Clinical Trials for Opioid Use Disorder

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Abstract

This chapter describes recent clinical trials for opioid use disorder (OUD), an area that has rapidly accelerated in response to the opioid overdose crisis in the USA and newly appropriated funding. Trials involve a wide range of compounds including cannabinoids and psychedelics, new and existing compounds targeting

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domains emerging from addiction neuroscience, agents repurposed from other indications, and novel strategies including vaccines, enzymes, and other biologicals. In parallel, new formulations of existing compounds offer immediate promise, as do a variety of web-based interventions and smartphone-delivered apps. Trials focused on implementing existing effective interventions in mainstream healthcare settings, and others focused on special populations, e.g., adolescents, criminal justice, pregnant women, native Americans, etc., have the potential to vastly expand treatment in the near term. Given the range of ongoing and recent trials, this chapter is not intended to be an exhaustive review but rather to present an overview of approaches within the framework of the opioid treatment cascade and the context of current OUD pharmacotherapies.

Keywords
Addiction · Clinical trial · Opioid · Opioid use disorder

1 Background

Well before modern pharmacology, and even pharmacology itself, opioids were widely used, and it is likely that the ancients had an intuitive grasp of concepts now described as tolerance, dependence, withdrawal, and craving, which now form the underpinnings of our understanding of addiction and its treatment. More deliberate, empirical behavioral and pharmacological approaches to understanding and treating opioid addiction began with work in the early part of the past century led largely by the Addiction Research Center in Lexington, KY, and work done in the middle of the past century at The Rockefeller University in NY (Kreek et al. 2002; Kreek and Vocci 2002; Stimmel and Kreek 2000; Kreek 2000). Much of the current impetus and funding for treatment development stems from the present opioid crisis, which is not the first in the USA and, while devastating, of lesser magnitude than that in China in the early to mid-nineteenth century which led to the opium wars.

The present opioid crisis in the USA is really a combination of an urban minority heroin epidemic dating back to the mid-1900s and a more recent epidemic affecting all sociodemographic groups and rural and suburban communities, largely attributable to opioid painkiller overprescribing. Recent widespread availability of exceptionally potent fentanyl(s), which currently contributes to more than 80% of deaths in some regions of the country, has greatly increased overdose fatalities. This is also a global problem: the World Health Organization reported that roughly 450,000 people died worldwide as a result of drug use in 2015, and of those deaths, about 160,000 were directly associated with drug use disorders and about 118,000 with opioid use disorders (WHO 2019).

Currently, drug overdoses (most of them opioid-related) are killing more Americans each year than died at the peak of the HIV epidemic or during the entire 20-year duration of the Vietnam conflict. Geographic hotspots include northern New England, Appalachia and the Ohio Valley, Florida and the Gulf Coast, the Southwest, Northern California and the Pacific Northwest, and the Canadian border, but virtually every state has pockets of high use and high morbidity. Over the past

decade, painkiller prescribing and related overdose fatalities have declined as its causative role has become more widely recognized; however prescription opioids continue to play a role in initiation. Many of those starting on pills now switch to heroin and fentanyl(s), largely because of the scarcity and high "street" cost of the former and the increased availability and lower cost of the latter (heroin prices are nearly an order of magnitude lower than a decade ago).

This led to the launch of a broad effort supported by federal, state, and local agencies and by industry, philanthropy, and public-private partnerships to develop new molecular entities working via opioid and non-opioid mechanisms; to develop new formulations of existing effective pharmacotherapies; to develop behavioral interventions, devices, and mHealth applications; and to vastly expand access to effective interventions by expanding their implementation from addiction specialty settings to mainstream healthcare settings such as primary care, HIV clinics, and emergency departments and also to criminal justice and other community settings. While this chapter will focus primarily on pharmaceutical clinical trials, we will touch on all of these areas insofar as other approaches may have equal or greater public health impact.

This chapter will first review currently used OUD treatments to contextualize recent and current clinical trials. The latter encompass a diverse suite of interventions, reviewed in the following order: novel pharmacotherapies, including new compounds and repurposing of drugs approved for other indications; vaccines and other biologicals; new formulations of existing compounds aimed to improve drug delivery; trials to expand use of existing marketed agents and new models of care; the National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) initiative; trials aimed at special risk populations; and devices, apps, and behavioral interventions intended to expand and improve treatment. This is not an exhaustive review of all OUD clinical trials but rather is intended to include the major and, in our opinion, most promising drugs and interventions. Throughout, current and developing OUD treatments are contextualized in terms of molecular targets (e.g., opioid receptors, dopamine receptors, transporters, etc.), clinical targets (e.g., craving, withdrawal, relapse, etc.), and targets defined by the "opioid treatment cascade" (Williams et al. 2018) (e.g., treatment engagement, initiation, retention, re-engagement, etc.). For novel drugs, findings are included that are relevant to how these agents impact neurobiological addiction domains such as negative affect or cognitive and emotional regulation (Koob and Volkow 2016; Volkow et al. 2018). A summary then discusses the scope of current treatments and clinical trials and highlights limitations and areas for further development.

2 Current OUD Pharmacotherapies

Current OUD pharmacotherapies are nearly all opioid based, i.e., their efficacy depends on actions at the mu opioid receptor. These include methadone, a full mu receptor agonist; buprenorphine (BUP), a partial mu receptor agonist; and naltrexone (NTX) and naloxone (NX), full mu receptor antagonists. Methadone and BUP are

the cornerstones of opioid *maintenance therapy*. In contrast, NTX, particularly in its extended-release formulation, is approved for *relapse prevention*. NX, a short-acting mu antagonist, is used primarily for acute *overdose reversal*. Beyond these, there are a handful of non-opioid medications that are often used to mitigate the aversive symptoms of opioid withdrawal and to facilitate detoxification. These include clonidine and lofexidine, both alpha-2 agonists, muscle relaxants, and sleep medications. Methadone, BUP, and NTX are sometimes referred to as "MAT" for "medication-assisted therapy". This terminology is rejected by some who believe that medication *is* therapy in and of itself, instead preferring to rebrand MAT as "medication addiction therapy"; this term then evolved to "MOUD" for "medication for opioid use disorder". We will also use the term "addiction pharmacotherapy."

Although all three of the opioid addiction pharmacotherapies owe their efficacy to actions at the mu receptor, there are striking pharmacological, philosophical, logistical, economic, and societal differences between them. Agonists (methadone and BUP) replace opioids at the receptor, thereby preventing craving, withdrawal, and other effects of addiction while at the same time maintaining tolerance and dependence and leading to withdrawal on discontinuation. At high doses, methadone, due to its full agonist properties, blocks the effects of all but extremely high doses of heroin or other opioids and blunts the "rush" even from high doses (Kreek et al. 2002; Kreek and Vocci 2002; Stimmel and Kreek 2000; Kreek 2000). BUP accomplishes the same due to its high mu receptor affinity and its partial mu agonist and kappa antagonist properties (Gowing et al. 2017; Nielsen et al. 2016; Mattick et al. 2014). In contrast, naltrexone, a full mu receptor antagonist with no agonist properties, is devoid of opioid-like effects and does not maintain tolerance or dependence, i.e., in contrast to agonists, there are no subjective consequences upon discontinuation (Krupitsky et al. 2011).

There are striking and important differences in transitioning from opioid misuse to treatment with each of these medications ("induction"). Because it is a full receptor agonist, patients misusing opioids can simply begin taking methadone at a low dose and begin to increase toward a "blocking" dose, usually considered to be in the 80–100 mg/day range. BUP, a partial agonist, has a very high affinity for the mu receptor and will displace most full agonists, precipitating withdrawal symptoms; hence BUP shouldn't be started until a patient has abstained from opioid use for hours to a day or so (depending on the half-life of the opioid being used) and is experiencing at least mild to moderate withdrawal symptoms, at which point BUP can be administered and escalated to an effective dose, usually considered to be in the 8–24 mg/day range. At the other extreme is NTX which should not be administered until all or nearly all opioid is washed out, usually requiring several days to several weeks of detoxification. The need for full or nearly full detoxification adds costs (frequently including inpatient care), and because many patients don't tolerate detoxification and walk away, a substantial proportion of patients intending to start naltrexone are lost before they get a first dose. Fortunately, there are recent and ongoing clinical trials aimed at facilitating and hastening NTX induction.

Because agonists can be abused, there are diversion risks and controlled substance restrictions (in some cases quite burdensome); neither is the case for antagonists. From a societal and a family perspective, it is sometimes perceived to be important to be "drug-free" meaning "opioid agonist-free" which precludes methadone and BUP and which can only be achieved via "abstinence-based" or "drug-free" programs or with a full antagonist (i.e., naltrexone). Some countries (e.g., Russia) and some systems (e.g., criminal justice systems (CJS) in some jurisdictions) discourage or absolutely prohibit agonist therapy.

These pharmacological and societal differences have led to regulatory restrictions that limit widespread treatment. Methadone is typically administered only in tightly controlled settings that don't and likely won't exist in many parts of the USA and the Russian Federation and, even where they do, are often off-putting to patients. In the USA, BUP can only be prescribed by providers who complete intensive training and obtain a special waiver, a significant barrier, particularly for busy primary care providers. Extended-release NTX (XR-NTX) can be prescribed by any provider and therefore provides a way around this barrier. However, because of the induction hurdle, the absence (until recently) of comparative effectiveness data and high cost, XR-NTX has only infrequently been prescribed. It should come as no surprise that there are long-standing controversies in the field – fueled in part by the absence of data – as to whether pharmacologically and conceptually quite opposite agonist or antagonist approaches are preferable or even acceptable. This is one of many lenses through which clinical trials, development, marketing, and regulation of these three pharmacotherapies should be viewed and the foundation upon which new opioid and non-opioid medications, behavioral therapies, and devices and applications will be built.

