid withdrawal symptom categories between animal and human models of opioid withdrawal, although the expression of symptoms within each category is often species specific. Withdrawal in rodents generally includes increased jumping, self-directed behaviors (increased grooming and penile licking), hyperactivity (locomotion, digging, and rears), vocalization, ptosis, wet dog shakes, teeth chattering, secretions (lacrimation, rhinorrhea, and salivation), respiration, and gastrointestinal motility (increased defecation and loose stools/diarrhea). Human withdrawal expression is comprised of several symptoms (as indicated in Fig. 1; Table 1) that vary across individuals with regard to incidence and severity; no demographic or drug use characteristics have been identified that reliably predict the severity of human opioid withdrawal symptoms. An exception to this is gender, for which there is substantial preclinical evidence to support causal associations between gonadal hormones and opioid effects (Huhn et al., 2018), and some limited human empirical evidence that gender may moderate withdrawal severity (Dunn et al., 2018b).

Reviewed papers were identified through PubMed searches inclusive of all years using the following search terms: opioid, opiate, withdrawal AND dopamine, serotonin, 5-HT, cannabinoid, cannabis, THC, orexin, hyopcretin, and glutamate (where THC denotes tetrahydrocannabinol). Eligible studies included outcome data about the opioid withdrawal syndrome and were conducted in rodents, nonhuman primates, or humans with opioid physical dependence and administered an agent that acted on one or more of the systems of interest. A total of 68 preclinical and 30 human studies were identified and reviewed. Preclinical studies examined withdrawal in animals with opioid physical dependence either by administering an opioid antagonist (in a precipitated withdrawal model) or through abrupt opioid discontinuation (in a spontaneous withdrawal model). Since only

TABLE 1
Withdrawal systems and symptoms conserved across species
Only symptoms for which there is correspondence across species are presented; additional symptoms exist that are species specific but are not included here.

Withdrawal System and Symptoms	Human	Rat	Mouse
Anhedonia			
Brain stimulation threshold		X	X
Conditioned aversion		X	X
Depression	X		
Anxiety/escape behaviors (rodents)			
Anxiety	X		
Burrowing		X	X
Digging		X	X
Jumping		X	X
Rearing		X	X
Changes in body temperature			
Hot and/or cold flashes	X		
Hypothermia		X	X
Piloerection (gooseflesh)	X	X	X
Teeth chattering		X	X
Gastrointestional			
Defecation		X	X
Diarrhea, Loose stool	X	X	X
Nausea	X		
Vomiting	X		
Hyperactivity, self-directed behaviors			
Chewing		X	X
Grooming		X	X
Licking		X	X
Locomotion	X	X	X
Penile licking		X	X
Restlessness	X		
Motivation to use			
Craving	X		
Progressive ratio breakpoint	X	X	X
Reinstatement		X	X
Pain, hyperalgesia			
Joint aches and pains	X		
Muscle aches and pains	X		
Reactive to touch		X	X
Ultrasonic vocalizations		X	X
Writhing		X	X
Ptosis		X	X
Secretions			
Lacrimation	X	X	X
Rhinorrhea	X	X	X
Salivation		X	X
Urination		X	X
Tremors/shaking			
Facial tremor		X	X
Forepaw tremors		X	X
Hand tremors	X		
Head shakes		X	X
Limb shakes		X	X
Wet dog shakes		X	X

a limited number of human empirical studies ($n = 16$) were available for this review, case reports ($n = 7$), retrospective chart reviews ($n = 3$), a prospective cohort study ($n = 1$), an online survey or quality-assurance surveys ($n = 2$), and a secondary outcome analysis ($n = 1$) were included to provide breadth of coverage. All of the results discussed subsequently refer to opioid withdrawal symptoms that were observed during the acute (vs. protracted) opioid withdrawal. Specific study details are provided in accompanying tables, which have been organized into preclinical tables for dopamine (Table 2), serotonin (Table 3), cannabinoids (Table 4), orexin (Table 5), glutamate (Table 6), and medications acting on multiple systems (Table 7), and human tables categorized as empirical (Table 8) and nonempirical (Table 9) reports.

Results

Dopamine System

Dopamine neurotransmission occurs via two families of G protein–coupled receptor families, the D_1-like receptors that include D_1 and D_5 receptor subtypes, and the D_2-like receptors that include D_2, D_3, and D_4 receptor subtypes. DA is frequently implicated in substance use disorders (for a review, see Volkow et al., 2017) and there is clear evidence of clinically meaningful DA and opioid interaction in humans. For instance, many methadone patients begin using cocaine during methadone maintenance (Leri et al., 2003) and methadone has been shown empirically to increase the reinforcing effects of cocaine (Preston et al., 1996). The following section reviews only preclinical research because no human studies met the inclusion criteria.

Preclinical Withdrawal. Preclinical behavioral evidence clearly implicates DA in the expression of opioid withdrawal, and drugs acting on this system often exert positive effects at one dose and negative effects at another dose. Drugs that increase DA, including the DA transport reuptake inhibitors amphetamine and cocaine and the DA precursor L-DOPA,

TABLE 2

Preclinical examinations of the dopamine system on the opioid withdrawal syndrome

Only results pertaining to effects of non-opioid drugs on opioid withdrawal symptoms are presented.

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
Ary and Lomax (1976)	Apomorphine (20 μg); Dopamine (10, 50, 100, and 200 μg), Pimozide (0.5 and 1 μg, i.p.). Administered to rostral hypothalamus and lateral ventricle unless indicated.	Rat	≥5	Precipitated, naloxone (1 mg/kg; i.p.) on day 3	Morphine (75 mg) subcutaneous implant	Body temperature	Rostral hypothalamus injections: apomorphine (D_2 agonist; 20 μg) increased the hypothermia produced by naloxone, pimozide (D_2 antagonist; 0.5 and 1 μg) and dopamine had no effect. Lateral ventricle injections: no effects on naloxone-induced hypothermia.
Cox et al. (1976)	Apomorphine (1.25 mg/kg) and pimozide (0.5 mg/kg) administered intraperitoneally; pimozide (0.5 μg) administered intracerebroventricularly.	Rat	NR	Precipitated, naloxone (1 mg/kg; i.p.) on day 3	Morphine (75 mg) subcutaneous implant	Body temperature, chewing, diarrhea, head shakes, facial tremor, grooming, licking, sneezing, teeth chatter, wet dog shakes, and writhing. Total withdrawal score	Apomorphine (D_2 agonist) (1.25 mg/kg, i.p.) decreased chewing, teeth chattering, wet dog shakes, and writhing. Pimozide (D_2 antagonist) (0.5 mg/kg, i.p.) reduced hypothermia and increased chewing, head shakes, and writhing. Intracerebroventricularly: pimozide (0.5 μg, i.p.) significantly blocked hypothermia.
el-Kadi and Sharif (1998)	Apomorphine (0.5, 1, 2.5, 5, 10, 20, and 30 mg/kg); L-DOPA (100 and 500 mg/kg); haloperidol (0.2 and 1.0 mg/kg); pimozide (2 and 5 mg/kg); domperidone (5 and 10 mg/kg); flupenthixol (0.05 and 0.1 mg/kg); sulpride (5 mg/kg). Administered intraperitoneally.	Mouse	8–10	Precipitated, naloxone (1 mg/kg, i.p.) on day 7	Escalating morphine doses up to 160 mg/kg, s.c., by day 6	Body temperature, body weight, burrows, jumping, and wet dog shakes	L-DOPA (dopamine precursor) (100 and 500 mg/kg) reduced jumping, burrows, body weight loss, hypothermia (100 and 500 mg/kg), and wet dog shakes (500 mg/kg). Apomorphine (D_2 agonist) increased burrows and jumping at low doses (2.5 and 5 mg/kg) and decreased them at high doses (10, 20, and 30 mg/kg). Apomorphine also decreased body weight loss (2.5, 5, and 10 mg/kg) and increased wet dog shakes (2.5, 5, 10, and 20 mg/kg) and hypothermia (all doses). Haloperidol (D_2 antagonist) reduced jumps (0.2 and 1 mg/kg), wet dog shakes (0.2 and 1 mg/kg), burrows (0.2 and 1 mg/kg), and body weight loss (1 mg/kg). Pimozide (D_2 antagonist) decreased jumps (2 and 5 mg/kg), and wet dog shakes, burrows, and body weight loss (5 mg/kg). Domperidone (D_2 antagonist) decreased jumping and hypothermia (10 mg/kg) but increased body weight loss (10 mg/kg). Flupenthixol (D_2 antagonist) decreased wet dog shakes and burrows (0.05 and 0.1 mg/kg), and jumping, body weight loss, and hypothermia (0.1 mg/kg). Sulpride (D_2 agonist) (5 mg/kg) increased all symptoms.
Herz et al. (1974)	d-Amphetamine (0.5, 1, 2, and 5 mg/kg); cocaine (5, 10, and 25 mg/kg); L-DOPA (100 mg/kg); apomorphine (1, 2.5, and 5 mg/kg); desipramine (2.5, 5, and 10 mg/kg). Administered intraperitoneally.	Rat	8–16	Precipitated, levallorphan (1 mg/kg, i.p.) on day 10	Morphine subcutaneous implant (dose NR), six pellets implanted over 10 days	Eye twitching, diarrhea, flying, jumping, lacrimation, ptosis, rhinorrhea, salivation, teeth chattering, wet dog shakes, and writhing	d-Amphetamine increased jumping (0.5 and 1, 2 mg/kg) and teeth chattering (1 mg/kg), and decreased wet dog shakes (0.5 and 1 mg/kg). All signs decreased at 2 and 5 mg/kg. Cocaine increased jumping (10 mg/kg) and decreased wet dog shakes (10 mg/kg). All signs decreased at 25 mg/kg. L-DOPA (dopamine precursor) decreased ptosis and diarrhea (100 mg/kg) but increased eye twitching (100 mg/kg).

(*continued*)

TABLE 2—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
							Apomorphine (D_2 agonist) decreased ptosis and increased eye twitching at 1 mg/kg, increased ptosis and decreased diarrhea at 2.5 mg/kg, and decreased ptosis and diarrhea but increased eye twitching at 5 mg/kg. Desipramine decreased ptosis and diarrhea but increased eye twitching at all doses, and increased jumping at 5, 10, and 20 mg/kg.

NR, not reported.

dose dependently increase several symptoms while simultaneously decreasing others (Herz et al., 1974; el-Kadi and Sharif, 1998). Numerous studies have reported that low doses of the D_2 agonist apomorphine exacerbates withdrawal, evidenced by increased jumping, wet dog shakes, burrows, and hyperthermia, whereas higher doses decrease jumping, burrowing, and other responses (Herz et al., 1974; Ary and Lomax, 1976; Cox et al., 1976; el-Kadi and Sharif, 1998). The D_2 receptor antagonists domperidone, fluenthixol, and pimozide also reduce several opioid withdrawal symptoms, whereas the D_2 receptor agonist sulpride increased the severity of all symptoms measured (Cox et al., 1976; el-Kadi and Sharif, 1998).

Serotonin System

Extracellular levels of serotonin are moderated by the membrane protein 5-HT transporter, and with the exception of the ionotropic 5-HT_3 receptor, 5-HT exerts effects through seven families of G protein–coupled receptors (5-$HT_{1–7}$) with $\geq$14 subtypes (for a review, see Berger et al., 2009). A large number of commercially available medications act on the 5-HT system and could be evaluated for OUD withdrawal management. For instance, tricyclic medications that inhibit 5-HT reuptake are recommended and widely used for pain management (Finnerup et al., 2015; Obata, 2017). Several 5-HT medications are also formally approved for mood disturbance and anxiety, two prominent opioid withdrawal symptoms that are present during both the acute and protracted withdrawal phases (Handelsman et al., 1987; Latowsky, 1996; Wesson and Ling, 2003). Intracerebroventricular injections of 5-HT to nondependent rats have also been observed to directly and dose dependently produce wet dog shakes (Drust et al., 1979), which is a prominent sign of opioid withdrawal in rodents.

Preclinical Withdrawal. Similar to DA, the 5-HT system can both increase and decrease the severity of withdrawal symptoms depending on the dose of drug administered; for instance, administration of the antidepressant fenfluramine, which promotes 5-HT release and inhibits 5-HT reuptake, decreased jumping (Cervo et al., 1981; Romandini et al., 1984) but not wet dog shakes or other symptoms (Romandini et al., 1984). The 5-HT_2 receptor agonists meta-chlorophenylpiperazine and lorcaserin also decreased jumping (Samanin et al., 1980; Cervo et al., 1981; Shahidi and Hashemi-Firouzi, 2014; Wu et al., 2015) as well as diarrhea (Samanin et al., 1980) and paw licking (Shahidi and Hashemi-Firouzi, 2014), although another study found that lorcaserin only reduced wet dog shakes, paw licking, and penile grooming but not jumping or other withdrawal signs (Zhang et al., 2016). The 5-$HT_{2A/3}$ receptor agonist quipazine selectively decreased jumping but did not decrease other signs of opioid withdrawal (Samanin et al., 1980) and the 5-HT_7 receptor agonist AS19 has been observed to block jumping, grooming, shaking, teeth chattering, and writhing (Shahidi and Hashemi-Firouzi, 2014).

Similar to agonists of 5-HT receptors, antagonists also block some withdrawal behaviors while exacerbating others. For example, pretreatment with the 5-HT_2 antagonist cyproheptadine and the mixed $5HT_2$ antagonist/$5HT_1$ agonist methysergide reduced jumping, wet dog shakes, and burrows but increased weight loss and hypothermia (el-Kadi and Sharif, 1995). The 5-HT_3 antagonist ondansetron reduced jumping, defecation, and wet dog shakes in one study (Pinelli et al., 1997) but had no effect on wet dog shakes, paw shakes, or

TABLE 3

Preclinical examinations of the serotonin system on the opioid withdrawal syndrome

Only results pertaining to effects of non-opioid drugs on opioid withdrawal symptoms are presented.

