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Substance Use Disorders (FG Moeller, Section Editor)

Future Directions Incorporating Novel Medications to Reduce Repeat Overdose

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Abstract

Purpose of review The use of opioids has risen dramatically in the USA and led to an increase in opioid use disorders and deaths due to opioid-related overdoses. Current treatments for opioid use disorder are not without drawbacks, so that new treatments may be helpful in reducing opioid use. This paper reviews current pharmacologic treatments for opioid use disorder as well as emerging novel treatments that may change or improve approaches to treatment.

Recent findings The current treatments for opioid use disorder are methadone, buprenorphine, and naltrexone. Of the three, methadone has been the most studied and longest treatment used. However, because of limitations with prescribing and safety concerns with methadone, buprenorphine is becoming a widely used pharmacologic treatment alternative. Naltrexone remains less commonly utilized. New treatments such as lorcaserin and medicinal cannabis have potential to make an impact in addressing the opioid epidemic; however, controlled human studies are needed to assess their full potential.

Summary Current treatments for opioid use disorder are beneficial, but have the disadvantage of abuse potential, compliance concerns, and prescribing limitations. Novel pharmacologic treatments may be able to address these concerns. Future research should continue to evaluate the efficacy of novel medications for the treatment of opioid use disorder.

Introduction

There has been a surge in use of prescription opioid medications and other opioids such as heroin in the USA, leading to what is being called an opioid epidemic. In 2016, an estimated 11.8 million people aged 12 or older misused opioids in the past year in the USA [1]. Prescription opioids have been used in the treatment of pain and have the highest prevalence of medication misuse in comparison to stimulants, tranquilizers, and sedatives. In the past year, 2.7 million people, aged 12 and older, had a prescription drug use disorder; the most commonly used reason for the misuse of prescription pain relievers was to alleviate physical pain [2••].

Misusing prescription opioids has been linked to heroin use. A study found that youth that misused prescription opioids even once were more likely to have heroin and injection drug use [3]. Heroin use has steadily increased in the USA. In 2016, an estimated 626,000 people aged 12 or older had a heroin use disorder. Heroin, as well as prescription opioid misuse, is straining the medical system. According to the CDC, prescription opioids contributed to more than 40% of overdose deaths in the USA, with the highest rates among people aged 25 to 54 years [4]. Heroin-related overdoses have also increased, with rates increasing by 20% from 2015 to 2016, and the highest death rate occurring in males aged 25–44 [4]. There has been a surge in admission to treatment facilities for opioid dependence and addiction. As of 2016, an estimated 3.6 million adults aged 18 or older received treatment for substance use in the past year. Of those estimated, 629,000 adults received treatment for the misuse of prescription pain relievers and 636,000 adults received treatment for heroin use [5].

Emergency departments have seen a 30% increase in hospitalizations related to opioid overdoses [6]. In the USA, the Midwest region has exhibited a significant increase in opioid overdose-related emergency department (ED) visits, notably in Wisconsin, Illinois, Indiana, Ohio, and Missouri [6]. In 2016, Virginia reported a significant increase in ED visits for heroin use among people aged 25 to 34 years and opioid-related overdoses among people aged 15 to 34 years. Rates of overdoses due to fentanyl and heroin have also increased [7]. Consequently, Virginia instituted prescription drug monitoring, programs increasing accessibility for naloxone training, and calling public awareness for the opioid crisis. With the number of individuals with opioid use disorder continuing to increase, it is essential to understand the impact of current and novel treatments for opioid use disorder.

Current treatments for opioid use disorder

Methadone

Methadone is a full mu opioid receptor agonist that has been used for the treatment of opioid use disorder since the 1960s and is considered a mainstay of maintenance therapy. Methadone is the most studied of all the opioid treatment medications; it has consistently been found to be more effective than non-medication approaches in keeping patients engaged in recovery care and reducing heroin use [8••].

Initially developed during World War II in Germany as a rapidly absorbed oral synthetic opioid analgesic with a long half-life, it was first used to help treat soldiers' pain during an opioid shortage. The utility of methadone as a treatment for opioid addiction was not recognized until years later. It was during the 1960s when Dr. Vincent P. Dole introduced the idea of using methadone for treatment of heroin addiction. Methadone was noted to be beneficial in helping to prevent symptoms of withdrawal and opioid cravings when given to soldiers returning from the Vietnam War that had become addicted to heroin while overseas. Due to the long half-life and need for only once daily dosing, methadone became, at that time, the only pharmacologic treatment for opioid addiction. It was noted to help socially "rehabilitate" individuals with the goal of keeping them off illicit

substances, keeping them out of jail and keeping them employed [9•]. It was during this time that the concept of medication-assisted therapy was developed with the first clinic being opened in New York in 1964 [10•].