Methadone was initially developed in Germany in 1937 by Hoechst chemists seeking synthetic opioids to address Germany's opium shortage. It was marketed shortly thereafter and used widely during the World War II. Following the war, the patent was confiscated by the US Department of Commerce Intelligence and brought to the USA. In 1947 Eli Lilly (and subsequently Roxane Laboratories and Mallinckrodt Pharmaceuticals) began manufacturing methadone as an analgesic under the trade name Dolophine. Yet it was not until the heroin crisis of the 1960s that it was developed as a treatment for opioid addiction, largely by Drs. Vincent Dole, Marie Nyswander, and Mary Jeanne Kreek at The Rockefeller University, often in collaboration with Robert Newman and others at Beth Israel Hospital in NY City (Kreek et al. 2002; Kreek and Vocci 2002; Stimmel and Kreek 2000; Kreek 2000). Methadone is by far the best-studied OUD pharmacotherapy and is the gold standard for treatment. It is used both for short-term detoxification, usually 3–5 days in inpatient or outpatient settings, and for long-term, sometimes lifetime, opioid maintenance therapy in methadone maintenance treatment programs (MMTPs). Methadone maintenance is associated with reduced illicit opioid use, reduced criminality, reduced HIV transmission, reduced morbidity and mortality, and improved physiological and health outcomes, societal functioning, and employment. In the USA and in many other parts of the world, methadone can only be dispensed through

highly regulated MMTPs which limits access geographically and which is perceived by some as being overly controlling and stigmatizing.

Buprenorphine (BUP) was synthesized by Reckitt and Colman (now Reckitt Benckiser) in 1969. It was initially developed as an analgesic lacking some of the undesirable properties of full mu agonists. Clinical trials began in 1971 leading to approval in the UK in 1978 of an injectable formulation and in 1982 for sublingual use. BUP is a partial mu receptor agonist and an antagonist at kappa and delta receptors. Development to treat OUD was begun in the 1990s, initially as a monotherapy (Subutex) and later in combination with naloxone (Suboxone) to prevent diversion. Many of the clinical trials were supported by NIDA in partnership with Reckitt Benckiser and the Department of Veterans Affairs Cooperative Studies Program, through VA CSP trials CS-999, CS-1008, and CS-1018, leading to approval for the present OUD indication in 2002. A specific goal was to develop BUP for "office-based" treatment (in contrast to MMTP clinic-type treatment with all its associated constraints) made possible by its partial agonist properties and the formulation including naloxone, both of which were expected to reduce overdose risk and diversion risk. Current labeling in the USA reflects involvement from the FDA, Drug Enforcement Administration (DEA), Substance Abuse and Mental Health Services Administration (SAMHSA), and other federal and local agencies and, while permitting office-based use, imposes regulatory burdens that are hurdles to more widespread use. In contrast, France (and other countries) allows widespread essentially unrestricted prescribing which had a rapid and dramatic impact on OUD-associated overdose fatalities (Auriacombe et al. 1994; Dupouy et al. 2017). Like methadone, BUP is used both for detoxification (several days) and for long-term maintenance. A focus of much ongoing and planned work is to expand BUP treatment in the community.

Methadone and BUP are classified as Schedule II and III drugs, respectively. While methadone is available by prescription as a pain medication, and commonly used for brief inpatient medical supervised withdrawal in hospital settings, it can be dispensed only at an outpatient opioid treatment program certified by SAMHSA and registered with the DEA or to a hospitalized patient in an emergency. BUP on the other hand is relatively less restricted and is available for outpatient use, and refills can also be provided.

Naltrexone (NTX) was first synthesized in 1963, and although it received FDA approval for opioid dependence in 1984 and for alcohol dependence in 1994, its use and effectiveness in the form of once-a-day tablets for oral administration have been sharply limited by poor adherence. To address this, a longer-acting formulation consisting of NTX embedded in polylactide-co-glycolide microspheres for once-monthly injection (extended-release NTX, XR-NTX) was developed in the 1990s and tested in clinical trials in the USA leading to approval for alcoholism in 2006 (Garbutt et al. 2005). A single trial in Russia led to US approval for opioid addiction in 2010 (Krupitsky et al. 2011). XR-NTX (Vivitrol) is administered by deep intramuscular injection following which naltrexone plasma concentrations rise to a

transient initial peak in a few hours, followed 2–3 days later with a second peak. Plasma concentrations then gradually decrease but usually maintain therapeutic levels for about 4 weeks. It is important to recognize that XR-NTX's FDA labeling is for "relapse prevention," a contrast to BUP's labeling for "maintenance treatment of opioid dependence." There is good efficacy and effectiveness data from across a number of trials conducted in the CJS (Lee et al. 2016; McDonald et al. 2016; Murphy et al. 2017; Lee et al. 2015) which largely rejects agonist interventions, from a large NIDA Clinical Trials Network (NIDA CTN) trial comparing XR-NTX to buprenorphine/naloxone (Lee et al. 2018) and from a smaller parallel Norwegian trial (Tanum et al. 2017) with a similar design. Current clinical trials focus on improving and accelerating induction so as not to lose patients before a first injection and improving retention rates following initial treatment. Additional challenges remain around detoxification costs, XR-NTX costs, and providers' interest and perceived competence in treating OUD.

Naloxone (NX) is a rapidly acting and short-acting opioid receptor antagonist developed in 1961 and approved for use in treating opioid overdose in 1971 (Chou et al. 2017; Robinson and Wermeling 2014; Kim and Nelson 2015; Strang et al. 2016). Until recently it was available primarily in injectable form and used primarily in emergency department settings. Naloxone administration rapidly reverses the effects of opioid agonists and precipitates an acute withdrawal syndrome. As its effects wear off, signs and symptoms of overdose – most importantly respiratory depression, which can be fatal – re-emerge, sometimes requiring repeated administration or constant slow infusion, particularly in the case of overdose from long-acting opioids. More recently, NX has been reformulated for administration via intranasal spray and widely distributed to opioid users (including both addicts and those prescribed potent opioids), families, first responders (fire, police, EMS), and others in affected communities. Ongoing studies including clinical trials are focused on how best to distribute and educate the community to optimize outcomes, i.e., overdose reversals and overall reduction in overdose fatalities. Naloxone in usual doses may not be sufficient in reversing overdose from fentanyl and even higher-potency fentanyl derivatives, and the effects of NX also wear off rapidly. In highly affected regions of the USA, this has strained the budgets of first responder agencies. Wristwatch-like devices in development use biosensors to detect changes in heart rate and respiration and use algorithms to ascertain overdose and activate naloxone auto-injection. These have the potential to save lives in cases of unobserved overdose, yet fear of accidental auto-injection and precipitated withdrawal may sharply limit use.

Clonidine and Lofexidine are alpha-2 adrenergic receptor agonists used to modulate symptoms of opioid withdrawal. Clonidine has been marketed as an antihypertensive agent in the USA since 1966. Clonidine is not approved for opioid withdrawal but has been widely used off-label for this indication since the early 1980s (Gold et al. 1979, 1980a, b; Gold 1993), particularly in settings where opioid

detoxification (methadone or BUP) is not available. Lofexidine (Gorodetzky et al. 2017; Cox and Alcorn 1995; Gowing et al. 2009) was also developed and initially used as an antihypertensive but received FDA approval in 2018 for "mitigation of withdrawal symptoms to facilitate abrupt discontinuation of opioids." Lofexidine was developed for this indication by US WorldMeds and is the first non-opioid approved for use in treating withdrawal symptoms of OUD. Both agents are used for periods of a few days to two weeks. Lofexidine may be less sedating and produce less orthostasis than clonidine, but otherwise there is little difference except in cost.

3 Novel Pharmacotherapies Under Study

3.1 Opioid Receptor Modulators

Nalmefene is a mu opioid receptor antagonist which contrasts with naloxone in also being a delta opioid receptor antagonist and partial kappa opioid receptor agonist. Intravenous (IV) nalmefene was FDA approved in 1995 to treat opioid overdose and then withdrawn from the market in 2008 due to low sales, with no significant safety issues. Nalmefene is also currently approved to treat alcohol use disorder (AUD) in France and the UK. Given nalmefene's longer half-life (6–8 h) and ~5× higher affinity at mu opioid receptors compared with NX (Krieter et al. 2019), it has the potential to address the important goal of developing stronger and longer-acting opioid antagonists (Volkow and Collins 2017) – this need stems from NX's relatively short half-life, necessitating repeated doses in overdose rescue situations. Evidence for the potential of nalmefene in treating opioid overdose in humans is currently limited to IV formulations. A double-blind study in patients reporting to the emergency department with suspected narcotic overdose compared IV nalmefene (1 or 2 mg) with naloxone (2 mg), given every 5 min as needed for up to 4 doses. Nalmefene and NX treatment led to a similar reduction in opioid withdrawal scale scores and improvement in respiratory depression and more nonfatal adverse events in the nalmefene 2 mg group (Kaplan et al. 1999). Toward intranasal (IN) nalmefene formulations, a recent Phase I study (NCT03129347) compared the pharmacokinetic properties of IN nalmefene (3 mg) in the presence of an absorption enhancer dodecyl maltoside to intramuscular nalmefene (1.5 mg) (Krieter et al. 2019). Results showed IN nalmefene with the enhancer had a relatively long half-life compared to NX and a comparable time to peak plasma level, making it suitable for reversing overdose. Studies are also underway to develop a much longer-acting (>28 days) nalmefene prodrug (NRS-033) for OUD treatment as (opposed to overdose reversal) (Grant number UG3DA048234).