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
Cervo et al. (1981)	d-fenfluramine (5 mg/kg), cyproheptadine HLC (10 mg/kg), clonidine (0.1 mg/kg), phentolamine methane sulphonate (5 mg/kg), piperoxane HCL (5, 10 mg/kg), phenoxybenzamine HCL (20 mg/kg), prazosin HCL (10 mg/kg), propranolol (10 mg/kg), haloperidol (1 mg/kg), piribedil monometane sulphonate (60 mg/kg). Administered intraperitoneally.	Rat	≥18	Precipitated, naloxone (1 mg/kg, i.p.) on day 11	Escalating morphine (route NR) doses up to 160 mg/kg by day 7	Diarrhea, flat posture, jumping, ptosis, salivation, teeth chattering, vocalization on touch, and wet dog shakes	d-fenfluramine (SSRI) reduced jumping only. Clonidine (α_2 agonist) reduced diarrhea and ptosis. Phenoxybenzamine (adrenergic antagonist) reduced diarrhea. The adrenergic antagonists piperoxane, phentolamine methane sulphonate, prazosin (α_1), propranolol (β_1), haloperidol, and peribedil monometane sulphonate (α_2) had no effects.
el-Kadi and Sharif (1995)	Cyproheptadine (0.5, 1, 5, and 10 mg/kg), methysergide (0.1, 1, 3, and 6 mg/kg). Administered intraperitoneally.	Mouse	8–10	Precipitated, naloxone (1 mg/kg, i.p.) on day 7	Escalating morphine doses up to 160 mg/kg, s.c., by day 6	Body temperature, body weight, burrowing, jumping, and wet dog shakes	Cyproheptadine (5-$HT_{2A,2C}$ antagonist) increased jumping (0.5 and 1 mg/kg) and hypothermia (all doses) and decreased jumping (5 and 10 mg/kg), wet dog shakes (all doses), burrows (10 mg/kg), and body weight loss (5 and 10 mg/kg). Methysergide (5-HT_2 antagonist and 5-HT_{1A} agonist) decreased burrowing, jumping, and wet dog shakes (all doses), and body weight loss (1, 3, and 6 mg/kg) but increased hypothermia (1, 3, and 6 mg/kg).
Higgins et al. (1991)	Ondansetron (0.01, 0.1, and 1 mg/kg), MDL 7222 (1 and 3 mg/kg). Administered subcutaneously.	Rat	6	Precipitated, naloxone (0.5 mg/kg, s.c.) on days 3 and 4	Morphine (75 mg) subcutaneous implant	Body temperature, paw shakes, mouth movements, salivation, startle, rhinorrhea, penile grooming, teeth chattering, weight loss, and wet dog shakes	Ondansetron (5-HT_3 antagonist) attenuated body weight loss (0.1 and 1 mg/kg). MDL 7222 (5-HT_3 antagonist) also attenuated body weight loss (3 mg/kg).
Pang et al. (2016)	Glemanserin (0.5 mg/kg). Administered intraperitoneally.	Mouse	10	Precipitated, naloxone (5 mg/kg, i.p.) on day 7	Escalating morphine doses up to 100 mg/kg, s.c., by day 6	Body grooming, burrowing, digging body, extended posture, face grooming, head shakes, jumping, paw licking, penile licking, rearing, scratching, and wet dog shakes	Glemanserin (5-HT_{2A} antagonist) decreased jumping (0.5 mg/kg).
Pinelli et al. (1997)	Ondansetron (0, 1, 2, and 4 mg/kg). Administered intraperitoneally.	Rat	8	Precipitated, naloxone (30 mg/kg, i.p.) on day 4	Escalating morphine doses up to 100 mg/kg, i.p., by day 4	Body temperature, defecation, jumping, salivation, urine excretion, and wet dog shakes	Ondansetron (5-HT_3 antagonist) reduced defecation (1, 2, and 4 mg/kg), body temperature (4 mg/kg), and jumping (2 and 4 mg/kg), but increased wet dog

(*continued*)

TABLE 3—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
							shakes (1, 2, and 4 mg/kg).
Romandini et al. (1984)	(+)-Fenfluramine (5 mg/kg); m-chlorophenylpiperazine (CPP; 2.5 mg/kg), Clonidine (0.5 mg/kg). Administered intraperitoneally.	Rat	≥16	Precipitated, naloxone (1 mg/kg, i.p.). Experiment 1 tested on Day 3; Experiment 2 on Day 5	Experiment 1: Morphine (75 mg) subcutaneous implant; Experiment 2: Escalating morphine doses up to 40 mg/kg, i.p., by day 5	Abnormal posture, diarrhea, jumping, ptosis, salivation, teeth chattering, vocalization on touch, wet dog shakes	(−)-fenfluramine (SSRI) and and m-CPP (5-HT agonist) decreased jumping. Clonidine (α_2 agonist) reduced wet dog shakes and increased jumping.
Samanin et al. (1980)	Quipazine (5 mg/kg), m-CPP (2.5 mg/kg); clonidine (0.5 mg/kg), haloperidol (0.5 mg/kg), propranolol hydrochloride (10 mg/kg). Administered intraperitoneally.	Rat	NR	Precipitated, naloxone (1 mg/kg, i.p.) on day 11	Escalating morphine doses up to 160 mg/kg, s.c., by day 7	Diarrhea, dyspnea, flat posture, jumping, ptosis, teeth chattering, salivation, vocalization on touch, and wet dog shakes	m-CPP (5-HT_{2C} agonist) decreased diarrhea and jumping. Quizapine (5-$HT_{2A/3}$ agonist) decreased jumping. Clonidine (α_2 agonist) decreased diarrhea and ptosis. Propranolol and haloperidol had no effect.
Shahidi and Hashemi-Firouzi (2014)	AS19 (3, 5, and 10 mg/kg); SB269970 (1, 3, and 10 mg/kg). Administered intraperitoneally.	Mouse	8	Precipitated, naloxone (3 mg/kg, s.c.) on day 5	Escalating morphine doses up to 45 mg/kg, s.c., by day 5	Body grooming, body weight, face grooming, head shakes, jumping, limb shakes, sniffing, standing, teeth chattering, and writhing	AS19 (5-HT_7 agonist) decreased weight loss (all doses); jumping, head shaking, standing, and writhing (5 and 10 mg/kg); and teeth chattering and limb shaking (10 mg/kg). SB269970 (5-HT_{7A} antagonist) increased teeth chattering (10 mg/kg) and limb shaking (1 mg/kg).
Wu et al. (2015)	Lorcaserin (0.5 mg/kg), clonidine (0.05 mg/kg). Administered intraperitoneally.	Mouse	10	Precipitated, naloxone (5 mg/kg, i.p.) on day 5	Escalating diacetyl morphine doses up to 50 mg/kg, s.c., by day 5	Body grooming, burrowing, digging body, extended posture, head shakes, jumping, paw licking, penile grooming, rearing, and wet dog shakes	Lorcaserin (5-HT_{2C} agonist) decreased jumping and paw licking. Clonidine (α_2 agonist) decreased jumping and paw licking.
Zhang et al. (2016)	Lorcaserin (0.5, 0.75, and 1.0 mg/kg), SB242084 (1.0 mg/kg), Clonidine (0.2 mg/kg). Administered intraperitoneally.	Mouse	9 to 10	Precipitated, naloxone (5 mg/kg, i.p.) on day 7	Escalating morphine doses up to 100 mg/kg, s.c., by day 6	Body grooming, burrowing, defecation, digging body, extended posture, face grooming, head shakes, jumping, paw licking, penile licking, piloerection, ptosis, rearing, scratching, urination, vocalization on touch, and wet dog shakes	Lorcaserin (5-HT_{2C} agonist) decreased jumping, burrowing, body grooming, rearing, wet dog shakes, paw licking, penile licking, and scratching (all doses). Clonidine (α_2 agonist) decreased jumping, burrowing, body grooming, rearing, wet dog shakes, head shakes, paw licking, penile licking, and scratching (0.2 mg/kg). SB242084 (5-HT_{2C} antagonist; 0.2 mg/kg) pretreatment blocked lorcaserin (0.5 mg/kg) suppression of jumping.

m-CPP, meta-chlorophenylpiperazine; SSRI, selective serotonin reuptake inhibitor; NR, not reported.

TABLE 4

Preclinical examinations of the cannabis system on the opioid withdrawal syndrome

Only results pertaining to effects of non-opioid drugs on opioid withdrawal symptoms are presented.

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Doses and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
Bhargava (1976)	THC (2.5, 5, and 10 mg/kg). Administered intraperitoneally.	Mouse	NR	Precipitated, naloxone (30 mg/kg, s.c.) on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Defecation, jumping, and rearing	THC (all doses) decreased defecation, jumping, and rearing.
Cichewicz and Welch (2003)	THC (0, 20, and 50 mg/kg). Administered orally.	Mouse	6	Precipitated, naloxone (1 mg/kg, s.c.) 12 hours after final morphine dose	Escalating morphine (oral) doses up to 300 mg/kg by day 7	Diarrhea and jumping	THC (all does reduced jumping.
Del Arco et al. (2002)	AM404 (2 and 10 mg/kg). Administered intraperitoneally.	Mouse	8–10	Precipitated, naloxone (1 mg/kg, route NR) on day 6; spontaneous withdrawal on day 6, 7, 8, or 9	Escalating morphine doses up to 100 mg/kg, i.p., by day 5	Abdominal constrictions, body weight, jumping, locomotor activity, piloerection, swallowing movements, and wet dog shakes	AM404 (anandamide transport inhibitor) had no effect on naloxone-precipitated withdrawal. AM404 decreased spontaneous withdrawal signs of jumping (all doses) and locomotor activity (10 mg/kg).
Gamage et al. (2015)	THC (1, 3, and 10 mg/kg), JZL184 (4 and 40 mg/kg), PF-3845 (1, 3, and 10 mg/kg), and SA-57 (1.25, 5, and 12.5 mg/kg). JZL184, PF-3845, and SA-57 administered intraperitoneally; THC administered subcutaneously.	Mouse	16–28	Precipitated, naloxone (0.3, 1 mg/kg, s.c.) on day 2	Morphine (75 mg) subcutaneous implant for 2 days	Diarrhea, head shakes, jumping, and paw tremors	THC (3 and 10 mg/kg), JZL184 (MAGL inhibitor; 40 mg/kg), SA-57 (dual FAAH/MAGL inhibitor; 5 and 12.5 mg/kg) decreased jumping. PF-3845 (FAAH inhibitor) had no effect.
Hine et al. (1975a)	THC (1, 2, 5, and 10 mg/kg). Administered intraperitoneally.	Rat	7	Precipitated, naloxone (4 mg/kg, i.p.) on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Abnormal posture, chewing, defection, diarrhea, ear blanching, ptosis, teeth chattering, vocalization, wet dog shakes, and total withdrawal score	THC (5 and 10 mg/kg) reduced total withdrawal scores, defection, diarrhea, and wet dog shakes.
Hine et al. (1975b)	Groups 1 and 2: THC (1 mg/kg). Group 3: THC (10 mg/kg). Administered intraperitoneally.	Rat	8–11	Precipitated, naloxone (4 mg/kg, i.p.) on day 13 (group 1) or day 26 (groups 2 and 3)	Group 1: daily methadone injections (10 mg/kg, s.c.) for 13 days. Groups 2 and 3: daily methadone injections (up to 30 mg/kg, s.c.) for 26 days	Abnormal posture, body temperature, chewing, defecation, ear blanching, escapes, ptosis teeth chattering turning, vocalization on touch, wet dog shakes, and total withdrawal score	THC (1 mg/kg) decreased defecation, diarrhea, earn blanching, vocalization on touch, and total withdrawal score in animals in group 1 who received 13 days of methadone exposure. THC (10 mg/kg) decreased defecation, diarrhea, escapes, turns, wet dog shakes, and total withdrawal score in group 3 who received 26 days of methadone exposure.
Hine et al. (1975c)	THC (2 mg/kg), cannabidiol (10 mg/kg),	Rat	8–9	Precipitated, naloxone	Morphine (75 mg) subcutaneous	Abnormal posture, audible grinding,	THC (2 mg/kg) decreased total

(*continued*)