3.2 Cannabidiol, THC, and Cannabis

Cannabidiol (CBD) is a phytocannabinoid present in *Cannabis sativa* that is non-psychotomimetic and nonintoxicating and pharmacologically distinct from

tetrahydrocannabinol (THC), the major psychoactive constituent in cannabis. CBD has broad-spectrum pharmacological actions that are not yet fully understood (Zuardi 2008). Those linked to anti-addictive or anxiolytic actions relevant to its potential for treating OUD are detailed below. Several pharma companies have developed purified formulations of CBD with negligible THC content for oral or transdermal delivery; synthetic forms also exist. Epidiolex (pure oral CBD manufactured by GW Pharmaceuticals) was recently FDA approved for the treatment of childhood seizures.

CBD has been evaluated in Phase II and III trials for diverse medical and neuropsychiatric disorders, including nicotine (Morgan et al. 2013) and alcohol addiction (NCT03252756), and showed anxiolytic effects in human laboratory studies (Blessing et al. 2015). Completed clinical trials confirmed CBD's lack of psychotomimetic, intoxicating, and other adverse effects (apart from possible mild sedation and diarrhea) up to high (1,200 mg) repeated doses (Iffland and Grotenhermen 2017). Animal model, human laboratory and clinical trial evidence suggests potential for multiple therapeutic effects, including anti-addictive, anticonvulsive, anxiolytic, antipsychotic, anti-inflammatory, and neuroprotective (Fasinu et al. 2016; Crippa et al. 2018). CBD did not exhibit abuse liability in cannabis users (Babalonis et al. 2017).

CBD has not yet been evaluated for reducing substance use in OUD clinical trials, but has shown promising effects for reducing heroin craving and anxiety in abstinent heroin users. Hurd et al. recently assessed the acute (1, 2, and 24 h), short-term (3 consecutive days), and protracted (7 days after the last of three consecutive daily administrations) effects of oral CBD (400 or 800 mg, once daily for 3 consecutive days) on drug cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder in a double-blind randomized placebo-controlled trial (Hurd et al. 2019): CBD (vs placebo) substantially and significantly reduced both craving and anxiety induced by the presentation of drug cues, with protracted effects. This study replicated results from a smaller pilot study with a similar design (Hurd et al. 2015).

The human laboratory studies add to highly promising rodent model evidence showing CBD's potential to reduce behavioral vulnerabilities that drive relapse. Ren et al. demonstrated that CBD inhibited cue-induced heroin drug-seeking and reinstatement of this behavior in rats, with long-lasting effects (2 weeks) (Ren et al. 2009). In another study, CBD reduced cocaine and ethanol reinstatement with long-lasting effects (months) beyond drug action and also reduced context- and stress-induced ethanol seeking, anxiety, and impulsivity (Gonzalez-Cuevas et al. 2018). Receptor mechanisms linked to CBD's anxiolytic and pro-fear extinction effects include 5-HT_{1a} receptor agonist and indirect cannabinoid 1 receptor (CB1R) agonist actions in the extended amygdala, hippocampus, and medial prefrontal cortex (Blessing et al. 2015). Mechanisms underlying anti-addictive actions are less well studied; however one study showed correction of dependence-related neuroplasticity involved in normalization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) GluR1 and CB1Rs in the nucleus accumbens (Ren et al. 2009). More broadly, CBD has multiple actions within the endocannabinoid system,

which plays a central role in activity-dependent neuroplasticity and closely interacts with the opioid system (Scavone et al. 2013); CBD is also an allosteric modulator of the mu and delta opioid receptors (Kathmann et al. 2006).

Overall, CBD seems to offer promise for reducing relapse and anxiety in OUD, as will likely be explored in further clinical trials. Potential challenges include CBD's capacity, demonstrated in vitro, to inhibit cytochrome P450 enzymes that metabolize several prescribed and recreational opioids including fentanyl (CYP2D6 and CYP34A and others) (Yamaori et al. 2011a, b). Given the genetic variation in these enzymes, rigorous Phase I trials would be necessary to investigate the potential for CBD to increase opioid levels. Clinical trials to address these issues are in planning.

THC (Dronabinol) has also been investigated in humans for treating withdrawal in OUD, based upon findings in animal models showing that CB1 receptor agonists reduce opioid withdrawal symptoms. THC is a partial agonist at the CB1 receptor and, like CBD, is also an allosteric modulator of the mu and delta opioid receptors. Synthetic forms of THC or its analogues (dronabinol) are approved for neuropathic pain and treating nausea and vomiting associated with chemotherapy. In a study of opioid-dependent participants, dronabinol (30 mg/day for 5 weeks) was found to be superior to placebo in reducing withdrawal symptoms during detoxification but did not increase rates of induction onto XR-NTX or treatment retention relative to placebo (Bisaga et al. 2015). In another study of physically dependent opioid users, moderate-to-high doses of dronabinol were associated with elevated heart rate, anxiety, and panic raising safety concerns (Jicha et al. 2015; Lofwall et al. 2016).

Whole Cannabis Pharmacologically, cannabis includes the actions of CBD, THC, and other cannabinoids present in lower amounts. Most recreational cannabis (marijuana) contains minimal CBD and high levels of THC, whereas other cannabis varieties such as hemp (classified as cannabis containing less than 0.3% of THC according to the Agriculture Improvement Act of 2018) can contain upward of 50% CBD. Medical use of cannabis from a designated dispensary for a specified range of conditions is legal in 33 states. Very few or no clinical trials have been conducted with medical cannabis, and limited data are available on the potential therapeutic effects of recreational marijuana use. One clinical trial in 63 opioid-dependent users reported that intermittent marijuana use was associated with greater adherence with naltrexone treatment compared to no use or consistent use (Raby et al. 2009). Several epidemiological studies have suggested that overdose rates and opioid use may be lower in states where cannabis is legalized (Bachhuber et al. 2014; Liang et al. 2018); however, a recent prospective study in the USA showed that cannabis use (according to National Epidemiological Survey on Alcohol and Related Conditions data) was associated with a substantial increase in opioid use 3 years later (Olfson et al. 2018). Ongoing clinical trials are exploring subjective and safety interactions between cannabis and opioid use (NCT03705559); medical marijuana for reducing opioid analgesic use in HIV patients (NCT03268551), and the effects of naltrexone on cannabis use (NCT00403117).

3.3 Psychedelics

Ketamine and Other NMDA Antagonists Ketamine is a nonselective noncompetitive NMDA receptor antagonist (Zorumski et al. 2016) that is approved for use in general anesthesia. Long-lasting (post-drug) therapeutic effects that are observed in treating depression and other disorders suggest disease-modifying effects that are not currently understood (Strong and Kabbaj 2018). Three published studies have evaluated the efficacy of ketamine for OUD-related measures. Krupitsky et al. (Krupitsky et al. 2002) conducted a randomized controlled trial of ketamine-assisted psychotherapy in heroin-dependent participants. They compared the efficacy of high (2 mg/kg IM)- vs low (0.2 mg/kg IM)-dose ketamine with psychotherapy for maintaining abstinence from heroin, delivered at intervals over 24 months. The higher dose was associated with higher rates of abstinence (85%) compared to the lower dose (55%) and a greater reduction in craving. The same authors conducted a follow-up study in which they evaluated single vs repeated sessions of ketamine-assisted psychotherapy for maintaining heroin abstinence (Krupitsky et al. 2007). Repeated treatments were associated with 50% abstinence at 1-year follow-up, compared to 22% of single treatments, and a greater reduction in craving. In 58 opiate-dependent patients, Jovaisa et al. (2006) studied the effects of ketamine (0.5 mg/kg/h infusion) vs placebo on withdrawal symptoms following rapid opiate antagonist induction under general anesthesia, assessed immediately, at 48 h, and at 4 months. Ketamine was associated with reduced immediate and 48 h withdrawal symptoms. At 4 months, there was no difference from placebo. A trial is near completion for CI-581, an NMDA receptor antagonist, to facilitate induction into naltrexone (NCT02437344).

Ibogaine is a psychedelic alkaloid extracted from the root bark of *Tabernanthe iboga* or bark of *Voacanga africana* that has been in tribal ritual use for many centuries. Interest in ibogaine as a treatment for addiction including OUD is long-standing (>50 years), and it was marketed in France (Lambrene) until ~1970, but has never been approved in Europe or the USA for clinical trials, in part because of neuro- and cardiotoxic effects, especially QTc prolongation (Litjens and Brunt 2016; C Mash 2018). It has multiple pharmacological actions that are not fully characterized, including serotonergic, dopaminergic, and glutamatergic, and CYP2D6-mediated drug-drug interactions (Litjens and Brunt 2016). A considerable number of small, uncontrolled, open-label retrospective clinical studies as well as observational studies conducted in countries outside the USA have evaluated the efficacy of ibogaine for reducing withdrawal symptoms and drug use in OUD patients following detoxification. These studies reported promising results: administration of a single ibogaine dose between 10 and 30 mg/kg was associated with substantially reduced withdrawal symptoms including physiological measures – Clinical Opioid Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS) – craving, and drug use, with long-lasting effects (Malcolm et al. 2018; Brown and Alper 2018; Noller et al. 2018). Ibogaine's complex pharmacokinetics and high inter-individual variability in metabolism (Litjens and Brunt 2016;

C Mash 2018) as well as its neuro- and cardiotoxicity remain challenges to further development. Based on preclinical evidence, there is now new focus on 18-methoxycoronaridine (18-MC), an ibogaine analogue specifically developed to be devoid of neuro- and cardiotoxicity. It is an orally active and relatively specific α3β4 nicotinic cholinergic receptor antagonist which indirectly modulates the dopaminergic mesolimbic pathway via actions in the habenulo-interpeduncular pathway and the basolateral amygdala. There are no clinical trials as yet for 18-MC in OUD.

Lysergic Acid Diethylamide (LSD) is a recreationally used classic hallucinogen, the psychoactive effects of which have been linked to serotonergic 2A agonist actions (Preller et al. 2017). One controlled clinical trial of LSD assisted psychotherapy was conducted in OUD patients in the early 1970s (Savage and McCabe 1973). The study was conducted in an outpatient clinic for paroled heroin addicts. Volunteer inmates with heroin addiction were discharged following release from prison and randomized to either an outpatient abstinence-based treatment program of 4–6 weeks of residential treatment in conjunction with high-dose LSD and psychedelic therapy (37 completers), or a control outpatient abstinence-based treatment-as-usual program with group therapy (37 completers). In both groups urine was monitored daily for opioid use. Results were promising: 25% of the treatment group were continuously abstinent during the 12-month follow-up, compared with 5% of the control group.

3.4 Neuropeptides and Neuropeptide Receptor Modulators

Dynorphin is an endogenous ligand for the kappa opioid receptor (KOR), which is widely distributed in the central nervous system. The dynorphin-KOR system plays a central role in modulation of nociception and the stress response, among other diverse physiological roles (Bruchas et al. 2010). Activation of this system is proposed to drive the addiction cycle by increasing stress and negative valence (Koob and Volkow 2016; Koob 2013; Koob et al. 2014). This hypothesis is consistent with findings that KOR activation consequent to dynorphin release increases corticotropin release in the extended amygdala and increases behaviors consistent with averse, dysphoric states; in addition, KOR activation reduces dopamine release in the VTA and glutamate release in the nucleus accumbens (Bruchas et al. 2010). Accordingly, KOR antagonists have been proposed to potentially combat addiction by reducing hyperactivation of the KOR system associated with stress surfeit in withdrawal states or stress-related psychiatric disorders (Butelman et al. 2012). A study evaluating the efficacy of a single dose of IV dynorphin (porcine fragment A 1-13) for reducing craving and other measures during acute withdrawal is near completion (NCT00000244). The rationale for using a partial agonist of the KOR (porcine dynorphin fragment) may be to block activation by endogenous dynorphin and thereby maintain a more constant tone in the dynorphin-KOR system; this hypothesis is based on the understanding that this system is upregulated and sensitized in addiction states (Bruchas et al. 2010; Butelman et al. 2012; Wee and Koob 2010).

Oxytocin is a neuropeptide that is synthesized in the magnocellular neurons of the paraventricular, supraoptic, and accessory magnocellular nuclei of the hypothalamus and released into the bloodstream from the posterior pituitary. Oxytocin regulates a variety of physiological functions and behaviors related to social bonding via dopaminergic interactions, which may contribute to its anti-addictive effects (Kovacs et al. 1998). Results from several clinical trials of oxytocin in AUD and cocaine use disorder have been published but thus far only one study in OUD. In a randomized, double-blind, placebo-controlled crossover study, the efficacy of intranasal oxytocin (40 international units) was evaluated for reducing cue-induced craving and improving measures of social cognition in 36 abstinent heroin-addicted patients who were stable on buprenorphine BUP or methadone (Woolley et al. 2016). Oxytocin did not reduce craving relative to placebo and had mixed effects on social cognition (Woolley et al. 2016). In rodent models of OUD, oxytocin reduced opioid tolerance and stress- and cue-induced drug seeking in dependent animals (Kovacs et al. 1998; Leong et al. 2018). Clinical trials evaluating oxytocin for several OUD indications including craving and withdrawal with concurrent assessment of social cognition are underway (NCT02548728, NCT02028533, NCT03016598, NCT02052258).

Aprepitant is a neurokinin 1 receptor (NK1R) antagonist that is clinically approved as an antiemetic. The NK1R is expressed throughout the reward system and autonomic midbrain and brainstem nuclei (Hargreaves 2002). Aprepitant blocks NK1R activation by the endogenous agonist substance P, which, in addition to reducing the vomiting reflex, modulates nociception (De Felipe et al. 1998), stress responsivity (Commons 2010), and reward behavior (Mannangatti et al. 2017), in part via interactions with opioid, dopaminergic, and serotonergic systems (Sandweiss and Vanderah 2015). Two preliminary human laboratory studies did not support the efficacy of aprepitant for OUD: Walsh et al. assessed subjective and physiologic responses to the mu agonist oxycodone in eight healthy adults who reported prescription opioid misuse, but were not physically dependent, and found that aprepitant (0, 40, and 200 mg, p.o. given as a 2-h pretreatment) substantially *increased* euphoria and liking and physiological effects (Walsh et al. 2013). Jones et al. reported that aprepitant 80 mg p.o. daily over 4 weeks was associated with a trend toward reduction in withdrawal symptoms, but increased methadone liking in 15 OUD subjects maintained on methadone (Jones et al. 2013).

These findings add to mixed results in rodent studies regarding the potential of NK1 antagonists for OUD treatment: these agents reduced naloxone-induced morphine withdrawal syndrome (Maldonado et al. 1993) and attenuated morphine-induced locomotor activity (Placenza et al. 2006), but also increased heroin self-administration (Placenza et al. 2006). Genetic modifications were more promising: NK1R knockout mice had reduced opioid-induced addictive behaviors (Murtra et al. 2000), and ablation of NK1Rs in the amygdala reduced morphine conditioned place preference (CPP) (Gadd et al. 2003). Clinical trials in alcohol use disorder (AUD) have shown some promising results: 4 weeks treatment with 50 mg daily NK1 antagonist LY686017 reduced cue-induced craving and stress-induced cortisol release in detoxified AUD

patients with high trait anxiety (George et al. 2008), and aprepitant 125 mg/day daily over 4 weeks increased ventromedial prefrontal activation to aversive stimuli in subjects with comorbid post-traumatic stress disorder (PTSD) and AUD, but did not affect PTSD symptoms or alcohol craving (Kwako et al. 2015). Further trials in OUD, AUD, and cocaine use disorder are in progress, and mixed opioid receptor agonist/NK1R antagonist compounds targeted for nociception without addictive features are in development (Olson et al. 2017).

3.5 Serotonin Receptor Modulators

Buspirone is a 5-HT_{1a} receptor agonist approved for the treatment of anxiety and depression that has shown initial efficacy in treating opioid withdrawal symptoms. In a small double-blind, placebo-controlled trial (Buydens-Branchey et al. 2005), heroin-dependent subjects undergoing a 5-day methadone taper from their opioid pain medications were randomized to either buspirone 30 mg daily, buspirone 45 mg daily, continuing methadone, or placebo over 12 days. Both 30 mg and 40 mg buspirone doses showed similar efficacy to methadone and greater efficacy than placebo in reducing SOWS and COWS scores. A further clinical trial (NCT03521960) evaluating the efficacy of buspirone for reducing withdrawal symptoms during a supervised taper from opioid pain medications is currently underway.

Ondansetron is a 5-HT_3 receptor antagonist that is marketed as an antiemetic. A double-blind randomized crossover study in chronic back pain patients evaluated the efficacy of ondansetron vs placebo pretreatment in reducing withdrawal symptoms induced by naloxone following treatment with sustained-release oral morphine (Chu et al. 2018). No significant treatment vs placebo differences were observed in objective or subjective opioid withdrawal symptoms. A further trial is underway for withdrawal (NCT01549652).

Lorcaserin is an agonist at the $5HT_{2C}$ receptor that is approved for weight loss. Preclinical studies in nonhuman primate and rodent models show promising effects of lorcaserin: it reduced the reinforcing effects of heroin (Kohut and Bergman 2018) and heroin-induced reinstatement in opioid-dependent rhesus monkeys (Gerak et al. 2019) and reduced naloxone-precipitated withdrawal (Zhao et al. 2016) and oxycodone seeking and reinstatement in mice (Neelakantan et al. 2017). Three studies of lorcaserin are underway in OUD patients: one examining effects on brain activity (NCT03143543), another efficacy when administered in combination with XR-NTX for reducing relapse (NCT03169816), and, a third, subjective responses to oxycodone (NCT03143855).

3.6 Anti-inflammatory and Immunomodulatory Agents

Ibudilast (MN-166), previously AV411, is a proinflammatory cytokine macrophage migration inhibitory factor and phosphodiesterase inhibitor which has been

in use for over 20 years in Japan and some other Asian countries for the treatment of asthma, among other conditions, but is not yet approved outside Asia. A series of studies from the Comer lab at Columbia and NYSPI have evaluated ibudilast for OUD. A small human laboratory inpatient study in nontreatment-seeking opioid-dependent subjects with 10 participants per group evaluated the analgesic, subjective, and physiological effects of oxycodone in patients treated with ibudilast (20 or 40 mg, p.o., BID for 7 days) vs placebo-treated groups following 14 days treatment with morphine (Cooper et al. 2017). Compared to placebo, ibudilast increased oxycodone analgesia following the cold pressor test, but did not increase subjective drug ratings. In a follow-up study with a similar design, population, and sample size, ibudilast (50 mg BID for 7 days) was found to significantly reduce subjective liking of oxycodone and heroin craving and to improve analgesic effects of oxycodone (Metz et al. 2017). A third study with a similar population and design evaluated ibudilast (20 or 40 mg, p.o., BID for 7 days) for reducing SOWS and COWS scores, finding a trend in SOWS improvement for the combined treatment arms (Cooper et al. 2016).