TABLE 4—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Doses and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
	THC (2 mg/kg) + cannabidiol (10 mg/kg). Administered intraperitoneally.			(4 mg/kg, i.p.) on day 3	implant for 3 days	chewing, defecation, escapes, diarrhea, ear blanching, ptosis, teeth chattering, vocalization on touch, wet dog shakes, and writhing	withdrawal scores, defecation, and diarrhea. Cannabidiol alone had no effect. THC (2 mg/kg) + cannabidol (10 mg/kg) decreased total withdrawal scores, defecation, ear blanching, escapes, and wet dog shakes.
Li et al. (2019)	AM1710 (5 mg/kg). Administered intraperitoneally.	Mouse	8	Precipitated, naloxone (5 mg/kg, i.p.) after final morphine dose	Daily morphine injections (10 mg/kg, i.p.) for 12 days	Body temperature, body weight, and jumping	AM1710 (CB_2 agonist; 5 mg/kg) decreased jumping.
Lichtman et al. (2001)	THC (0, 0.1, 0.3, 1, 3, and 10 mg/kg). Administered subcutaneously.	Mouse	6	Precipitated, naloxone (1 mg/kg, i.p.) on day 5	Morphine (75 mg) subcutaneous implant for 5 days	Diarrhea, head shake, jumping, paw tremor, ptosis, scratching, and writhing	THC dose dependently reduced head shakes and paw tremors (specific doses that produced effects NR).
Mas-Nieto et al. (2001)	Rimonbant (10 mg/kg), rimonobant (10 mg/kg) + morphine (dose escalated to 100 mg/kg by day 5). Administered intraperitoneally.	Mouse	7–10	Precipitated, naloxone (1 mg/kg, s.c.) on day 6	Escalating morphine up to 100 mg/kg, i.p., by day 5	Body tremor, jumping, paw tremor, ptosis, sniffing, and wet dog shakes	Rimonobant (CB_1) inverse agonist/ antagonist; 10 mg/kg) coadministered with morphine decreased jumping and wet dog shakes. SR141716A had no effect when administered alone.
Ramesh et al. (2013)	THC (dose NR), rimonabant (dose NR), JZL184 (4, 16, and 40 mg/kg), PF-3845 (1, 3, and 10 mg/kg), SA-57 (2.5, 5, and 12.5 mg/kg). Rimonabant, JZL184, PF-3845, and SA-57 administered intraperitoneally; THC administered subcutaneously.	Mouse	10 to 11	Spontaneous, morphine pellets extracted on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Body weight, diarrhea, head, shakes, and paw tremors	JZL184 (MAGL inhibitor) decreased body weight, diarrhea, and paw tremors at all doses, and head shakes and jumping at 16 and 40 mg/kg. Rimonabant reversed all effects of JZL184 (40 mg/kg). PF-3845 (FAAH inhibitor) decreased head shakes, jumping, and paw tremors (10 mg/kg). THC blocked all withdrawal signs. JZL184 (4 mg/kg) + PF-3845 (10 mg/kg) decreased all withdrawal signs. SA-57 (dual FAAH/ MAGL inhibitor) decreased diarrhea, jumping, and paw flutters (2.5 and 5 mg/kg), and head shakes (5 mg/kg).
		Rat	≥6				

(*continued*)

TABLE 4—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Doses and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
Rubino et al. (2000)	Rimonobant (10 mg/kg per day). Administered intraperitoneally.			Precipitated, naloxone (10 mg/kg, i.p.) on day 5 (AM and PM sessions)	Morphine (75 mg) subcutaneous implant for 5 days	Digging, grooming, head shakes, jumping, penile licking, rearing, salivation, teeth chattering, wet dog shakes, writhing, and total withdrawal score	Rimonobant (CB_1 inverse agonist/ antagonist; 10 mg/kg per day) decreased diarrhea, digging, teeth chattering, penile licking, and total withdrawal score. SR141716A increased salivation.
Shahidi and Hasenein (2011)	URB597 (0.03, 0.1, 0.3, 0.5, and 1 mg/kg). Administered intraperitoneally.	Rat	9	Precipitated, naloxone (3 mg/kg, s.c.) on day 8	Escalating morphine doses up to 66 mg/kg, s.c., by day 7	Body weight, face grooming, jumping paw tremor, penile licking, rearing, sniffing standing, teeth chattering, and wet dog shakes	URB597 (FAAH inhibitor) decreased body weight loss, face grooming, jumping, penis licking, sniffing, and teeth chattering (all doses tested). URB597 also decreased standing and wet dog shakes (0.1, 0.3, 0.5, and 1 mg/kg), paw tremors (0.5 mg/kg), and rearing (1 mg/kg).
Vela et al. (1995)	THC (10 mg/kg; experiment 1 only), anandamide (0.1, 1, and 5 mg/kg). Administered intravenously.	Mice	8–15	Experiment 1: precipitated, naloxone (1 mg/kg, i.p.) on day 3; experiment 2: precipitated, naloxone (5 mg/kg, s.c.) on day 5	Experiment 1: morphine (75 mg) subcutaneous implant for days; experiment 2: escalating, morphine (route NR) doses up to 45 mg/kg by day 5	Body weight and jumping	Experiment 1: anandamide decreased jumping (5 mg/kg) and body weight loss (1 mg/kg). THC (10 mg/kg) decreased jumping and body weight. Experiment 2: anandamide decreased body weight loss (1 and 5 mg/kg); THC, not tested.

AM404, *N*-(4-hydroxyphenyl) arachidonylethanolamide; CB_2, cannabinoid type 2 receptor; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NR, not reported.

salivation in another study (Higgins et al., 1991). The 5-HT_{2A} antagonist glemanserin has also been found to selectively reduce jumping and self-directed behaviors (Pang et al., 2016); however, the 5-HT_7 receptor–specific antagonist SB269970 increased jumping, grooming, teeth chattering, and shaking (Shahidi and Hashemi-Firouzi, 2014).

Human Withdrawal. Two studies have reported on whether the 5-HT_3 antagonist ondansetron modifies opioid withdrawal severity in humans. The first was a case report that suggested ondansetron might reduce human opioid withdrawal syndrome severity (Wakim, 2012); however, the second was a placebo-controlled within-subject empirical evaluation that found no benefit of ondansetron relative to placebo following naloxone-precipitated withdrawal (Chu et al., 2017).

Cannabinoid System

Arachindonoylethanolamide (anandamide) and 2-arachidonoylglycerol are two primary (but not sole) endogenous cannabinoid ligands that bind to and activate cannabinoid type 1 (CB_1) and type 2 receptors. CB_1 receptors are often colocalized with μ-opioid receptors (for a review, see Bloomfield et al., 2019), and cannabinoid agonists, antagonists, and endocannabinoid catabolic enzyme inhibitors have all been examined for opioid withdrawal suppression.

Preclinical Withdrawal. Several studies have reported that Δ^9-THC, the primary psychoactive cannabinoid in the cannabis plant and a partial agonist at CB_1 receptors, reduced withdrawal-related jumping and other escape behaviors, wet dog shakes, gastrointestinal symptoms, and shaking in rodents (Hine et al., 1975a,b,c; Bhargava, 1976; Lichtman et al., 2001; Cichewicz and Welch, 2003), although additional studies reported no beneficial effect of THC on jumping (Lichtman et al., 2001) or diarrhea (Lichtman et al., 2001; Cichewicz and Welch, 2003). Direct administration of the endogenous cannabinoid anandamide was found to decrease jumping and weight loss (Vela et al., 1995); however, increasing anandamide through inhibition of its catabolic

TABLE 5
Preclinical examination of the orexin/hypocretin system on the opioid withdrawal syndrome
Only results pertaining to effects of non-opioid drugs on opioid withdrawal symptoms are presented.

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)[a]	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
Ahmadi-Soleimani et al. (2014)	SB-334867 (100 μM/0.2 μl). Direct administration to LPGi nucleus.	Rat	8–13	Precipitated, naloxone (2 mg/kg, i.p.). Injection occurred following morphine escalation, specific time NR	Escalating mrophine (drinking water) increasing in concentrations up to 0.4 mg/ml and maintained for 15 days	Chewing, defecation, digging, genital licking, grooming, rearing, sniffing, teeth chattering, and wet dog shakes	SB-334867 decreased chewing, genital licking, grooming, rearing, and sniffing.
Azizi et al. (2010)	SB-334867 (100 μM/0.2 μl). Direct administration to locus coereleus.	Rat	9	Precipitated, naloxone (1 mg/kg, i.p.) 2 hours after morphine administration on day 10	Morphine (10 mg/kg) delivered every 12 hours for 10 days	Chewing, diarrhea, head tremor, jumping, rearing, scratching, sniffing, teeth chattering, ptosis, and wet dog shakes	SB-334867 decreased chewing, diarrhea, head tremor, scratching, teeth chattering, and wet dog shakes.
Davoudi et al. (2016)	SB-334867 (3 mM/0.2 μl). Bicuculline (15 μM/0.2 μl). Direct administration to locus coereleus.	Rat	7	Precipitated, naloxone (3 mg/kg, s.c.) on day 8	Escalating morphine doses up to 66 mg/kg, s.c., by day 7	Defecation, head tremor, genital licking, rearing, scratching, sniffing, teeth chatttering, wet dog shake, and writhing	SB-334867 decreased defecation, head tremor, gential licking, rearing, scratching, sniffing, wet dog shakes, and writhing. Bicuculline (GABA antagonist) had no effect by itself but when coadministered with SB-334867 reversed effects on head tremor, rearing, scratching, teeth chattering, wet dog shakes, and writhing.
Erami et al. (2012)	SB-334867 (1 mM/5 μl). Administered intracerebroventricularly.	Rat	8	Precipitated, nalozone (2 mg/kg, s.c.) on day 10	Morphine (10 mg/kg, s.c.) delivered every 12 hours for 10 days	Chewing, climbing, defecation, diarrhea, head tremor, jumping, rearing, scratching, sniffing, teeth chattering, and wet dog shakes	SB-334867 decreased chewing, climbing, diarrhea, jumping, rearing, rhinorrhea, and teeth chattering.
Ghaemi-Jandabi et al. (2014)	Orexin A (100 μM/200 nl); SB-334867 (100 μM/200 nl). Direct administration to locus coereleus.	Rat	6 to 7	Precipiated, OXA (0.2 μl) injection to locus coereleus on day 10	Morphine (10 mg/kg, s.c.) delivered every 12 hours for 9 days	Chewing, head tremor, paw tremor, rearing, scratching, sniffing, teeth chattering, and wet dog shakes	OXA increased chewing, head tremor, rearing, scratching, and wet dog shakes. SB-33847 decreased chewing, head tremor, paw tremor, scratching, sniffing, rearing, and teeth chattering.
Hooshmand et al. (2017)	SB-334867 (3 mM/200 nl) + glutamate (100 nM/200 nl). Direct administration to locus coereleus.	Rat	NR	Precipitated, glutamate (100 nM/200 nl) injection to locus coereleus on day 7	Escalating morphine up to 66 mg/kg, s.c., by day 7	Chewing, defecation, head tremor, paw tremor, rearing, scratching, sniffing, teeth chattering, wet dog shakes, and writhing	Glutamate increased chewing, paw tremor rearing, scratching, sniffing, wet dog shakes, and writhing. SB-334867 pretreatment did not attenuate glutamate-precipitated withdrawal during the day (rest phase) but decreased chewing, head tremor, paw tremor, rearing, sniffing, scratching, teeth chattering, wet dog shakes, and writhing during the night (active phase).
Hooshmandi et al. (2017)		Rat	12			Activity, chewing, diarrhea, head tremor, freezing,	SB-334867 decreased chewing, diarrhea, freezing, penile licking,

(*continued*)

TABLE 5—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)[a]	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
	SB-334867 (0.5 μg/0.5 μl). Direct administration to dorsal hippocampus.			Precipitated, naloxone (1.5 mg/kg, i.p.) on day 10	Morphine (10 mg/kg, s.c.) delivered every 12 hours for 9 days.	penile licking, ptosis, rearing, rubbing, scratching, sniffing, teeth chattering, wet dog shakes, and writhing	ptosis, scratching, teeth chattering, wet dog shakes, and writhing.
Laorden et al. (2012)	SB-334867 (20 mg/kg). Administered intraperitoneally.	Rat	4–8	Precipitated, naloxone (1 mg/kg, s.c.) on day 6	Morphine (150 mg) subcutaneous implant for 6 days	Diarrhea, jumping, mastication, paw tremor, piloerection, ptosis, sniffing, teeth chattering, tremor, wet dog shakes, and writhing	SB-334867 decreased body tremor, diarrhea, mastication, piloerection, ptosis, sniffing, wet dog shakes, and writhing. Global withdrawal score also decreased.
Sharf et al. (2008)	SB-334867 (0, 20 mg/kg). Direct administration to nucleus accumbens.	Mouse	9	Precipitated, naloxone (1 mg/kg, s.c.) 2 hours after morphine administration	Escalating morphine doses up to 100 mg/kg, i.p., for 2.5 days	Backward walking, gnawing, head swoops, jumping, paw tremors, ptosis, tremors, and wet dog shakes	SB-334867 decreased backward walking, ptosis, tremors, wet dog shakes, and global withdrawal score (sum of withdrawal symptoms).

LPGi, lateral paragigantocellularis; NR, not reported.
[a]All drugs were administered to specific brain regions, except where noted.

enzymes using the fatty acid amide hydrolase inhibitor URB597, monoacylglycerol lipase inhibitor JZL184, or dual fatty acid amide hydrolase/monoacylglycerol lipase inhibitor SA-57 increased jumping again (Shahidi and Hasanein, 2011; Gamage et al., 2015). In addition, URB597 also decreased signs of wet dog shakes, teeth chattering, tremors, and self-directed behaviors (Shahidi and Hasanein, 2011). However, this effect may be compound specific since the fatty acid amide hydrolase inhibitor PF-3845 had no effect on jumping when administered alone (Gamage et al., 2015), although reductions in jumping, tremors, shakes, and diarrhea were observed when a high dose of PF-3845 was combined with low doses of JZL184 and SA-57 (Ramesh et al., 2013). Further complicating this issue is the fact that the anandamide-transport inhibitor *N*-(4-hydroxyphenyl) arachidonylethanolamide, which increases synaptic anandamide levels, blocked signs of spontaneous but not naloxone-precipitated withdrawal (Del Arco et al., 2002), suggesting these two syndromes may have different underlying mechanisms. The only study to examine a cannabinoid type 2 receptor–specific agonist (AM1710) on opioid withdrawal found it also reduced jumping (Li et al., 2019).

Finally, chronic exposure to the CB_1 inverse agonist/antagonist SR141716A (Rimonobant) selectively reduced jumping (Rubino et al., 2000; Mas-Nieto et al., 2001), wet dog shakes (Mas-Nieto et al., 2001), teeth chattering, self-directed behaviors, and diarrhea (Rubino et al., 2000), while not changing other measured behaviors.