These preliminary findings are a promising translation of in vitro and rodent studies that showed, first, that opioids activated microglia (Watkins et al. 2007) and, second, that inhibition of microglial activation decreased opioid tolerance, reward responsivity, and withdrawal symptoms and increased analgesic effects (Watkins et al. 2007; Johnston et al. 2004; Watkins et al. 2005; Hutchinson et al. 2008; Ledeboer et al. 2007) and stress responsivity (Zhao et al. 2016). Therefore drugs with the potential to inhibit microglial activation may be a promising approach to reducing opioid dependence related to pain treatment and to treating OUD in general (Cooper et al. 2012).

Pioglitazone is an agonist at the peroxisome proliferator-activated receptor gamma (PPARγ), which is a nuclear hormone receptor that regulates gene expression as a ligand-activated transcription factor and, in the central nervous system, is expressed on oligodendrocytes and astrocytes as well as neurons in multiple brain areas including the VTA, nucleus accumbens, and hippocampus (de Guglielmo et al. 2015; Sarruf et al. 2009). Pioglitazone is marketed for treatment of diabetes via its peripheral role in adipogenesis and glucose metabolism. In the brain, PPARγ agonists modulate dopaminergic transmission (de Guglielmo et al. 2015) and also inhibit microglial activation (Bernardo and Minghetti 2006). As discussed for ibudilast (see above), this latter process is induced by opioids and may reduce opioid withdrawal and improve opioid analgesia. Three small human laboratory clinical studies have evaluated pioglitazone for opioid addiction indications with mostly negative findings. A nonrandomized crossover study in nondependent users found pioglitazone (up to 45 mg daily p.o. over 3 weeks) did not affect subjective ratings of opioids (Jones et al. 2016). A similar negative result was reported from a placebo-controlled RCT of pioglitazone (45 mg daily p.o. over 3 weeks) in OUD subjects stabilized on BUP (Jones et al. 2018); however pioglitazone did reduce heroin craving and general anxiety. Another recent placebo-controlled RCT in OUD patients found that pioglitazone (45 mg/day for 11 weeks) did not reduce withdrawal

symptoms (COWS or SOWS), opioid use, or inflammatory cytokines following discharge from inpatient treatment (Schroeder et al. 2018). No ongoing clinical studies were identified in ClinicalTrials.gov.

These findings contrast with mostly positive findings in rodent studies, in which PPARγ agonists were associated with the following effects: reduced heroin self-administration, reduced heroin-induced VTA neuron activation and extracellular dopamine increase in the nucleus accumbens shell (de Guglielmo et al. 2015), reduced heroin (de Guglielmo et al. 2017) and morphine (Ghavimi et al. 2014, 2015) withdrawal behaviors (although see (Javadi et al. 2013)), reduced heroin seeking (de Guglielmo et al. 2017) and heroin-induced reinstatement (de Guglielmo et al. 2017), as well as reduced stress responsivity in non-opioid-related addiction models (Ryan et al. 2012). This discrepancy with clinical studies may possibly reflect insufficient doses or species differences.

3.7 Other: Analgesics, Calcium Channel Blockers, and Acetyl-Cholinesterase Inhibitors

Pregabalin and Gabapentin Pregabalin (Lyrica) is similar in structure to γ-amino butyric acid (GABA), but is a ligand for the α2δ voltage-gated calcium channel subunit, at which it acts to suppress Ca2+-dependent presynaptic neurotransmitter release (Taylor et al. 2007). Pregabalin is currently approved for the treatment of neuropathic pain and fibromyalgia and as an adjunctive treatment for seizures. To date, results (intermediate analysis) from only one clinical trial in OUD (Krupitsky et al. 2016) have been published. A single-blind randomized symptom-regulated protocol with an active control evaluated withdrawal symptoms (OWS), craving, fatigue, and need for analgesia in inpatients undergoing opioid detoxification. Patients were randomized to either pregabalin (up to 600 mg per day, 19 patients) or clonidine (600 micrograms per day, 15 patients) for 6 days, in addition to as needed medications. While OWS outcomes did not differ, pregabalin showed greater efficacy compared to clonidine in reducing craving, fatigue, and need for analgesia and was associated with a higher detoxification completion rate. This preliminary evidence adds to case reports of pregabalin reducing withdrawal in OUD patients (Kammerer et al. 2012) and to preclinical studies in which it suppressed naloxone-precipitated withdrawal in morphine-dependent mice (Hasanein and Shakeri 2014; Vashchinkina et al. 2018); further, pregabalin was effective in reducing craving, withdrawal symptoms, and relapse in AUD clinical trials (Freynhagen et al. 2016). Finally, a randomized clinical trial in postsurgical patients found that compared to placebo, pregabalin reduced postoperative opioid use (Myhre et al. 2017). While these studies suggest pregabalin has significant promise in treating OUD, this is complicated by evidence of abuse potential (Schjerning et al. 2016; Bonnet and Scherbaum 2017). Further studies for withdrawal in OUD (NCT03017430) are ongoing.

Gabapentin is structurally and pharmacologically similar to pregabalin, and is approved for the treatment of neuropathic pain. In a two-stage double-blind, randomized study, two doses of gabapentin (900 mg/day or 1,600 mg/day) plus methadone were compared with placebo plus methadone for efficacy in reducing

opioid withdrawal in heroin-dependent patients (Kheirabadi et al. 2008; Salehi et al. 2011). The higher, but not the lower dose, reduced subjective and physiological manifestations of withdrawal. In another RCT, gabapentin (increased from 200 to 1,600 mg and tapered back down over 5 weeks) was found to be effective in reducing recreational opioid use in OUD patients during a 10-day BUP detoxification protocol (Sanders et al. 2013). In a recent large placebo-controlled RCT, gabapentin (1,200 mg/day for 72 h peri- and postoperatively) was also effective at reducing prescription opiate use following surgery (Hah et al. 2018). Multiple clinical trials are underway evaluating gabapentin for postoperative opioid use. Similar concerns exist regarding gabapentin misuse (Bastiaens et al. 2016).

Tramadol is a centrally acting serotonin-norepinephrine reuptake inhibitor and a mild to moderate agonist at the μ, κ, and δ opioid receptors that is approved as an analgesic. It has relatively less abuse liability than other opioid agonists. Published studies in OUD, all evaluating tramadol for reducing withdrawal symptoms, include controlled RCTs, human laboratory studies, and retrospective reviews. Initial smaller placebo-controlled RCTs evaluating tramadol hydrochloride extended release in heroin- or prescription opioid-dependent patients showed that tramadol was superior to clonidine and placebo and comparable to buprenorphine and methadone for suppressing opioid withdrawal symptoms (Lofwall et al. 2007, 2013; Chattopadhyay et al. 2010; Sobey et al. 2003). Mild withdrawal symptoms following cessation of tramadol were reported in some studies. A recent large RCT (Dunn et al. 2017) involving OUD patients in a residential setting compared the efficacy of tramadol hydrochloride extended release (tapered up to 600 mg/day during a 7-day taper), clonidine, or BUP for withdrawal, after which patients were crossed over to double blind placebo. Results confirmed previous findings, showing tramadol was more effective than clonidine and similar to BUP in reducing SOWS and COWS. Multiple clinical trials with similar designs are in progress (NCT00142896, NCT00301210, NCT00980044, NCT03678792).

Isradipine is a dihydropyridine L-type calcium channel (LTCC) blocker that is approved for treatment of hypertension and is being evaluated as a treatment for several psychiatric conditions including bipolar disorder and schizophrenia. Consistent with the role of LTCCs in modulating the activity of VTA neurons responsible for phasic dopamine signaling in the nucleus accumbens, israpidine was recently shown to attenuate cocaine seeking in rats when injected into the VTA (Addy et al. 2018). A trial is currently nearing completion for evaluating the efficacy of isradipine (10 mg/day) as an adjunct to BUP for reducing opioid withdrawal symptoms, craving, and use (NCT01895270).

Galantamine is a naturally occurring acetylcholinesterase inhibitor used in treating Alzheimer's disease and vascular dementias. An ongoing clinical trial (NCT03547622) is testing galantamine versus placebo, both in combination with web-based cognitive behavioral therapy (CBT4CBT), for preventing relapse to

opioid use in patients tapering from opioid receptor agonist maintenance (methadone or BUP). The premise for the trial is that galantamine may enhance the efficacy of cognitive behavioral therapy (CBT), particularly in patients with mild cognitive impairment. Primary outcomes include successful taper, opioid withdrawal symptoms, and opioid use for the 3 months following the completion of taper. A double-blind placebo-controlled trial of galantamine for methadone-maintained individuals with cocaine use disorder conducted by Carroll et al. demonstrated in their secondary analysis of opioid use that a significant main effect for galantamine was seen over placebo on percent of urine specimens that were negative for opioids, both within treatment (77% for galantamine vs 62% for placebo), and through a 6-month follow-up (81% vs 59%, respectively). This effect was seen regardless of whether participants used nonprescribed opioids during the baseline period. Galantamine effects were seen early in treatment, leading to the conclusion that it may hold promise across multiple drugs of abuse, including opioids (Bonnet and Scherbaum 2017).

4 Vaccines

Vaccines for addictive disorders including OUD induce antibodies that bind the drug of abuse in the periphery, preventing it from crossing the blood-brain barrier and activating relevant targets including opioid receptors in the brain. Vaccines generally consist of small molecule haptens that mimic the opioid drug structure conjugated to a larger carrier protein and an adjuvant. This complex stimulates the immune system to generate drug-specific antibodies. The idea of using vaccines to treat addiction was tested in animal models over 40 years ago (Bonese et al. 1974), with incremental progress toward clinical use (Pravetoni 2016; Pravetoni and Comer 2019). For opioid-targeted vaccines in particular, data from only one clinical trial have been published; however several clinical trials are now underway (see next paragraph). In the one published trial (Akbarzadeh et al. 2009), conducted in Iran, safety and tolerability of a morphine-bovine serum albumin conjugate were evaluated in 347 morphine-addicted volunteers, showing that it was well-tolerated with no serious adverse events; efficacy data was not included and has not yet been published from any trial in OUD (Pravetoni and Comer 2019). By contrast, clinical trials of vaccines for nicotine and cocaine use disorders are at a more advanced stage, with Phase II or III clinical trials either underway or completed in both disorders – though none of these have yet produced sufficient titers of high-affinity antibody to be commercialized (Pravetoni 2016). This latter outcome has been a key challenge in vaccine research, owing in large part to substantial inter-individual heterogeneity in immune responses (Pravetoni 2016; Pravetoni and Comer 2019).

Recent preclinical work is promising. Vaccines against heroin were shown to reduce drug-induced reinstatement of drug seeking in rats (Schlosburg et al. 2013) and overdose lethality in mice (Bremer et al. 2016); in rhesus monkeys, a vaccine against fentanyl substantially reduced fentanyl's potency in assays of operant responding and antinociception (Tenney et al. 2019). Several initiatives, still in

early stages, have been funded to develop similar vaccines for clinical treatment of OUD; they are current in the early stages of developing and evaluating the safety, immunogenicity, and preliminary efficacy of multivalent vaccines targeting oxycodone, heroin, and morphine (1UGD3DA047711-01), fentanyl and fentanyl derivatives (1UGD3DA047711-01), and prescription opioids oxycodone, hydrocodone and hydromorphone (1UGD3DA047711-01). Given the potential benefits of vaccines, including among other things their capacity to be used without the need for detoxification and to be co-administered with other OUD pharmacotherapies, these approaches remain promising.

5 New Formulations of Existing Drugs

In light of nearly universal problems with treatment adherence, a number of extended-release formulations of BUP and NTX have been and are being developed. Probuphine is a long duration of action implantable rod preparation containing BUP embedded in flexible ethylene vinyl acetate rods from which the BUP elutes over a 6-month period (Brown and Alper 2018; White et al. 2009; Ling et al. 2011; Smith et al. 2017). Probuphine was approved by the FDA in 2016. Each rod contains 80 mg BUP, and up to six rods are usually implanted subcutaneously on the inner aspect of the bicep. Spent rods need to be surgically removed at the end of 6 months, and new rods are then implanted on the other arm. Plasma levels achieved are relatively low, and clinical trials in support of approval were limited to patients on low doses of sublingual BUP, 8 mg/day or less.

There are three new long-acting formulations of BUP for subcutaneous injection. An Indivior formulation (Sublocade) (https://www.sublocade.com) (No Authors Listed 2018) was FDA approved in 2017 and provides a month of coverage. Sublocade is marketed in prefilled syringes containing BUP in a biodegradable 50:50 poly (DL-lactide-co-glycolide) polymer and a biocompatible solvent, *N*-methyl-2-pyrrolidone. Two Braeburn Camurus formulations (CAM2038) (Walsh et al. 2017; Haasen et al. 2017), including a 1-week and a 1-month duration-of-action product, were determined to be approvable by the FDA in 2018, but marketing has been delayed on the basis of and exclusivity determination for Sublocade. CAM2038 is planned to be marketed in prefilled syringes containing BUP in a proprietary FluidCrystal® technology (based on soy phosphatidylcholine and diglyceride lipid) which on injection converts to a crystalline gel which slowly releases the BUP. Sublocade labeling requires that patients be maintained or stabilized on sublingual BUP for at least 7 days prior to an initial injection. In contrast, CAM2038 is expected to be approved without that restriction, perhaps requiring only a single sublingual test dose, making the latter a more ideal preparation for use in emergency department settings. Use in such settings has the potential to provide as long as a month's coverage, protecting patients from relapse and overdose fatalities, while longer-term continuing care is being arranged. Clinical trials in planning for these XR-BUP products include head-to-head comparisons with XR-NTX in clinical justice system (CJS) populations; comparisons with sublingual-buprenorphine

(SL-BUP) in OUD patients on discharge from hospital settings; similar comparisons in pregnant OUD patients with a focus on fetal, neonatal, and maternal outcomes; and studies in rural settings where XR interventions may afford advantages as a consequence of travel burdens. All of the extended-release preparations (BUP and NTX) are substantially more expensive, which is likely to preclude their use as a first-line treatment unless clinical trials can establish favorable cost-effectiveness.

Implantable NTX pellets with durations of action up to about 6 months have been used outside of the USA for several years. A very long-acting subcutaneous implantable pellet formulation of NTX, the O'Neil Long-Acting Naltrexone Implant (OLANI), has been under development for close to two decades, and work is currently underway (NCT03810495) to move it toward FDA approval for OUD relapse prevention. Several formulations have been tested in RCTs and have been used clinically in Australia. The formulation being tested in the US trials has higher drug loading; it is manufactured under GMP conditions and has been used in over 800 patients.

6 Trials to Expand Use of Existing Marketed Agents, New Models of Care

As efficacious as currently approved agents are, there's a vast gap between research and community practice. Only between 5 and 10% of people who would benefit from treatment are ever seen in addiction specialty programs, and many of these are "drug-free," meaning that these programs do not use medication. Bringing effective treatment to a larger proportion of the population by introducing existing established medications into specialty programs and into mainstream healthcare settings, e.g., primary care, emergency departments, and the CJS, can have a greater and certainly more immediate impact than developing new drugs. NIDA has supported numerous clinical trials and implementation studies in these settings, many of them through its Clinical Trials Network (NIDA CTN). Studies deemed most relevant to advances or innovations in clinical trial design will be briefly reviewed here, though there are many others of equal importance.

Buprenorphine for Acute Detoxification NIDA CTN-0001 and CTN-0002 (Ling et al. 2005) compared buprenorphine/naloxone (BUP/NX) to clonidine for inpatient and outpatient detoxification, respectively. Prior to these studies, opioid-based detoxification was largely unavailable outside of the restrictive confines of narcotic treatment programs, and clonidine-based detoxification was of limited value for a large number of patients. In the inpatient setting, 77% of patients assigned to BUP/NX met predefined success criteria compared to 22% of the clonidine cohort. In the outpatient setting, the parallel contrast was 29% vs 5%. These studies supported the benefits of BUP/NX as well as the relative benefits of inpatient settings for detox. The benefits were so striking that a previously "drug-free" program withdrew from the trial and established BUP/NX as "treatment-as-usual" because it was so much more effective in retaining patients, reducing the chaos associated

with revolving admissions and discharges, and improving bottom-line revenues. Note the striking success rate differences between inpatient and outpatient settings, which emphasize the need for improved outpatient detoxification strategies.

Buprenorphine Tapering CTN-0003 (Ling et al. 2009) compared a rapid (7 day) versus a gradual (28 day) BUP-NX tapering schedule following 4 weeks of BUP/NX stabilization. Counterintuitively the rapid taper beats the gradual taper insofar as at the end of the taper, 44% of the rapid taper group provided opioid-negative urine samples compared to 30% of the gradual taper group. By the time of 1-month and 3-month follow-up visits, only 12–18% of participants from the rapid taper group provided negative urines highlighting the importance of longer-term treatment.

Buprenorphine for Adolescents and Young Adults Adolescents with heroin use disorder are typically treated with detoxification and counseling. CTN-0010 (Woody et al. 2008) compared a relatively short BUP/NX treatment (9 weeks +3 weeks taper) to a 2-week BUP/NX detox, both conditions with 12 weeks of counseling. The longer BUP/NX treatment was associated with less opioid use, better treatment retention, less injection, and less cocaine and marijuana use.

Buprenorphine Hepatotoxicity and Long-Term Treatment CTN-0027 (Saxon et al. 2013) was a head-to-head comparison of BUP/NX to methadone with a primary focus on hepatotoxicity, a study mandated by the FDA as a condition of initial labeling. A long-term follow-up study of the same patients was completed in CTN-0050 (Hser et al. 2016). The key finding from CTN-0027 was that there was no evidence of hepatotoxicity with 6 months of either treatment, encouraging use of BUP/NX in primary care and other settings. Retention in treatment was better for the methadone cohort. Long-term follow-up occurring between 3 and 10 years after randomization revealed no differences in mortality, but higher opioid use in the BUP/NX group largely owing to lower retention. For those retained in treatment, there were no differences in opioid use across the two medications, highlighting the importance of treatment retention.

Treatment of Prescription Opioid Dependence Until recently, most opioid pharmacotherapy research has focused on heroin addiction. With increasing use of – and addiction to – prescription opioids, CTN-0030 (Weiss et al. 2011) (POATS, Prescription Opioid Addiction Treatment Study) examined whether adding traditional individual drug counseling to BUP/NX in the context of standard lean medical management improved outcomes. The primary findings were that patients reduced opioid use during BUP/NX treatment, individual counseling didn't make any difference, and most importantly within a few weeks of completing BUP/NX treatment, close to 90% of patients were again using, highlighting the importance of long-term treatment.

Comparative Effectiveness: XR-NTX Versus BUP/NX CTN-0051 (Lee et al. 2018) was a head-to-head comparison of 6 months of treatment with two office-based medications, BUP/NX and XR-NTX. Key findings were that it was more

difficult to initiate treatment with XR-NTX because of the detoxification hurdle (28% of participants randomized to XR-NTX were not successfully inducted compared to 6% of those assigned to BUP/NX) but that once treatment was initiated, the outcomes did not differ. Over the course of 6 months, more than 50% of participants in each group discontinued treatment. These findings highlight the importance of developing more effective induction procedures for XR-NTX and of developing and testing strategies to improve treatment retention. A smaller and shorter but otherwise almost identical study conducted at the same time in Norway yielded similar findings (Tanum et al. 2017).