Human Withdrawal. The human clinical evidence for the therapeutic effectiveness of cannabinoids during opioid withdrawal is limited and focused largely on the cannabis plant or THC. The earliest evidence of a potential therapeutic application of cannabis for opioid withdrawal is a case report from 1889, wherein a patient being withdrawn from the opioid laudanum showed immediate improvement in symptoms following cannabis administration, evidenced by being able to "take a turn around the verandah with the aid of a stick" (Birch, 1889). More recent retrospective reports have provided mixed support for cannabis treatment of opioid withdrawal. One secondary analysis of patients undergoing a methadone taper found no evidence that urine samples, which indicated recent cannabis use, were associated with better outcomes, concluding that cannabis use did not meaningfully improve withdrawal management (Epstein and Preston, 2015). A second retrospective chart review reported that 33% and 66% of patients using cannabis during opioid withdrawal found it to increase and decrease withdrawal severity, respectively (Gossop et al., 1991). Human empirical studies have generally examined whether the synthetic THC product dronabinol improves opioid withdrawal management. One randomized study in patients undergoing opioid-assisted withdrawal reported lower withdrawal ratings in participants receiving dronabinol versus placebo (Bisaga et al., 2015), and a second randomized human laboratory study in participants undergoing abrupt opioid discontinuation found that dronabinol modestly reduced withdrawal relative to placebo (Lofwall et al., 2016). However, dronabinol administration during opioid withdrawal has been observed to produce clinically significant levels of tachycardia (Jicha et al., 2015) and intoxication (Lofwall et al., 2016); suggesting its therapeutic window for this indication may be narrow.

TABLE 6

Preclinical examinations of the glutamate system on the opioid withdrawal syndrome

Only results pertaining to effects of non-opioid drugs on opioid withdrawal symptoms are presented.

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Doses and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specified Results
Fundytus and Coderre (1994)	MK-801, GYKI 52466, (*S*)-4C-PG, and L-AP3 (same dose schedule: 1.6, 8, and 40 nmol). Administered intracerebroventricularly.	Rat	4–10	Precipitated, naloxone (1 mg/kg, s.c.), on day 7	Morphine (36.65 μmol/day) administrated subcutaneously via pump	Jumping, teeth chattering, wet dog shakes, and writing	MK-801 (NMDA antagonist). (*S*)-4C-PG (metabotropic receptor antagonist), and L-AP3 (metabotropic receptor antagonist) dose dependently reduced teeth chattering and writing, as well as time spent in withdrawal. GYKI 52466 (AMPA/kainate receptor antagonist had no effect.
Fundytus and Coderre (1997)	(1*S*,3*R*)-ACPD, DHPG, and L-AP4 (same dose scheduled: 0.12, 0.6, and 3 nmol), DCG-IV (4.8 or 24 pmol). Administrated intracerebroventricularly.	Rat	11–18	Precipitated, naloxone (1 mg/kg, s.c.), on day 7	Morphine (36.65 μmol/day) administrated subcutaneously via pump	Diarrhea, eye twitch, salivation, teeth chattering, and writing	(1*S*,3*R*)-ACPD (mGlu nonspecific) decreased eye twitch severity and time spent in withdrawal. DCG-IV ($mG1u_{2/3}$ antagonist) decreased diarrhea, eye twitch, salivation, and time spent in withdrawal. L-AP4 ($mGlu_4$ antagonist) increased eye twitch. DHPG ($mGlu_{1/5}$ antagonist) had no significant effect.
Fundytus et al. (1997)	MCPG, MCCG, and MAP4 (same dose schedule: 1.6, 8, and 40 nmol/day). Administrated intracerebroventricularly.	Rat	17–20	Precipitated, naloxone (1 mg/kg, s.c.), on day 7	Morphine (75 mg) subcutaneous implant for 3 days	Chewing, diarrhea, lacrimation, penile grooming, ptosis, salivation, stretching, teeth chattering, vocalization on touch, wet dogs shakes, and total withdrawal score	MCPG (mGlu nonselective antagonist) decreased jumps, vocalization, wet dog shakes, and time spent in withdrawal. MCCG ($mGlu_{2/3}$ antagonist) decreased jumping, wet dog shakes, and time spent in withdrawal. MAP4 ($mGlu_{4,6,7,8}$ antagonist) decreased time spent in withdrawal.
Kosten et al. (1995)	Felbamate (100 and 300 mg/kg), D-cycloserine (3 and 10 mg/kg), ± HA-966 (3, 10 mg/kg), Administered intraperitoneally.	Rat	6	Precipitated, naloxone (10 mg/kg, s.c.) on day 4	Morphine (75 mg) subcutaneous implant for 3 days	Chewing, diarrhea, lacrimation, penile grooming, ptosis, salivation, stretching, teeth chattering, vocalization on touch, wet dog shakes, and total withdrawal score	Felbamate (glycine antagonist) decreased frequency of chewing, penile grooming, teeth chatterin, and severity of salivation in a linear manner across doses. D-cycloserine (glycine agonist) decreased withdrawal severity at both doses but not in a linear way. ± HA-966 (partial glycine agonist) had no effect.
Kotlinkska and Bochenski (2007)	MTEP (23 and 10 mg/kg), EMQMCM (5 and 20 mg/kg) Administered intraperitoneally.	Mouse	8–10	Precipitated, naloxone (4 mp kg, i.p.) on day 3	Morphine sensitization procedure for 13 days (10 mg/kg, i.p., every 3 days)	Jumping	MTEP ($mGlu_5$ antagonist) 10 mg decreased jumping.

(*continued*)

TABLE 6—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Doses and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specified Results
					followed by morphine (37.5 mg) subcutaneous implant for 3 days		EMQMCM ($mGlu_1$ antagonist) had no effect.
Leal et al. (2003)	Ibogaine (40 and 80 mg/kg), MK-801 (0.15, and 0.3 mg/kg), Ibogaine (40 mg/kg) + MK-801 (0.15 mg/kg). Administered intraperitoneally.	Mouse	10–13	Precipitated, nalaxone (5 mg/kg, i.p.) on day 4	Escalating morphine doses up to 225 mg/kg, i.p., by day 3	Jumping	All doses of ibogaine and MK-801 (NMDA antagonist) decreased jumping. Ibogaine (40 mg/kg) and MK-801 (0.15 mg/kg) coadministration decreased jumping at the level observed for the high dose of each drug independently.
Medrano et al. (2015)	Ceftriaxone (100 and 200 mg/kg), Topiramate (20 and 40 mg/kg). Administered intraperitoneally.	Rat	8–10	Precipitated, naltrexone (10 mg/kg, i.p.) on day 4	Morphine (200 mg/kg) subcutaneous implant for 3 days	Abnormal posture, body weight, diarrhea, exploring, ear blanching, eye twitching, jumping, lacrimation, mastication, penile erection, ejaculation, piloerection, ptosis, rhinorrhea, teeth chattering, vocalization on touch, and wet dog shakes	Ceftriaxone (glutamate transporter inhibitor) (200 mg/kg) decreased jumping, mastication, teeth chattering, and total withdrawal. Topiramate (glutamate release inhibitor) (40 mg/kg) reduced exploring, jumping, mastication, wet dog shakes, and total withdrawal score.
Pałucha-Poniewiera et al. (2009)	ACPT-1 (2.5, 10, 30 mg/kg). Administered intraperitoneally.	Mouse	8–10	Precipitated, naloxone (4 mg/kg, i.p.) on day 4	Morphine (30 mg/kg, i.p.) for 3 days, with an additional dose on day 4	Body tremor, body weight, jumping, paw shake, and wet dog shakes	ACPT-1 ($mGlu_{2/3}$ agonist) decreased body tremor (all doses), body weight (10 and 30 mg), jumping (10 mg), paw shakes (10 and 30 mg), and wet dog shakes (all doses).
Rasmussen et al. (1996)	LY293558 (0.1, 10, and 30 mg/kg). Administered intraperitoneally.	Rat	10–12	Precipitated, naltrexone (10 mg/kg, s.c.) on day 4	Morphine (150 mg) subcutaneous implant for 2 days	Body weight, chewing, diarrhea, digging, erections, irritability, jumping, lacrimation, ptosis, salivation, stereotyped head movements, teeth chattering, tremor, wet dog shakes, writhing, and total withdrawal score	LY293558 (AMPA antagonist) dose dependently decreased total withdrawal score; specific dose-dependent decreases in chewing, diarrhea, lacrimation, ptosis, salivation, stretching head movements, wet dog shakes, and writhing.
Rasmussen et al. (2005)	MPEP (1, 3, and 10 mg/kg), MTEP (1, 3, and 10 mg/kg). Administered intraperitoneally.	Rat	6–16	Precipitated, naltrexone (10 mg/kg, s.c.) on day 3	Morphine (75 mg) subcutaneous implant for 2 days	Body weight, chewing, diarrhea, digging, erection, irritability, jumping, lacrimation, ptosis, salivation, teeth chattering, wet dog shakes, writhing, and total withdrawal score	MPEP ($mGlu_5$ antagonist) reduced total withdrawal score at all doses tested and decreased body weight, chewing, digging, erection (1 mg/kg only), jumping, and teeth chattering (3 mg/kg only). MTEP ($mGlu_5$ antagonist) 3 and 10 mg/kg reduced total withdrawal score and body weight, chewing, digging,

(*continued*)

TABLE 6—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Doses and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specified Results
							erection (1 and 3 mg/kg only), and writhing.
Sekiya et al. (2004)	DL-TBOA (1, 3, 10 nmol). Administered intracerebroventricularly.	Rat	6–7	Precipitated, naloxone (0.1 mg/kg, i.p.) on day 5	Morphine (150 mg) subcutaneous impart for 5 days	Backward walking, body weight, ejaculation, head shaking, jumping, paw shaking, stretching, teeth chattering, wet dog shakes	DL-TBOA (glutmate uptake inhibitor) dose dependently increased ejaculation, rhinorrhea, salivation, teeth chattering, and wet dog shakes.
Tanganelli et al. (1991)	MK-801 (0.1, 0.3, and 1 mg/kg), glutamatic acid dyethylester (100–500 mg/kg), pyroglutamic acid (500–1000 mg/kg). Administered intraperitoneally.	Mouse	15–20	Precipitated, naloxone (3 mg/kg, s.c.) on day 2	Morphine (75 mg) subcutaneous implant for 2 days	Hyperactivity and jumping	MK-801 (NMDA antagonist) 0.3 and 1 mg/kg decreased jumping. Glutamatic acid dyethylester had no effect. Pyroglutamic acid (non-NMDA antagonist) 1000 mg/kg decreased jumping.
Tokuyama et al. (1996)	MK-801 (0.1 mg/kg). Administered intraperitoneally.	Rat	10–14	Precipitated, naloxone (48 nmol/5 μl, LC) or glutamate (1 and 10 nmol/5 μl, LC) 2 hours after last opioid infusion	Morphine (26 nmol/μl per hour) or butorphanol (26 nmol/μl per hour) intracerebroventricular osmotic minipump infusions for 3 days	Body weight, escape behavior, locomotion, penis licking, ptosis, rearing, salivation, scratching, teeth chattering, and wet dog shakes	Glutamate increased all withdrawal signs at both doses. MK-801 (NMDA antagonist) decreased all signs of withdrawal that were precipitated by either glutamate or naloxone.
Tokuyama et al. (1998)	H-7 (1 and 10 nmol/μl per hour) intracerebroventricular osmotic minipump infusions.	Rat	7	Precipitated, naloxone (24 and 48 nmol/5 μl, i.c.v.) or glutamate (1 and 10 nmol/ 5 μl, LC) 2 hours after opioid infusion	Morphine (26 nmol/μl per hour) or butorphanol (26 nmol/μl per hour) intracerebroventricular osmotic minipump infusion for 3 days	Body weight, escape behavior, locomotion, penile licking, ptosis, rearing, salivation, stretching, teeth, chattering, and wet dog shakes	Glutamate increased all signs except weight loss and salivation. H-7 (cAMP inhibitor) dose dependently decreased escape behavior, locomotion, penis licking, ptosis, rearing, salivation, streching, and teeth chattering. Outcomes are dependent on dependence and withdrawal method used.
Vandergriff and Rasmussen (1999)	LY354740 (3, 10, and 30 mg/kg), LY317207 (30 mg/kg). Administered subcutaneously.	Rat	8	Precipitated, naltrexone (10 mg/kg, s.c.) on day 3	Morphine (300 g) subcutaneous implant for 2 days	Body weight, chewing, diarrhea, digging, erections, irritability, jumping, lacrimation, ptosis, salivation, stereotyped head movements, teeth chattering, wet dog shakes, writhing, and total withdrawal score	LY354740 (mG1u$_{2/3}$ agonist) dose dependently decreased total withdrawal score, chewing, diarrhea, digging, and salivation. Wet dog shakes and ptosis significantly decreased at 30 mg/kg only. LY317207 (inactive LY354740 enantiomer) had no effect.
Watanabe et al. (2002)	CNQX (10 and 30 nmol), MK-801 (10 and 30 nmol), D-CPPene (0.001, 0.1, and 0.1 nmol) infusion to central nucleus of the amygdala	Rat	5–9	Precipitated, naloxone (0.3 mg/kg, i.p.) on day 4	Morphine (75 mg) subcutaneous implant for 2 days	Backward walking, body weight, diarrhea, head shakes, jumping, lacrimation, paw shakes, ptosis, rearing, rhinorrhea, salivation, stretching, teeth chattering, and wet dog shakes	CNQX (AMPA/kainate antagonist) decreased backward walk, body weight loss, diarrhea, head shakes, paw shakes, ptosis, rhinorrhea, teeth chattering, and wet dog shakes. MK-801 (NMDA antagonist) and D-CPPene (NMDA antagonist) had no effect.

CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; LC, locus coeruleus; NR, not reported.

Orexin/Hypocretin System

The orexin (OX)/hypocretin system (hereinafter referred to as orexin) is composed of two endogenous peptides (OXA and OXB) and two receptors (OX_{1R} and OX_{2R}) (for a review, see Wang et al., 2018). Orexin is the most recently discovered of the systems reviewed herein (de Lecea et al., 1998; Sakurai et al., 1998), and there is a correspondingly limited number of pharmacological probes available to assess its role in opioid withdrawal. However, there is substantial rationale for evaluating this system. Orexin signaling generally promotes wakefulness, and the FDA has recently approved the dual OX_{1R}/OX_{2R} antagonist suvorexant (Belsomra) based on evidence that it promotes sleep and improves sleep architecture (Herring et al., 2016). Acute opioid withdrawal significantly disrupts sleep (Oyefeso et al., 1997), and pronounced protracted abnormal rapid eye movement sleep patterns are evident during both preclinical (Khazan and Colasanti, 1972; Colasanti et al., 1975) and human withdrawal (Mehtry et al., 2014). Since less sleep impairment is significantly associated with better withdrawal outcomes (Warden et al., 2012; Dunn et al., 2015), the orexin system is a logical target to address withdrawal-precipitated insomnia. Despite this evidence base, no preclinical or human studies have assessed the role of orexin in opioid-related insomnia; rather, the following studies all provide evidence that the orexin system confers benefits on other non-sleep–related withdrawal symptoms. There are no human studies examining the orexin system during withdrawal; therefore, herein only preclinical studies are reviewed.

Preclinical Withdrawal. Direct administration of OXA (which preferentially binds to OX_{1R}) increases self-directed behaviors, wet dog shakes, teeth chattering, and tremors, which can be blocked by pretreatment with the OX_{1R} antagonist SB-334867 (Ghaemi-Jandabi et al., 2014). SB-334867 also reduced chewing, diarrhea, jumping, ptosis, shaking, wet dog shakes, and other signs when administered by itself (Azizi et al., 2010; Erami et al., 2012; Ahmadi-Soleimani et al., 2014; Hooshmandi et al., 2017) or prior to naloxone-precipitated withdrawal (Laorden et al., 2012), although in the latter case it did increase teeth chattering (Laorden et al., 2012). This, combined with evidence that direct administration of SB-334867 to the nucleus accumbens reduced self-directed behaviors, wet dog shakes, tremors, ptosis, gnawing, and global withdrawal scores (Sharf et al., 2008), strongly implicates the orexin system in the expression of some withdrawal symptoms. However, when SB-334867 is administered to the locus coeruleus following $GABA_A$ antagonist pretreatment, its beneficial effects on withdrawal are attenuated, suggesting that orexin modulation of opioid withdrawal may be due to OX_{1R} and GABA interactions in the locus coeruleus (Davoudi et al., 2016). The complexity of orexin's role in opioid withdrawal is further illustrated by a study that found OX_{1R}-dependent withdrawal reduction was limited to the active dark cycle phase, suggesting orexin-specific effects on withdrawal may be dependent on circadian rhythms and relegated to wakefulness and possibly drug seeking (Hooshmand et al., 2017).

Glutamate System

The glutamate system is comprised of ionotropic glutamate [(iGlu), AMPA and NMDA] and metabotropic glutamate [(mGlu), $mGlu_{1–5}$] receptors that are ubiquitously distributed throughout the brain and are being actively investigated for their role in a wide range of substance use disorders (for a review, see Niciu et al., 2012). A convergence of evidence suggests that iGlu antagonists, $mGlu_{2/3}$ agonists, and $mGlu_5$ antagonists reduce the severity of some opioid withdrawal symptoms.

Preclinical Withdrawal. Glutamate appears to increase, and glutamate antagonism appears to decrease, opioid withdrawal severity. For instance, increasing glutamate levels by directly injecting glutamate into the locus coeruleus (Tokuyama et al., 1998) or through pretreatment with the glutamate transporter inhibitor DL-TBOA, increases stretching, wet dog shakes, and teeth chattering (Sekiya et al., 2004). Decreasing glutamate levels through administration of the β-lactam antibiotic ceftriaxone (which upregulates the glutamate transporter) decreased jumping and teeth chattering in rats (Medrano et al., 2015), and increasing glutamate by coadministering dihydrokainic acid to block ceftriaxone increased withdrawal symptoms again (Medrano et al., 2015). Opioid withdrawal was also completely suppressed in rats that received an infusion of the protein kinase inhibitor H-7 to reduce glutamate in the locus coeruleus (Tokuyama et al., 1996).

Additional evidence supports targeting the iGlu NMDA and AMPA receptors for opioid withdrawal. Pretreatment with the NMDA receptor antagonist dextromethorphan reduced chewing and paw shakes relative to a control condition and independent of the coadministration of the CYP2D6-inhibitor quinidine, which is generally required for humans to achieve a therapeutic effect of dextromethorphan (Bisaga et al., 2008). The NMDA antagonist MK-801 reduced jumping and the overall duration of withdrawal (Tanganelli et al., 1991; Fundytus and Coderre, 1994; Tokuyama et al., 1996; Leal et al., 2003), although it increased wet dog shakes (Fundytus and Coderre, 1994). Pretreatment with felbamate and D-cycloserine (an antagonist and agonist, respectively) at the glycine site of the NMDA receptor decreased withdrawal, although only felbamate did so in a linear, dose-dependent manner (Kosten et al., 1995). Both AMPA-receptor antagonists topiramate and LY293558 reduced jumping, wet dog shakes, gastrointestinal signs, mastication, ptosis, lacrimation, chewing, and writhing (Rasmussen et al., 1996; Medrano et al., 2015), and microinjection of an AMPA/kainite-glutamate-receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione into the central nucleus of the amygdala significantly reduced teeth chattering, diarrhea, and rhinorrhea (Watanabe et al., 2002). However, intracerebroventricular administration of the AMPA/kainite antagonist GYKI did not improve withdrawal (Fundytus and Coderre, 1994).

Medications targeting iGlu receptors generally have poor receptor specificity and potential for abuse or other negative side effect profiles that may limit their adoption in clinical settings (Herman et al., 1995). Research evaluating mGlu medications as alternatives to iGlu suggest they are also promising targets. For instance, the nonselective mGlu agonist (1*S*,3*R*)-ACPD and the selective $mGlu_{2/3}$ agonist DCG-IV both reduced signs of diarrhea and salivation, as well as the overall duration of opioid withdrawal (Fundytus and Coderre, 1997). The $mGlu_{2/3}$ receptor agonist LY354740 also dose dependently decreased wet dog shakes, hyperactivity, ptosis, gastrointestinal signs, writhes, salivation, and chews (Vandergriff and Rasmussen,

TABLE 7

Preclinical examinations of medications with multiple mechanisms of action on the opioid withdrawal syndrome

Only results pertaining to effects of non-opioid drugs on opioid withdrawal symptoms are presented.

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
Aceto and Bowman (1993)	Buspirone (0.2, 0.4, and 0.8 mg/kg)	Rhesus Monkey	≥3	Precipitated, naloxone (0.05 mg/kg, s.c.) 2 to 3 hours after last morphine administration	Morphine (3 mg/kg, s.c.) at minimum for ≥3 months	Ataxia, body sag, fighting, jaw sag, lying down, ptosis, retching, restlessness, rigid abdominal muscles, slowing, vocalization, and wet dog shakes	Buspirone dose dependently reduced rigid abdominal muscles, fighting, lying down, retching, restlessness, and vocalization and increased wet dog shakes.
Berthold et al. (1989)	Clonidine (0.01, 0.03, 0.1, and 0.3 mg/kg), prazosin (0.1, 1, and 4 mg/kg), spiroperidol (0.05 and 0.5 mg/kg), 8-OH-DPAT (0.5, 1, 2, 4, 8 mg/kg); RU 24969 fumerate (0.125, 0.25, 0.5., 1, 2, and 4 mg/kg); Idazoxan; (−)-pindolol (1, 2, and 4 mglkg); (+)-SDZ 21-009 (1 mg/kg); (−)-SDZ 21-009 (1 mg/kg); buspironc (1, 2, 5, and 10 mg/kg); ipsapirone (1, 3, and 10 mg/kg); yohimbine (0.5 and 2 mg/kg); flesinoxan (0.5, 1, and 3 mg/kg); Rauwolscine (0.5 and 2 mg/kg), WY 26392 (0.5, 2 mg/kg), haloperidol (0.1, 0.5, and 1.0 mg/kg); pCPA (150 mg/kg). Administered subcutaneously.	Mouse	10	Precipitated, naloxone (1 mg/kg, i.p.) on day 5	Morphine (75 mg) subcutaneous implant for 5 days	Jumping	8-OH-DPAT (1 mg/kg), RU 24969 (0.25–4 mg/kg), buspirone (2 mg/kg) (5-HT_1 agonists), ipsapirone (10 mg/kg), and flesinoxan (all doses) (5-HT_1 agonists) decreased jumping. Idazoxan (all doses), prazosin (1 and 4 mg/kg), rauwolscine (2 mg/kg), WY 26392 (all doses), and yohimbine (all doses) (α-adrenoreceptor antagonists) also decreased jumping. Spiroperidol (5-HT_1 antagonist) pretreatment had no effect alone but increased jumping from 8-OH-DPAT and buspirone; no effect of spiroperidol pretreatment on RU24969 and idazoxan. Haloperidol pretreatment enhanced 8-OH-DAPAT–related jumping. Pretreatment (−)-pindolol and (−)-SDZ 21-009 (β-adrenoreceptor/5-HT_{1A} and 5-HT_{1B} antagonists) decreased ability of RU 24969 to suppress jumping. (+)-SDZ21-009 did not impact RU 24969. 8-OH-DAPAT unaffected by (−)-pindolol. pCPA, clonidine (α_2 agonist), and (−)-pindolol had no effects.
Cappendijk et al. (1994)	β-Carboline (20 mg/kg), Ibogaine (40 mg/kg). Administered intraperitoneally.	Rat	10	Precipitated, naloxone (4 mg/kg, i.p.) on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Chewing, diarrhea, grooming, jumping, penile licking, ptosis, rearing, rhinorrhea, teeth- chattering, wet dog shakes, vocalization on touch, and total withdrawal score	β-Carboline (20 mg/kg) decreased the total withdrawal score, chewing, diarrhea, grooming penile licking, rearing, and teeth chattering. Ibogaine decreased the total withdrawal score, chewing, diarrhea, penile licking, and teeth chattering.
Dzoljic et al. (1988)	Ibogaine (4, 8, and 16 μg). Administered intracerebroventricularly.	Rat	10	Precipitated, naloxone (5 mg/kg, i.p.) on day 3	Morphine (85 mg) subcutaneous implant for 3 days	Chewing, diarrhea, digging, ejaculation, grooming, head holding, head shakes, jumping, paw tremor, penile licking, ptosis, rearing,	Ibogaine significantly reduced jumping and salivation (8 and 16 μg), chewing, digging, head hiding, penile licking, rearing, teeth chattering, and writhing (all doses), relative to

(*continued*)

TABLE 7—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
						rhinorrhea, salivation, scratching, stretching, teeth chattering, urination, vocalization on touch, wet dog shakes, and writhing	cerebrospinal fluid control condition.
Francés et al. (1992)	Ibogaine (30 mg/kg). Administered intraperitoneally.	Mouse	5–32	Precipitated, naloxone (5 mg/kg, i.p.) on day 1, 2, 3, 4, or 5 (varied based on group)	Escalating morphine doses up to 100 mg/kg, i.p., for up to 5 days (varied based on group)	Body shakes, body weight, dropping, diarrhea, and jumping	Ibogaine (30 mg/kg) increased jumping and did not decrease any withdrawal signs.
Glick et al. (1992)	Ibogaine (20, 40, and 80 mg/kg). Administered intraperitoneally.	Rat	7–17	Precipitated, naltrexone (1 mg/kg, i.p.) on day 6	Morphine (50 mg) subcutaneous implant for 5 days	Burying, diarrhea, grooming, paw shaking, teeth chattering, and wet dog shakes	Ibogaine decreased diarrhea, teeth chattering, and wet dog shakes (40, 80 mg/kg), and grooming (all doses).
Hine et al. (1975a)	Cannabidiol (10 mg, kg). Administered intraperitoneally	Rat	7	Precipitated, naloxone (4 mg/kg, i.p.) on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Abnormal posture, chewing, defecation, diarrhea, ear blanching, ptosis, teeth chattering, vocalization, wet dog shakes, and total withdrawal score	Cannabidiol (10 mg/kg) had no effect.
Hine et al. (1975c)	THC (2 mg/kg), cannabidiol (10 mg/kg), THC (2 mg/kg) + Cannabidiol (10 mg/kg). Administered intraperitoneally.	Rat	8 to 9	Precipitated, naloxone (4 mg/kg, i.p.) on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Abnormal posture, audible grinding, chewing, defecation, escapes, diarrhea, ear blanching, ptosis, teeth chattering, vocalization on touch, wet dog shakes, and writhing	THC (2 mg/kg) decreased total withdrawal scores and defecation, and diarrhea. Cannabidiol alone had no effect. THC (2 mg/kg) + Cannabidiol (10 mg/kg) decreased total withdrawal scores, defecation, ear blanching, escapes, and wet dog shakes.
Kang et al. (2008)	Mirtazapine (3, 10, and 30 mg/kg). Administered intraperitoneally.	Rat	40	Precipitated, naloxone (1 mg/kg, i.p.) on day 10	Morphine 10 mg, s.c., twice a day for 10 days	Body weight, chewing, digging, escape attendance, grooming, rearing, scratching, teeth chattering, and wet dog shakes	Mirtazapine reduced chewing (10 and 30 mg/kg), and escape attendance, grooming, and teeth chattering (all doses). Mirtazepine (10 and 30 mg/kg) reduced total withdrawal score.
Koyuncuoğlu et al. (1990)	Ketamine (0.5 and 1 mg/kg, i.v.), dextromethorphan (1 and 2 mg/kg, i.p.).	Rat	10–16	Precipitated, naloxone (2 mg/kg, i.p.) on day 3	Morphine (225 mg) subcutaneous implant + F16 for 3 days	Defecation, diarrhea, flying jumping, ptosis, teeth chattering, wet dog shakes, and writhing	Ketamine (1 mg/kg) decreased defecation, jumping, and teeth chattering, but increased wet dog shakes. Dextromethorphan (1 mg/kg) decreased flying and teeth chattering, and (2 mg/kg) decreased all signs except writhing.
Leal et al. (2003)	Ibogaine (40 and 80 mg/kg), MK-801 (0.15 and 0.3 mg/kg), ibogaine (40 mg/kg) + MK-801 (0.15 mg/kg). Administered intraperitoneally.	Mouse	10–13	Precipitated, naloxone (5 mg/kg, i.p.) on day 4	Escalating morphine doses up to 225 mg/kg, i.p., by day 3	Jumping	All doses of ibogaine and MK-801 (NMDA antagonist) decreased jumping. Ibogaine (40 mg/kg) and MK-801 (0.15 mg/kg) coadministration decreased jumping at the level observed for the high dose of each drug independently.
Lu et al. (2001)	Venlafaxine (10 and 20 mg/kg). Administered intraperitoneally.	Rat	12		Escalating morphine doses up to	Body weight, diarrhea, exploring, irritability,	Venlafaxine (10 and 20 mg/kg) decreased diarrhea, exploring,