Moving Addiction Screening, Assessment, and Treatment into Primary Care Settings: Use of the EHR Without appropriate screening, assessment, training, and resources, it is unlikely that opioid treatment will ever find its way into mainstream healthcare settings. CTN-0059 (McNeely et al. 2016) was a validation study of the TAPS Tool (Tobacco, Alcohol, Prescription Medications, and Substance Use/Misuse Brief Screen/Assessment Tool) in primary care settings, the key findings of which were that the tool has good sensitivity and specificity and that interviewer- and self-administered versions performed similarly in these settings. CTN-0062 builds on this and other screening tools by programming these and other NIDA addiction common data elements (CDEs) into electronic health records (EHRs), implementing these in primary care settings after conducting focus groups and providing training and establishing linkages with addiction specialty settings with the goal of reducing stigma and increasing screening, treatment, and referral. CTN-0074 (PROUD, Primary Care Opioid Use Disorders Treatment Trial) further builds on this by implementing and testing a collaborative care model (Massachusetts Model) (Saitz et al. 2008).

Initiating Buprenorphine in Emergency Department Settings Two NIDA CTN trials build on a recently published single-site study (D'Onofrio et al. 2015) showing that initiating BUP/NX treatment in an academic emergency medicine setting and providing a linkage to continuing care in a primary care setting improve 30-day treatment engagement rates. CTN-0069 (Project ED-Health) (Volkow et al. 2018) is a hybrid implementation-effectiveness study using a stepped wedge design currently being conducted in four large urban academic emergency settings. CTN-0079 (ED-CONNECT) (Koob and Volkow 2016) is a study of the feasibility, acceptability, and impact of introducing a clinical protocol for OUD including BUP/NX in rural and urban settings with high need, limited resources, and different staffing structures.

New Models of Care New models of care have been developed both to enhance initial engagement and to make it feasible for busy primary care practitioners to manage the complexities of an OUD population. Examples include establishing bridge clinics to temporarily treat patients identified (and sometimes initially treated) in emergency settings, the CJS, or elsewhere while they are waiting to be accepted into more structured programs: "interim buprenorphine" (Sigmon et al. 2016)

and the Massachusetts model (LaBelle et al. 2016) involving embedding a nurse care manager in primary care practices using a collaborative care approach.

Naloxone Kit Distribution and Training Several studies aim at improving the use and outcomes associated with distribution of naloxone kits. These focus on the need to modify existing training programs, improving accurate identification of opioid overdose, long-term follow-up, and inclusion of friends and family in training. It is expected that enhanced psychosocial interventions will improve outcome, that adverse events will be minimal, and that drug use patterns will not be affected (addressing concerns that the availability of naloxone would increase opioid use) (Grant number 5R01DA035207-05). A second study focuses on pharmacy-based naloxone distribution and training, working in the context of two large retail pharmacy chains (Grant number 1R01DA045745-01). A third study is evaluating the impact of emergency response communities (ERCs) which are "specialized smartphone-based social networks in which members are approved carriers" or users of naloxone and can support intervention in overdose emergencies (Grant number 5R34DA044758-02). The model combines GPS and IP location tracking.

Strategies to Transition Off Buprenorphine Either to Medication-Free Abstinence or to XR-NTX While some OUD patients continue to take BUP indefinitely, there are others who prefer not to remain dependent and are looking for safe, effective strategies to discontinue. These include rapid or slow taper to no medication which is often associated with relapse to opioid use and transition to XR-NTX for short-term or long-term relapse prevention. Recent and ongoing trials are comparing rapid transition strategies (rapid daily escalation from very low dose (0.25 or 0.5 mg) oral naltrexone to 25 mg followed by an initial XR-NTX injection) to more traditional gradual BUP taper. Primary outcomes are the percent of participants successfully transitioned off BUP and abstinent at 6 months; secondary outcomes include measures of withdrawal, sleep, mood, anxiety, opioid, and other drug use (Grant number R21DA042243-02). Transition to XR-NTX is expected to be associated with better outcomes than simple taper. A large about-to-be-initiated NIDA CTN study is CTN-0100 focused on optimizing retention, duration, and discontinuation strategies for medications for OUD.

7 Helping to End Addiction Long-Term (HEAL)

The US Congress's Fiscal Year 2018 Consolidated Appropriations Act designated $500 million for NIH to fund research to combat the opioid crisis, funding which is anticipated to continue as an addition to the NIH base (HEAL initiative). Half of the appropriation is designated for NIDA to address opioid addiction and half for NINDS to address management of chronic pain. The act also authorized the NIH Director to transfer some of these funds "specifically appropriated for opioid addiction, opioid alternatives, pain management, and addiction treatment to other Institutes and Centers of the NIH." Responding to this appropriation, the NIH

implemented the HEAL (Helping to End Addiction Long-term) initiative, an overarching and ambitious partnership with other agencies building on a track record of research across the translational spectrum – from basic science to behavioral and pharmacotherapy development and testing and to implementation research. NIDA's focus will be on prevention and treatment of OUD with the goal of achieving sustained recovery. For NIDA which has had a budget of approximately $1 billion annually for nearly the last decade, this represents a greater than 20% increase that will be used to build infrastructure and fund exciting new initiatives many of which involve clinical trials. Amongst these are:

NIH HEAL Vaccine Initiative Recognizing that expertise in vaccine development spans many NIH Institutes and Centers as well as academia and industry, NIAID, NIDA, and ORIP issued NOT-AI-18-0155 calling for administrative supplement requests to fund vaccine work, specifically optimization of immunogens, structural analysis of antibody-immunogen binding, opioid B cell epitopes, carrier platforms to improve immunogenicity, novel haptenation, and development of adjuvants for opioid vaccines. Additional areas of interest include IND-enabling studies, mechanisms of vaccine efficacy and safety, mucosal immunity, immune responsivity in OUD, and development of relevant animal models. In October 2018, these ICs sponsored an NIH symposium that brought together NIDA medications development staff, NIDA-funded addiction vaccine researchers, and staff from NIAID and others with expertise in adjuvants, linkers, and other aspects of vaccine development.

Laboratories for Early Clinical Evaluation of Pharmacotherapies This initiative focuses on building infrastructure and expertise to conduct Phase I and Phase II studies to look at safety, drug interactions, PK and PD studies, and human laboratory studies including proof of concept trials.

Medications Development to Prevent and Treat OUD and Overdose This initiative will expand NIDA's existing medications development program, now housed in NIDA's Division of Therapeutics and Medical Consequences.

Respiratory Stimulants Opioid overdose fatalities are nearly always a consequence of opioid-induced respiratory depression. By blocking opioid receptors, antagonists like naloxone rapidly reverse respiratory depression and save lives. But this is not always the case, and additional approaches are needed, particularly in the context of high-potency fentanyl(s). This initiative seeks to develop non-opioid molecules that can stimulate respiration even in the presence of significant opioid agonists. In addition to potential use in opioid overdose, such respiratory stimulants might be used in alcohol poisoning and for overdoses in combination with alcohol and benzodiazepines. Respiratory stimulants have the added advantage that they may be able to restore breathing without precipitating withdrawal.

Virtual Reality (VR) Tools This initiative focuses on moving beyond traditional technology-driven approaches such as text messaging, smartphone apps, and ecological momentary assessment, to include virtual reality approaches to mimic real social situations in which patients may be more prone to responding to drug cues and are at risk of relapse. VR approaches have the potential to enhance treatment effects by allowing patients to be exposed in realistic settings to extend treatment beyond clinical settings and to support digital phenotyping.

NIDA CTN HEAL Projects NIDA Clinical Trials Network is developing a number of large, high-impact trials including a trial to improve retention in MOUD (medication for opioid use disorder) treatment and to better understand how long treatment needs to continue, and for whom and how best to discontinue treatment when that is warranted; a trial to identify and intervene to prevent subthreshold OUD from progressing; a trial examining best approaches to providing MOUD in rural settings; a trial on interventions following hospitalization for medical/surgical indications; a trial focused on strategies to optimize MOUD in tribal communities; and additional trials focused on introducing addictions treatment, particularly buprenorphine BUP, in emergency department settings. In July 2019, five new nodes were added to the network to enhance clinical trial capacity.

Justice and Community Opioid Innovation Network (JCOIN) See below.

HEALing Communities Study By far the most ambitious, expensive, and far-reaching project is the HEALing Communities Study (http://ctndisseminationlibrary.org/protocols/ctn0080.htm) the goals of which are to "determine if an integrated set of evidence-based interventions within healthcare, behavioral health, justice systems, and community organizations can work to decrease opioid overdoses and to prevent and treat OUD." NIDA is leading this effort in partnership with the Substance Abuse and Mental Health Services Administration (SAMHSA) and coordinating with close to a dozen other federal agencies. NIDA recently funded four research sites in highly impacted states (Kentucky, Ohio, New York, Massachusetts) as well as a Data Coordinating Center. Each research site includes at least 15 communities of which 30% are in rural areas. Goals are to reduce overdose fatalities by 40% over 3 years, as well as to reduce overdose events and incidence of OUD and to increase the number of individuals on medication for OUD and those retained in treatment for over 6 months. Extensive linkages with local agencies and organizations are planned. NIDA expects to commit approximately $100 million in each of FY19, FY20, and FY21, and $50 million in FY22 for the research sites (in aggregate), and $6.5 million in each of the 4 years for the Data Coordinating Center.

8 Initiatives for Special Populations

CJS Involved Populations In the USA, the criminal justice system – which has become a de facto residential setting for those with mental illness and substance use disorders – is an important setting in which to screen for, assess, and initiate treatment. Most arrestees test positive for drugs, and of these, opioids are highly prevalent. Methadone maintenance at reentry to the community is well-established (Tomasino et al. 2001; Kinlock et al. 2007). More recently, BUP initiated in jails and prisons and linked to primary care settings for ongoing care has also been extensively studied and shown to be effective. Jail-released patients do as well in primary care as do community comparison groups in terms of retention, opioid use, and opioid abstinence (Lee et al. 2012). Opioid antagonists are often preferred by the CJS, and in a large multi-site trial in parolees, XR-NTX was found to be superior to treatment-as-usual in time-to-relapse, overall relapse, and opioid-negative urines (Lee et al. 2018). A small pilot study found that initiating XR-NTX just prior to release and linking continuing treatment to a primary care setting was acceptable and was associated with lower relapse rates and more negative urine samples (Lee et al. 2015); a large follow-up study focused on relapse and overdose prevention is just being completed.

The Justice and Community Opioid Innovation Network (JCOIN) JCOIN (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/justice-community-opioid-innovation-network) will build infrastructure in the form of a network of collaborating researchers and fund specific trials around improving access to treatment for CJS involved populations. It will also initiate a national survey on addiction services in CJS settings. Current work in this area includes bridging gaps in BUP treatment, improving access to OUD pharmacotherapies for veterans, drug injection surveillance in rural areas, optimizing OUD pharmacotherapies in CJS settings, and mining social media big data to monitor HIV. A head-to-head multi-site trial comparing extended-release BUP to extended-release naltrexone is currently pending review.

Optimizing MOUD in Tribal Communities (AI/AN) See above under HEAL CTN.

Maternal Opioid Management Support (MOMS) NIDA CTN-0080: The MOMS study (http://ctndisseminationlibrary.org/protocols/ctn0080.htm) grows out of the increasing prevalence of neonatal abstinence syndrome (NAS, also referred to as neonatal opioid withdrawal syndrome, NOWS) in the context of the opioid crisis. NAS is associated with compromised health outcomes for infants and with exorbitant costs for neonatal intensive care. The present standard of care for pregnant opioid-dependent women is SL-BUP, although problems like poor adherence and treatment dropout are well known. In addition, once-a-day BUP yields daily peaks and troughs which expose the fetus to cycles of sedation and withdrawal. It is hypothesized that replacing SL-BUP with XR-BUP will eliminate the daily cycling and result in

improved fetal and neonatal outcomes, e.g., heart rate variability, birth weight, head circumference, etc., as well as improved maternal outcomes, e.g., retention-in-treatment, opioid misuse, etc., and infant outcomes, e.g., early development.

The ABCD and bBCD Studies While not clinical trials per se, two very large and forward-thinking NIDA initiatives warrant mention because they will accrue populations and data-sets that have the potential to both identify need for future clinical trials and potential candidates for same. The ABCD study (Adolescent Brain and Cognitive Development study) https://abcdstudy.org (Lisdahl et al. 2018) was to some extent spurred by the rapid evolution of state medical and recreational marijuana laws, mostly by referendum. Given that THC has profound effects on the developing brain and that with wider availability and legalization of marijuana, teenagers may be using it more frequently, it is imperative to understand the impact on brain and cognitive development. The ABCD study is a 10-year prospective study enrolling 9–10-year-olds, following them through adolescence and into early adulthood and using a common protocol across 21 sites to collect repeated biological, social, behavioral, cognitive, and neuroimaging measures. Enrollment of 11,875 participants was completed in October 2018, and an initial data-set of de-identified baseline measures from ~4,500 participants, including structural MR, diffusion MR, resting-state MR, and task MR imaging as well as clinical and social data, was released through the NIMH Data Archive. Similar curated data will be released annually. ABCD represents a partnership between NIDA, NIAAA, NCI, NIMH, NICHD, CDC, and others. The bBCD study (babies, Brain and Cognitive Development (https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2018/the-trans-nih-baby-brain-cognitive-development-bbcd-study.html) is also a trans-NIH initiative stimulated in part by the opioid crisis and the increase in prenatal exposure to opioids and NOWS. The bBCD study is still in planning, but intends to recruit 7,500 pregnant women from highly impacted regions of the USA. Goals are to establish normative developmental trajectories against which to assess affected children.

9 Devices, Apps, and Behavioral Interventions

A large number of apps, web-based interventions, and devices have been and are being developed: widespread use of smart phones, text messaging, and geo-positioning, the relatively very low cost of app development and data analytical approaches including big data analytics, and the potential to use these as research tools and to commercialize them have led to an explosion of new approaches. We mention just a few examples to provide a taste of what's in development. The extent to which these are supported by clinical trials is highly variable. Building on the findings of CTN-0044 (NCT01104805), Pear Therapeutics has developed reSET, and reSET-O, apps that include educational and contingency management approaches. As far as we're aware, this is the only app presently available that has received FDA clearance. Pear is working with Sandoz to commercialize this:

CBT4CBT (www.CBT4CBT.com) is based on years of work showing that cognitive behavioral therapy approaches are effective, particularly in relapse prevention, and that web-based CBT is effective, cost-effective, and of higher fidelity than counselor-administered approaches. It can be used 24/7, requires no scheduling, and is often preferred by patients. Many text messaging approaches have been used to collect EMA (ecological momentary assessment) data which can be used both for research purposes and to drive temporally targeted interventions, including multiple sequential randomizations based on EMA outcome measures. Many apps use geo-mapping to gather information about "safe" and "dangerous" places (i.e., the street corner where your dealer deals, your favorite bar, etc.) and use those data to steer users away from dangerous locales, to safer, more supportive ones. Other apps, e.g., "emocha" (www.emocha.com), use real-time smartphone video apps and facial recognition software to monitor and reward for medication taking and adherence. DynamiCare combines many of these features in a single app. Datacubed (D3) (www.datacubed.com) combines many of the same features with "gamefied" decision science measures derived from neuroeconomics including measures of temporal discounting, risk-taking, and decision-making under ambiguous conditions which may predict vulnerability to relapse and provide opportunities for targeted intervention.

10 Summary, Conclusions, and New Directions

Recent clinical trials and interventions for OUD include diverse new pharmacotherapies, many of which are non-opioid based, enhancement of existing opioid-based medications, modernization of big data collection, and large-scale systemic interventions at the healthcare provider and societal levels to increase access to, and retention in MAT, and to prevent overdose. Novel non-opioid pharmacotherapies that have the potential to mitigate neurobiological alterations underlying addiction have been or are being evaluated for OUD indications, representing a change from current therapeutics, which are almost all opioid based. The outcomes of most of these trials were, or are, craving or withdrawal during or following detoxification, with a few also evaluating retention in MAT. In the context of addiction domains highlighted by Koob and Volkow (Koob and Volkow 2016), many relevant new pharmacotherapies, including CBD, THC, aprepitant, PPARγ agonists, dynorphin/KOPR agents, and buspirone, have the potential to reduce stress and negative affect. Relatively fewer agents – galantamine and potentially CBD – are known to improve prefrontal or executive function. Also prevalent among new OUD pharmacotherapies are medications that are approved for treating pain (ketamine, tramadol, pregabalin, and gabapentin) or are potential analgesics via direct actions, or via interactions with opioid-based nociception. These include ibudilast and pioglitazone via inhibition of glial activation; CBD and low-dose THC via endocannabinoid actions and cannabinoid-opioid interaction; aprepitant via neurokinin-related nociception; or the developing opioid agonist/NK1R antagonist compounds. Anti-inflammatory agents (ibudilast, pioglitazone,

CBD) are also represented. Most of these studies reported positive findings for at least one outcome.

Future directions and potential areas of need include improved strategies to combat the unique challenges raised by the potency and availability of fentanyl and related epidemic of overdose fatalities. Fentanyl is about 50–100 times more potent than morphine, and carfentanil and other fentanyl derivatives an order of magnitude greater or more. As a consequence, naloxone kits are less efficacious, and first responders frequently report needing to use five or ten or more kits for a single overdose. More potent, rapidly acting antagonists with user-friendly packaging need to be developed, possibly with longer durations of action (as noted, naloxone is short-lived and frequently needs to be readministered). In addition to this, fentanyl's potency may produce greater tolerance and greater dependence than do less potent opioids, rendering current agonist and antagonist interventions inadequate or requiring higher methadone or BUP dosing or that XR-NTX be administered every 2 weeks rather than every 4. All of this requires focused clinical trials.

While there are multiple pharmacotherapies that have the potential to reduce prescription opioid use in chronic pain (described above), relatively few trials were identified that included pain, opioid analgesic use, or tolerance as outcomes. Chronic pain is frequently comorbid with OUD and greatly increases the risk for overdose (Volkow et al. 2018). Developing non-opioid-based analgesics to replace opioid use was recently identified as a high priority for combating OUD (Volkow et al. 2018).

Finally, despite recent emphasis on the importance of precision medicine approaches, i.e., strategies for identifying individual patient characteristics that predict response for a given medication (Terry 2015; Litten et al. 2015), few OUD clinical trials to date have reported demographic, psychiatric, or biological measures that were or were not associated with treatment response. To achieve this, future clinical trials would need not only to include these measures, but also to employ statistical analyses that permit these measures to be causally linked to treatment outcome in sufficiently large clinical samples (as opposed to the current practice of testing for group mean differences in studies with relatively small sample sizes). A particularly important patient characteristic that is likely to influence treatment response, but which has been omitted from study in most clinical trials, is psychiatric comorbidity: psychiatric disorders, particularly mood disorders, are highly prevalent in OUD and interact with the addictive cycle in a mutually exacerbating manner that requires integrated treatment of both disorders (Volkow et al. 2018). Precision medicine approaches will also be necessary to incorporate recent findings that genetic and epigenetic variations between individuals both contribute to developing OUD, and may also be treatment targets (Hurd and O'Brien 2018).

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