(*continued*)

TABLE 7—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
				Precipitated, naloxone (2 mg/kg, i.p.) on day 5	40 mg/kg, s.c., by day 5	jumping, lacrimation, piloerection, ptosis, teeth chattering, wet dog shakes, and writhing	jumping, piloerection, and shakes. Venlafaxine (20 mg/kg per kilogram) also decreased irritability, lacrimation, wet dog shakes, and writhing.
Mash et al. (2016)	Noribogaine (10, 30, 56, and 100 mg/kg). Intragastric administration	Mouse	5–11	Precipitated, naloxone (3 mg/kg, i.p.) on day 4	Escalating morphine doses up to 75 mg/kg, s.c., for 4 days	Body tremors, diarrhea, jumping, and paw tremors	Noribogaine decreased body tremors (30 and 100 mg/kg), paw tremors (100 mg/kg), and jumping (30, 56, and 100 mg/kg).
Panchal et al. (2005)	18-MC (5, 10, and 25 μg/1 μl). Infused into intramedial habenula, locus coeruleus, or interpeduncular nucleus.	Rat	5–10	Precipitated, naltrexone (1 mg/kg, i.p.) on day 8 (immediately following intracerebral drug infusion)	Escalating morphine doses up to 80 mg/kg, s.c., 7 days	Burying, diarrhea, grooming, rearing, teeth chattering, and wet dog shakes	Intramedial habenula 18-MC decreased body weight loss (10 μg) and burying (10 μg). Teeth chattering decreased at 5 μg and increased at 10 μg. Intralocus coeruleus 18-MC dose decreased diarrhea (10 μg), burying (all doses), teeth chattering (5 and 20 μg), and wet dog shakes (10 μg). Intrainterpeduncular nucleus 18-MC decreased burying (5 μg) and rearing (10 μg) and increased diarrhea (5 μg) and teeth chattering (20 μg).
Parker and Siegel (2001)	Ibogaine (40 mg/kg). Administered intraperitoneally.	Rat	28 total (individual group size NR)	Precipitated, naloxone (1 mg/kg, s.c.) on day 3	Morphine (20 mg/ml) subcutaneous implant for 2 days	Mouth movements, penile licking, rearing, teeth chattering, and wet dog shakes	Ibogaine (40 mg/kg) decreased mouth movements, penile licking, and teeth chattering.
Rho and Glick (1998)	18-MC (10, 20, or 40 mg/kg). Administered intraperitoneally.	Rat	6–8	Precipitated, naltrexone (1 mg/kg, i.p.) on day 8	Escalating morphine up to 140 mg/kg, s.c., for 7 days	Body weight, burying, diarrhea, flinching, grooming, teeth chattering, and wet dog shakes	18-MC decreased body weight loss (40 mg/kg), burying (20 and 40 mg/kg), diarrhea (40 mg/kg), teeth chattering (20 and 40 mg/kg), and wet dog shakes (20 mg/kg).
Schreiber et al. (2003)	Mianserin (25 mg/kg), trazodone (50 mg/kg), mianserin (25 mg/kg) + trazodone (50 mg/kg). Administered subcutaneously.	Mouse	>10	Precipitated, naloxone (1 mg/kg, s.c.)	High morphine group: escalating morphine up to 160 mg/kg, s.c., by day 8; low morphine: escalating morphine up to 40 mg/kg, s.c., by day 8	Grooming, jumping, and rearing	Mianserin (25 mg/kg), trazodone (50 mg/kg), and mainserin (25 mg/kg) + trazodone (50 mg/kg) combination reduced jumping, rearing, and grooming in both high and low morphine groups.
Sharpe and Jaffe (1990)	Ibogaine (5, 10, 20, and 40 mg/kg). Administered subcutaneously.	Rat	6	Precipitated, naloxone (0.5 mg/kg, s.c.) on day 3	Morphine (75 mg) subcutaneous implant for 3 days	Activity, grooming, lacrimation, mouth movement, paw shakes, penile licking, rhinorrhea, salivation, stretching, teeth chattering, wet dog shakes, and total withdrawal score	Ibogaine decreased grooming (10 mg/kg) and increased teeth chattering (5 mg/kg).
Streel et al. (2005)	Ketamine (2.5 mg/kg), Midazolam (0.25 mg/kg). Administered intramuscularly	Rat	10	Precipitated, naloxone (1 mg/kg, s.c.) on day 3,	Escalating morphine up to 150 mg/kg, s.c., for 3 days	Abnormal posture, cheek tremors, defecation, escape attempts, head	Ketamine (2.5 mg/kg) decreased defecation, urination, and total withdrawal scores. Midazolam

(*continued*)

TABLE 7—*Continued*

Reference	Drugs Evaluated for Opioid Withdrawal Outcomes (Dose and Route)	Species	Sample Size	Withdrawal Method	Dependence Method	Withdrawal Signs Assessed	Summary of Withdrawal-Specific Results
				administered three times (total daily dose 3 mg/kg, s.c.)		lift, jumping, mastication, salivation, sniffing, teeth chattering, urination, vocalization on touch, wet dog shakes, and total withdrawal score	(0.25 mg/kg) decreased urination and total withdrawal scores.

pCPA, *para*-chlorophenylalanine; 18-MC, 18-methoxyroconaridine; NR, not reported.

1999), and pretreatment with the $mGlu_{2/3}$ receptor agonist ACPT-1 decreased jumping, wet dog shakes, and tremors (Pałucha-Poniewiera et al., 2009). The mGlu antagonists MCPG (nonselective), MCCG ($mGlu_{2/3}$), MAP4 (mGlu 4, 6, 7, and 8), and MPEP or MTEP ($mGlu_5$ antagonists) reduced several withdrawal signs including jumping, lacrimation, ptosis, and wet dog shakes, as well as time spent in withdrawal (Fundytus et al., 1997; Rasmussen et al., 2005; Kotlinska and Bochenski, 2007). Evidence of $mGlu_1$ receptor antagonists are mixed; while the $mGlu_1$ antagonist (*S*)-4C-PG reduced teeth chattering and writhing (Fundytus and Coderre, 1994), the $mGlu_1$ antagonist EMQMCM did not significantly modify overall opioid withdrawal scores (Kotlinska and Bochenski, 2007).

Human Withdrawal. Several studies have examined glutamatergic agents in humans. One series of three case studies reported that withdrawal improved in patients who were transitioned from clonidine to topiramate (Zullino et al., 2002). A second case report found that patients treated with topiramate required fewer concomitant medications during detoxification (suggesting they had lower severity opioid withdrawal) relative to patients treated with other medications (Zullino et al., 2004). Empirical studies support these reports. For instance, the NMDA-antagonist memantine and the partial μ-agonist buprenorphine suppressed opioid withdrawal at comparable levels in a randomized trial, although buprenorphine was significantly more effective when only subjective ratings were evaluated (Jain et al., 2011). Memantine also reduced naloxone-precipitated withdrawal severity in patients with OUD (Bisaga et al., 2001). Dextromethorphan has also been evaluated in randomized studies. The first study observed no difference in withdrawal suppression between dextromethorphan and placebo, although the authors thought a benefit of dextromethorphan might have started to emerge during the protracted period (Lin et al., 2014). The second study found that dextromethorphan + clonidine resulted in a more mild withdrawal syndrome than clonidine alone (Malek et al., 2013), and the third study found no difference between dextromethorphan + quinidine and placebo (Akerele et al., 2008).

Medications with Multiple Mechanisms of Action

Several preclinical and the majority of human studies examining medications for opioid withdrawal management have evaluated medications that act through multiple transmitter systems, which precludes determination as to what system might be mediating the observed effects on withdrawal. However, given that the majority of medications approved for use in humans act on several systems, it is important that these studies be reviewed.

Preclinical Withdrawal. Most medications reviewed herein have prominent 5-HT effects and show positive signals for opioid withdrawal management. First, buspirone, which has strong affinity for the $5\text{-}HT_{1A}$ receptor and moderate antagonist affinity at the D_3 and D_4 receptors, attenuated opioid withdrawal symptoms in rhesus monkeys (Aceto and Bowman, 1993) and rats (Berthold et al., 1989). Second, venlafaxine (an antidepressant that inhibits 5-HT and 5-HT noradrenergic reuptake) decreased jumping, hyperactivity, writhing, ptosis, lacrimation, and gastrointestinal symptoms in rats (Lu et al., 2001). Third, mirtazapine (a $5\text{-}HT_2$ and $5HT_3$

TABLE 8

Summary of human empirical studies on the opioid withdrawal syndrome

Note that only outcomes directly related to opioid withdrawal severity are discussed. Studies may have reported additional outcomes not presented here. All medications administered via oral route unless noted. Participants in all studies had OUD unless noted. Results from all participants are reported unless noted.

Reference	System	Medication + Dose	Design	Comparator	Sample Size	Male	Withdrawal Type	Additional Ancillary Medications Given	Primary Withdrawal-Specific Outcome	Result
						%				
Akerele et al. (2008)	Glutamate	Dextromethorphan (30 mg/day) + quinidine (30 mg/day)	RCT; randomized, double-blind, placebo controlled	Placebo	31 (22 dextromethorphan + quinidine, nine placebo)	68	Spontaneous, withdrawn from morphine (100 mg/day, s.c.) over 4 days	Acetaminophen, antacids (medication and doses NR)	MHOWS, VAS	Dextromethorphan (30 mg/day) + quindine (30 mg/day) did not differ significantly from placebo on any withdrawal measure (MHOWS).
Amiri et al. (2014)	Multiple mechanisms	Amantadine (200 mg/day) + clonidine (0.4–1.2 mg/day)	RCT; randomized, double-blind, controlled	Clonidine (0.4–1.2 mg/day)	69 [only completer sample (n = 60) reported: 30 amanatadine + clonidine, 30 clonidine]	100	Spontaneous, withdrawal from illicit opioids over 3 days	Clonazepam (1 mg), acetaminophen (500 mg)	COWS	Data from 60 completers. Amantadine (200 mg/day) + clodine (0.4–1.2 mg/day) reduced withdrawal severity significantly more than clondine (0.4–1.2 mg/day).
Bisaga et al. (2001)	Glutamate	Memantine (60 mg/day)	Human laboratory study; Modified multiple baseline, between-subjects comparison	Placebo	Eight (four memantine, four placebo)	75	Precipitated (naloxone, 0.4 mg, i.m.) after 4–7 days of stabilization on morphine (30 mg, four times a day)	NR	CINA, OOWS, SOWS	Memantine (60 mg/day) significantly reduced CINA and OOWS ratings of withdrawal relative to placebo when administered 6 and 54 (but not 126) hours after naloxone. Memantine also significantly reduced withdrawal AUC relative to baseline. Memantine did not significantly improve SOWS ratings relative to placebo.
Bisaga et al. (2015)	Cannabis	Dronabinol (30 mg/day)	RCT; randomized, double-blind, placebo controlled	Placebo	60 (40 dronabinol, 20 placebo)	85	Spontaneous, withdrawn from buprenophine (8 mg/day) over 2 days transitioned to naltrexone over 4 days	Clonidine (0.8 mg/day), clonazepam (up to SOWS 3.5 mg/day), zolpidem (10 mg/day), and other medicatons (unspecified)	SOWS	Dronabinol (30 mg/day) significantly reduced SOWS ratings relative to placebo during abrupt withdrawal period (days 2–4).
Buydens-Branchey et al. (2005)			RCT; randomized, double-	Placebo	31 (eight placebo, eight	100	Spontaneous, placebo and	NR	OOWS, SOWS	Buspirone (30 mg/day; 45 mg/day) dose

(*continued*)

TABLE 8—*Continued*

Reference	System	Medication + Dose	Design	Comparator	Sample Size	Male	Withdrawal Type	Additional Ancillary Medications Given	Primary Withdrawal-Specific Outcome	Result
	Multiple mechanisms	Buspirone (30 mg/day; 45 mg/day)	blind, placebo controlled, four group design		methadone taper, eight buspirone 30 mg, seven buspirone 45 mg)		buspirone group abruptly discontinued from methadone (30 mg/day); methadone group tapered off methadone (30 mg/day) over 7 days			dependently reduced OOWS and SOWS ratings to placebo. Buspirone 45 mg/day produced the lowest AUC value overall and conferred the most withdrawal suppression.
Chu et al. (2017)	Serotonin	Ondansetron (8 mg, i.v.)	Human laboratory study; double-blind, within-subject, randomized, crossover comparison	Placebo	33 (non-OUD persons with chronic back pain)	61	Precipitated (naloxone, 0.4 mg/70 kg, i.v., or 0.8 mg/70 kg, i.v., if no response to 0.4 mg/70 kg dose)	Docusate sodium (100 mg), metoclopramide (10 mg)	OOWS, SOWS	Ondansetron (8 mg, i.v.) did not significantly reduced naloxone-precipitated withdrawal severity relative to placebo on any measure.
Pérez de los Cobos et al. (2001)	Multiple mechanisms	Amantadine (flexible dosing of 200–300 mg/day)	RCT; two successive randomized, double-blind, placebo controlled trails	Trial 1: placebo, trial 2: methadone taper	Trial 1:40 (19 amantadine, 21 placebo); trial 2: 40 (21 amantadine, 19 placebo). Participants in both trials had OUD and cocaine-use disorder.	81	Spontaneous, withdrawn from methadone (maximum 50 mg/day) over 12 days	Diazepam (dose NR)	Craving VAS, OOWS, SOWS	Amantadine (200–300 mg/day) was not significantly different from placebo on any withdrawal measure in either trial.
Jain et al. (2011)	Glutamate	Memantine (20 mg/day)	Human laboratory study; randomized, double-blind, placebo controlled	Buprenorphine (2 mg, SL)	62 [only completer sample (n = 45) reported; 25 memantine, 20 buprenorphine]	100	Precipitated (naloxone, 0.4 mg, i.v.) following 5-day stabilization on dextropoxyphene (650 mg day)	Zolpidem (10 mg)	OOWS, SOWS	Data from 45 completers. Buprenorphine pretreatment prior to naloxone challenge significantly decreased SOWS ratings. Neither medication significantly decreased withdrawal as rated by the OOWS.
Jovaiša et al. (2006)	Multiple mechanisms	Ketamine (0.5 mg/kg bolus following by 0.5 mg/kg per hour infusion)	RCT; randomized, double-blind, placebo controlled	Placebo	58 [only completer sample (n = 50) reported: 22	86	Rapid anesthetic-assisted detoxification with series of naloxone (1.6	Clonidine (.002 mg), carbamaapine (200 mg),	OOWS	Data from 50 completers. Ketamine infusion significantly reduced OOWS ratings to

(*continued*)

TABLE 8—*Continued*

Reference	System	Medication + Dose	Design	Comparator	Sample Size	Male	Withdrawal Type	Additional Ancillary Medications Given	Primary Withdrawal-Specific Outcome	Result
					ketamine, 28 placebo]		mg, i.v.), naloxone (0.8 mg/h, i.v., infusion), and then naltrexone (100 mg via oro-gastric tube) under isofurane anesthesia	clonazepam (2 mg)		placebo during the first and second, but not third hour postanesthesia.
Lin et al. (2008)	Multiple mechanisms	Venlafaxine (300 mg/day)	RCT; randomized, double-blind, placebo controlled	Placebo	34 (15 venlafaxine, 19 placebo)	88	Spontaneous, withdrawn from illicit opioid use over 7 days using lorazepam (1 mg/day), fexofenadine hydrochloride (240 mg/day), flurazepam (30 mg/day), trazodone (100 mg/day)	Chlorpromazine (dose NR); clonidine (0.075 mg), ibuprofen (400 mg), metoclopramide hydrochloride (10 mg), loperamide (2 mg)	OOWS, VAS for withdrawal, time spent sleeping, and ancillary medication utilization	Data from 20 completers reported. Participants who received venlafaxine (300 mg/day) had significantly reduced OOWS and VAS ratings and more sleep relative to placebo. Venlafaxine participants also requested fewer ancillary medications.
Lin et al. (2014)	Multiple mechanisms	Dextromethorphan (240 mg/day)	RCT; randomized, double-blind, placebo controlled	Placebo	80 [only completer sample (n = 65) reported; 33 dextromethorphan, 32 placebo]	97	Spontaneous, withdrawn from illicit opioid use over 7 days using clonidine (0.075–0.3 mg/day), lorezepam (1 mg/day), fexofenadine hydrochloride (240 mg/day), nitrazepam (30 mg/day), trazodone (100 mg/day)	Ibuprofen (400 mg/day), lorezepam (1 mg/day), metoclopramide hydrochloride (10 mg/day), loperamide (2 mg/day), trazodone, flurazepam, or chlorpromazine (doses NR); none provided on session days	OOWS, time spent sleeping, and ancillary medication utilization	Data from 65 completers (33 dextromethorphan, 32 placebo) reported. Dextromethorphan (240 mg/day) significantly reduced OOWS ratings relative to placebo on Days 3–6. No group differences observed on time spent sleeping or ancillary medication utilization.
Lofwall et al. (2016)	Cannabis	Dronabinol (5, 10, 20, and 40 mg/day)	Human laboratory study; randomized, double-blind, within-subject, placebo controlled	Placebo, oxycodone (30, 60 mg/day)	18 [only completer sample (n = 12) reported]	50	Spontaneous, discontinued from oxycodone (120 mg/day) for each day-long session	None provided on session days	Opioid agonist/antagonist scale, OOWS, short opiate withdrawal scale	Data from 12 completers. Oxycodone decreased all withdrawal ratings. Dronabinol (20, 30 mg/day) significantly reduced withdrawal ratings on the antagonist, OOWS, and short opitate withdrawal

(*continued*)

TABLE 8—*Continued*

Reference	System	Medication + Dose	Design	Comparator	Sample Size	Male	Withdrawal Type	Additional Ancillary Medications Given	Primary Withdrawal-Specific Outcome	Result
										scales relative to placebo.
Malek et al. (2013)	Glutamate	Dextromethorphan (300 mg/day) + clonidine (0.4–1.2 mg/day)	RCT; randomized, double-blind, controlled	Clonidine (0.4–1.2 mg/day)	60 (30 dextromethorphan + clonidine, 30 clonodine)	100	Spontaneous, withdrawal from illicit opioid use using clonidine (0.4–1.2 mg/day), clonazepam (3 mg/day), acetaminophen (2000 mg/day) over 3 days	NR	COWS	Dexotromethorphan (300 mg/day) + clonidine significantly reduced ratings at 24, 48, and 72 hours relative to clonidine alone.
Pozzi et al. (2000)	Multiple mechanisms	Trazodone (600 mg/day)	RCT; randomized, single-blind design	Clonidine (0.45–0.9 mg/day)	45 (30 trazodone, 15 clonidine)	80	Spontaneous, withdrawn from methadone (20 mg/day) over 3 days transitioned to naltrexone over 4 days	Ranitidine (450 mg/day), flurazepam (30 mg), methoclopramide (doses NR), ketorolac or diclofenac (doses NR)	Study-specific observer (12 items) and self-report (13 items) withdrawal rating scales	Trazodone (up to 600 mg/day) significantly reduced self-reported withdrawal relative to clonidine during the first two taper days, no group differences in observer ratings of withdrawal.
Rose et al. (2003)	Multiple mechanisms	Buspirone (30 mg/day)	RCT; randomized, double-blind, placebo controlled	Placebo	20 (group sample size NR)	100	Spontaneous, abruptly discontinued from methadone (mean dose 95 mg/day) over 6 days	NR	OOWS, SOWS	Buspirone (30 mg/day) significantly reduced OOWS ratings on days 5–7 and 9, and SOWS ratings on day 8, relative to placebo.
Srisurapanont and Jarusuraisin (1998)	Multiple mechanisms	Amitriptyline (up to 100 mg/day)	RCT; randomized, double-blind, parallel design	Lorazepam (up to 4 mg/day)	27 (13 amitriptyline, 14 lorazepam)	100	Spontaneous, abruptly discontinued from methadone (M does 95 mg/day) over 6 days	Analgesis, nonsterois anti-inflammatory drugs (specific medications and doses NR)	Short opiate withdrawal scale and sleep evaluation question naire	Amitriptyline (up to 100 mg/day) did not differ significantly from lorazepam (up to 4 mg/day) on any withdrawal outcome. Amitriptyline produced lower ratings on the ease of awakening from sleep; subscale of the sleep evaluation questionnaire relative to lorazepam.

AUC, area under the curve; CINA, clinical inventory narcotic activity; COWS, clinical opiate withdrawal scale; MHOWS, modified Himmelsbach opioid withdrawal scale; NR, not reported; OOWS, objective opioid withdrawal scale; RCT, randomized controlled trial; SL, sublingual; SOWS, subjective opiate withdrawal scale; VAS, visual analog scale.

TABLE 9

Summary of non-experimental human studies on the opioid withdrawal syndrome

Note that only outcomes directly related to opioid withdrawal severity are discussed. Studies may have reported additional outcomes not presented here.

Reference	System	Medication	Study Type	Sample Size	Male	Result
					%	
Alper et al. (1999)	Multiple mechanisms	Ibogaine	Retrospective chart review	33	67	Ibogaine (mean = 19.3 ± 6.9 mg/kg) reduced withdrawal severity within 24 hours among 75% of individuals.
Birch (1889)	Cannabis	Cannabis	Case report	1	100	Cannabis reduced opioid withdrawal severity.
Brown and Alper (2018)	Multiple mechanisms	Ibogaine	Prospective cohort study	30	83	Ibogaine (mean = 1540 ± 920) reduced SOWS ratings from mean = 31 to mean = 14 within 3 days. Fifty percent of individuals reported opioid abstinence at 1-month follow-up.
Davis et al. (2017)[a]	Multiple mechanisms	Ibogaine	Survey (online)	88	73	Individuals stated ibogaine reduced or eliminated withdrawal symptoms (80% of respondents), led to sustained opioid abstinence (30%), and produced sustained reductions in opioid craving (25%).
Epstein and Preston (2015)	Cannabis	Cannabis	Secondary outcome from RCT	116	53	Participants completing a methadone-assisted taper (10-weeks) who did (n = 46) or did not (n = 70) provide a urine sample testing positive for cannabis during the treatment did not vary in their ratings of opioid withdrawal severity during the parent trial.
Gossop et al. (1991)	Cannabis	Cannabis	Retrospective chart review	50	70	Cannabis increased (24% of respondents) or decreased (12%) opioid withdrawal severity.
Lalanne et al. (2016)[b]	Multiple mechanisms	Ketamine	Case report	1	0	Patient reported ketamine (1 mg/kg) successfully assisted taper off opioid medications.
Malcolm et al. (2018)	Multiple mechanisms	Ibogaine	Retrospective chart review	50	61	Ibogaine (dose NR) eliminated ratings on COWS (78% of individuals), SOWS (68%), and opioid craving (79%) 2 days after abrupt opioid discontinuation.
Pinkofsky et al. (2005)	Multiple mechanisms	Quetiapine	Survey (quality assurance)	107	45	Quetiapine reduced cravings (74% of individuals), anxiety (49%), somatic pain (22%), and insomnia (21%), and improved appetite (13%). Only 4% felt quetiapine had no effect.
Quinlan (2012)[a]	Multiple mechanisms	Ketamine	Case report	11	NR	Patients who received ketamine-assisted opioid detoxification reported ketamine was well-tolerated. Patients reported feeling better after 2 months (73% of respondents) and remained abstinent from opioids at 6 months (27%).
Sheppard (1994)	Multiple mechanisms	Ibogaine	Case report	7	71	Ibogaine (700–1800 mg) reduced opioid withdrawal severity at 24–38 hours.
Strickler et al. (2018)[b]	Multiple mechanisms	Ketamine	Case report	1	100	Ketamine (10 mg/h infusion) + clonidine patch used to successfully taper patient off opioids over 7-day period.
Wakim (2012)[b]	Serotonin	Ondansetron	Case report	1	0	Ondansetron (16 mg/day) used to successfully taper patients off opioids over 10-day period.
Zullino et al. (2002)	Glutamate	Topiramate	Case report	3	67	Topiramate (up to 500 mg/day) used to successfully taper patients off opioids over 9–14 day period.

COWS, clinical opiate withdrawal scale; NR, not reported; RCT, randomized controlled trial; SOWS, subjective opiate withdrawal scale.

[a]Patient population had chronic opioid use (population unspecified).

[b]Patient population comprised of persons with acute or chronic pain and opioid use disorder.

receptor family antagonist that also blocks adrenergic autoreceptors) reduced wet dog shakes, rearing, and grooming in rats (Kang et al., 2008). Fourth, the tetracyclic mianserin, which antagonizes 5-HT and adrenergic receptors, and trazodone (a 5-HT antagonist and reuptake inhibitor) both reduced jumping, hyperactivity, and grooming in mice, although combining the two medications together did not increase either drug's effect (Schreiber et al., 2003). However, the cannabinoid cannabidiol (an inverse agonist at the CB_1 and cannabinoid type 2 receptors), which also acts as a $5HT_{1A}$ agonist (an allosteric modulator of μ- and δ-opioid receptors) and a positive modulator of the transient receptor vanilloid-1 (Kathmann et al., 2006), did not reduce withdrawal when administered alone but did reduce wet dog shakes and gastrointestional distress when coadministered with THC (Hine et al., 1975a,c). Finally, neither spiroperidol nor haloperidol, two antipsychotic medications with dual action as 5-HT (subtype unknown) and D_2 receptor antagonists, had an effect on withdrawal-related jumping (Berthold et al., 1989).

Several additional preclinical studies have examined whether medications with primary NMDA receptor activity reduce withdrawal severity. The most frequently researched compound is ibogaine, an NMDA antagonist that binds to κ-opioid and $\sigma 2$ receptors and inhibits nicotine receptors as well as 5-HT and DA transport (Mach et al., 1995; Alper, 2001; Bulling et al., 2012). Numerous studies have suggested that ibogaine, its primary metabolite noribogaine, and a related congener 18-methoxyroconaridine, decrease some opioid withdrawal symptoms in preclinical models (Dzoljic et al., 1988; Sharpe and Jaffe, 1990; Glick et al., 1992; Cappendijk et al., 1994; Rho and Glick, 1998; Parker and Siegel, 2001; Leal et al., 2003; Panchal et al., 2005; Mash et al., 2016), although at least one study found that ibogaine increased withdrawal severity in mice (Francés et al., 1992). Ketamine, an NMDA receptor antagonist with cholinergic and opioid activity, has also been observed to reduce withdrawal (Streel et al., 2005), although it may not be more effective than dextromethorphan (Koyuncuoğlu et al., 1990).

Human Withdrawal. The vast majority of human studies reviewed herein examined medications that act on the DA, 5-HT, and glutamate systems. A retrospective chart review reported the antipsychotic medication quetiapine, which antagonizes D_2 and 5-HT_2 receptors, benefited 96.3% of the patients undergoing opioid withdrawal, specifically improving opioid craving (73.8%), somatic pain (22.5%), and insomnia (20.5%) (Pinkofsky et al., 2005). Buspirone has also been shown to improve opioid withdrawal symptoms in both an open-label trial of men undergoing withdrawal from methadone (Rose et al., 2003) and in a randomized, controlled comparison of buspirone to placebo in men undergoing withdrawal from methadone (Buydens-Branchey et al., 2005). Amantadine, an NMDA antagonist that increases DA release and inhibits DA reuptake, has been shown in a randomized comparison to suppress more symptoms of withdrawal when coadministered with clonidine, relative to clonidine alone (Amiri et al., 2014). In contrast, a second study that examined amantadine for cocaine use in methadone-maintained patients observed no difference in opioid withdrawal outcomes, although the outcomes may have been impacted by ongoing cocaine (a DA reuptake inhibitor) use in that study (Pérez de los Cobos et al., 2001). An additional study that compared the tricyclic antidepressant amitriptyline (which inhibits norepinephrine and 5-HT reuptake) to the benzodiazepine lorazepam for insomnia management during opioid withdrawal reported no differences between the two medications, although the lack of placebo condition in this study makes it difficult to determine whether either medication improved insomnia (Srisurapanont and Jarusuraisin, 1998). A randomized comparison of trazodone + naltrexone to clonidine + naltrexone for rapid withdrawal from methadone reported trazodone was as effective as clonidine in reducing overall withdrawal symptom severity and outperformed clonidine with regard to insomnia, thirst, and shivers (Pozzi et al., 2000). Finally, a randomized evaluation reported significantly lower withdrawal symptoms among participants who received venlafaxine versus placebo (Lin et al., 2008).

Several studies support targeting the glutamate system for human withdrawal management. For instance, retrospective chart reviews, surveys, and case reports all provide associative evidence that ibogaine reduces the severity of opioid withdrawal in humans (Sheppard, 1994; Alper et al., 1999; Davis et al., 2017; Brown and Alper, 2018; Malcolm et al., 2018), although no empirical studies have been published to formally support these reports. However, the widespread clinical adoption of ibogaine for OUD seems unlikely (Hoelen et al., 2009; Paling et al., 2012; Asua, 2013; Jalal et al., 2013) because it has a very narrow therapeutic window and is dangerous for persons with preexisting cardiovascular problems (Alper et al., 2012) or who plan to combine it with opioids (Mazoyer et al., 2013). Ibogaine also produced significant head and body tremors in many of the studies reviewed herein. Efforts to develop the potentially safer metabolite noribogaine for opioid withdrawal are in the beginning stages and show initial promise (Glue et al., 2015a,b; Mash et al., 2016). Another alternative to ibogaine may be ketamine, which has been supported for opioid withdrawal management in case reports of patients with chronic pain (Quinlan, 2012; Strickler et al., 2018), and a patient with OUD (Lalanne et al., 2016), as well as a randomized study that found it lowered opioid withdrawal significantly more than placebo among patients undergoing rapid naltrexone-assisted detoxification under anesthesia (Jovaiša et al., 2006). The recent FDA approval of the ketamine derivative esketamine for severe depression provides a new potential pathway through which this drug class can be examined for human opioid withdrawal management.

Discussion

The OUD trajectory generally transitions from using opioids for euphoric or pain-relieving qualities to using opioids to avoid withdrawal or craving, and avoidance of withdrawal is believed to motivate continued opioid use despite the potential to incur negative health, financial, judicial, social, and personal consequences. Therefore, opioid withdrawal symptom management is a primary goal of most OUD treatments. This review summarized preclinical and clinical evidence supporting the involvement of the DA, 5-HT, cannabinoid, orexin, and glutamate systems in the opioid withdrawal syndrome. All of the reviewed systems appeared to contribute to some but not all symptoms of withdrawal, suggesting they likely modulate but do not independently drive the opioid withdrawal syndrome. The data reviewed

herein suggest it is unlikely that medications acting on these systems will be better at suppressing withdrawal than an opioid agonist. Rather, these data suggest that medications targeting these systems should be evaluated to determine whether their coadministration with opioid agonists can improve opioid withdrawal management. Empirically evaluating medications that work on these systems can help transition the OUD treatment field from using symptomatic concomitant medications (e.g., nonsteroidal anti-inflammatory drugs) to those supported by a mechanistic understanding of opioid withdrawal.

The fact that methadone, buprenorphine, and naltrexone are FDA approved for OUD treatment does not detract from the value of investigating additional pharmacotherapies for opioid withdrawal management—new medications to reduce opioid withdrawal are still needed. Supervised opioid withdrawal is the most frequently used form of OUD treatment (Jones et al., 2015); however, many patients leave treatment

TABLE 10
Summary of outcomes from preclinical and human empirical studies and prospective targets for evaluation

Neurotransmitter System	Prospective Medication Targets for Evaluation		
	Improved ≥1 Withdrawal Symptom[a]	Did Not Improve Any Withdrawal Symptoms	Approved for Use in Humans and Acts on Transmitter Systems of Interest[b]
Dopamine	Buspirone d-Amphetamine Desipramine Domperidone Flupenthixol Haloperidol L-DOPA Mianserin Pimozide Quetiapine	Sulpride	Acetophenazine Aripiprazole[c] Asenapine Clozapine[c] Domperidone Droperidol Fluphenazine Fluspirilene Iloperidone Loxapine Lurasidone[c] Mesoridazine Methotrimeprazine Metoclopramide Molindone Olanzapine[c] Paliperidone Perphenazine Pimozide Pipotiazine Proclorperazine Risperidone Sulpiride Ziprasidone[c]
Serotonin	Buspirone Cyproheptadine Fenfluramine Glemanserin Mianserin Mirtazapine Lorcaserin Ondansetron Quetiapine Trazodone Venlafaxine	Amitriptyline	Aripiprazole[c] Brexpiprazole Chlorpromazine Clozapine[c] Cyclobenzaprine Cyproheptadine Desipramine Lisuride Lorcaserin Lurasidone[c] Mirtazapine Olanzapine[c] Palonosetron Promethazine Risperidone Vortioxetine Ziprasidone[c]
Cannabinoid	Dronabinol	Cannabidiol	Cannabidiol Nabilone
Orexin	NR	NR	Suvorexant
Glutamate	Amantadine D-Cycloserine Felbamate Ketamine Memantine Noribogaine Topiramate	NR	Acamprosate Phenobarbital Esketamine Guaifenesin Pentobarbital Perampanel Rufinadmide Secobarbital

NR, none reported.
[a]Medications may be listed more than once if they act on multiple systems.
[b]The medications included here are approved for use in humans and could be evaluated for possible opioid withdrawal symptom management. Note that each medication should be assessed for its potential side effect profile and contraindications, and that some medications may have abuse liability or other features that might limit their adoption in clinical settings.
[c]Medication acts on more than one target that may alleviate withdrawal.

prematurely because their withdrawal is not adequately managed and those who complete it experience protracted withdrawal and ongoing cravings (Northrup et al., 2015). This leaves patients at significant risk for relapse and fatal overdose (Degenhardt et al., 2011). Further complicating this issue is the fact that no standardized guidelines for opioid withdrawal exist. Opioid-assisted detoxifications generally coadminister opioids with other concomitant medications to manage emergent withdrawal symptoms, and detoxifications that do not use opioids rely solely on these concomitant medications. Evidence suggests that patients vary considerably in their manifestation of withdrawal (Northrup et al., 2015; Dunn et al., 2018b) and may, therefore, benefit from having a range of mechanistically informed concomitant treatments available. Improved withdrawal management is also critical for improving patient access to extended-release naltrexone, a relapse prevention treatment that blocks exogenous opioid administration and is as effective a treatment as buprenorphine once patients are able to successfully taper off their opioid medications (Tanum et al., 2017; Lee et al., 2018). By increasing patient eligibility for naltrexone, efforts to mechanistically identify concomitant medications during withdrawal could help expand OUD treatment access.

Empirically supported concomitant medications could also be used to help patients who are receiving opioids for chronic pain management, either by augmenting their treatments and potentially reducing their opioid reliance, or by assisting them in transitioning off of long-term opioid therapy in favor of other pain management strategies. For instance, several epidemiologic studies have suggested that medicinal cannabis may produce an opioid-sparing effect (Bachhuber et al., 2014; Bradford and Bradford, 2016; Campbell et al., 2018). This is of major interest in the context of the current opioid crisis, since evidence that chronic opioid exposure may not be an appropriate treatment of pain (Busse et al., 2013) has led to new guidelines recommending patients be transitioned off long-term opioid treatments (Dowell et al., 2016). Notably, interest in the potential opioid-sparing effects of cannabis has prompted several states to legislatively define OUD as an approved indication for medicinal cannabis, despite a lack of empirical support for this approach (Humphreys and Saitz, 2019) and data suggesting cannabis exposure increases the risk of developing OUD (Olfson et al., 2018). Since there are also no standardized guidelines for tapering patients off of their clinically indicated pain medications, a mechanistic understanding of opioid withdrawal symptoms can help support the development of effective pain medication tapering protocols or studies on the opioid-sparing effects of cannabis and other targeted medications.

As shown in Table 10, all of the neurotransmitter systems evaluated here have corresponding medications that are FDA approved for other indications or are being actively investigated in humans, suggesting they could be repurposed for the indication of opioid withdrawal management. Advancing a medication from discovery to market can cost a billion dollars and take more than a decade (Vocci and Ling, 2005; Adams and Brantner, 2006), which is too slow a process to meaningfully impact the current opioid crisis. Examining approved medications for opioid withdrawal will also allow existing data to be leveraged to inform safety, doses, and participant eligibility. Although repurposing a medication may expedite treatment access, the need to examine medications in a randomized design still slows the development process. To circumvent this issue, the use of a human laboratory session to model clinical withdrawal experience could be investigated as a medication development pathway. For instance, a recent study in a human OUD clinical population showed that response to a precipitated naloxone challenge was significantly associated with withdrawal response in a subsequent double-blind randomized and controlled pharmacotherapy examination (Dunn et al., 2018b). A human laboratory model was also used in some of the empirical human studies reviewed herein (Bisaga et al., 2001; Jain et al., 2011; Chu et al., 2017) and has been regularly used to screen medications for alcohol and tobacco use disorders (Perkins et al., 2008, 2013; McKee, 2009; McKee et al., 2012). Together, this evidence suggests that a laboratory model could be a promising method for screening candidate opioid withdrawal medications prior to clinical trial investigations.

This review is complicated by the fact that many of the drugs evaluated preclinically are not yet approved for human consumption; although preclinical and human symptoms cluster into similar categories (as shown in Table 1), they may not directly generalize across species. The studies were also extremely heterogeneous in nature, and despite efforts to systematically review all available literature the diverse manner in which these studies were published and indexed may have resulted in some publications being accidentally omitted. Thus, this paper should be conceptualized as a narrative summary to stimulate future investigations. Finally, despite evidence that many opioid effects may be mediated by gonadal hormones (Huhn et al., 2018) the majority of preclinical and human studies reviewed herein evaluated predominately (and often exclusively) male samples. More research is needed to determine whether medications are equally effective for both sexes, particularly in light of data suggesting hormones impact craving and relapse vulnerability for other drugs of abuse (e.g., Carpenter et al., 2006; Franklin et al., 2008).

In summary, given the scale and impact of the opioid crisis and the vast number of people throughout the world who are prescribed opioids chronically for pain management, there is a pressing need to identify mechanistically informed medications that reduce the severity of opioid withdrawal symptoms. This review provides evidence that several nonopioid systems (DA, 5-HT, cannabinoid, orexin, and glutamate) contribute to opioid withdrawal symptom severity and identifies several potential FDA-approved medications (Table 10) that could be evaluated as concomitant medications for opioid withdrawal management. The repurposing of an existing medication is a less-expensive method for drug development than a discovery-to-market approach, and the familiarity and availability of existing medications may help them to be more readily adopted in clinical settings. Developing a solid mechanistically informed treatment regimen for persons with opioid physical dependence is essential to the advancement of patient care and to improving treatment outcomes for persons experiencing opioid withdrawal.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Dunn, Huhn, Bergeria, Gipson, Weerts.

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