Medication-assisted therapy with methadone decreases or eliminates the use of heroin or other opioids of abuse, reduces rates of death and criminality associated with opioid use, and allows patients to improve their health and social productivity [10•]. Medication-assisted therapy has been shown to decrease the chance of relapse by as much as 80% [11]. In addition, engaging in methadone maintenance treatment has the potential to reduce the transmission of infectious diseases associated with intravenous drug use, such as hepatitis and HIV [10•].

Despite having long-standing evidence of effectiveness, there are challenges involved in methadone therapy. The action of methadone at opioid receptors can lead to opioid-related side effects including sedation, respiratory depression, and constipation. These effects are additive with other medications that cause these effects as well as with concomitant medications that increase methadone levels. Benzodiazepines, barbiturates, alcohol, and of course, other opioids should be avoided in patients taking methadone. Sleep apnea, central nervous system injury, and severe lung disease can increase the risk of respiratory depression in patients taking methadone [12•].

Multiple enzymes extensively metabolize methadone by the liver's CYP450 system; thus, the risk of drug-drug interactions is high [13]. Methadone has a potential to cause serotonin syndrome when given with serotonergic medications such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRI), as well as certain tricyclic antidepressants (TCAs). Methadone should not be used with MAOIs. If methadone is used with SSRIs, SNRIs, or TCAs, it should be dosed conservatively with very careful monitoring for serotonin syndrome. Symptoms of serotonin syndrome can include agitation, clonus, and hyperreflexia as well as confusion, lethargy, coma, and seizures. Autonomic instability, particularly hyperthermia, is typically seen when serotonergic syndrome occurs [12•]. In addition to its activity at the NMDA receptor and serotonin and norepinephrine reuptake transporters, methadone can also cause QT prolongation, which can lead to Torsades de Point (TdP) and sudden cardiac death. Drug interactions that also prolong the QT interval or result in increased levels of methadone increase the risk of QT prolongation [12•].

Another challenge to providing methadone therapy is the restrictions that require treatment to be in a federally approved treatment center. These centers must deliver counseling, urine testing, and directly observed administration of medication [8••]. These restrictions can inhibit access to care, especially in rural communities or for people with limited access to transportation or areas with limited public transportation [14]. The programs are complicated to establish while meeting all regulatory requirements, discouraging them from being established in many centers.

Buprenorphine

The emergence of buprenorphine as an FDA-approved medication for detoxification and maintenance of opioid dependence has allowed both patients and providers more treatment options. Buprenorphine is a partial opioid agonist, which can be prescribed to minimize opioid withdrawal symptoms during

opioid recovery [11]. Buprenorphine has a higher affinity for opioid receptors than opioids such as heroin. It also, unlike methadone, exhibits a ceiling effect so that higher doses do not create more intense euphoric feelings or increase possible respiratory depression [11]. It is used in a combination formula with naloxone for substance abuse treatment. The addition of naloxone in buprenorphine-based treatment helps to assist in preventing intravenous misuse of buprenorphine.

Buprenorphine is available in several formulations. The different formulations of buprenorphine for addiction treatment include sublingual buprenorphine/naloxone film and tablet as well as a buprenorphine implant and recently approved depot buprenorphine injection formulation. Buprenorphine-naloxone is an excellent option to consider for patients who may be at high risk for methadone toxicity such as elderly patients, those at risk for prolonged QT intervals, and those who are at high risk for polypharmacy, as methadone can interact with many different medications [15]. It is important to keep in mind that due to its partial agonist properties at μ-opioid receptor, buprenorphine will precipitate opioid withdrawal in individuals who are physically dependent on full opioid agonists [16].

Buprenorphine-based treatment has been an important advancement in the effective management of opioid use disorder, but daily dosing strategies present challenges such as under-treatment due to non-compliance and concerns of misuse such as diverting the medication by sharing it with others or selling it illegally for recreational use. Injectable and implantable forms can be beneficial by reducing an individual's physical control of the medication, which increases the probability of medication adherence and reduces opportunity for diversion or misuse [16]. Injectable and implantable formulations are currently recommended for use after the patient has been stabilized on oral medication first.

Another opportunity for increasing access to buprenorphine treatment is initiation of buprenorphine treatment in the emergency department (ED). Recent studies have shown that it is feasible to initiate buprenorphine in the ED, with improved 30-day outpatient treatment engagement compared to a simple referral group [17]. Thus, ED-initiated buprenorphine maintenance treatment is an option to improve initial treatment engagement. However, outpatient buprenorphine treatment appointments need to be available to take advantage of ED-initiated buprenorphine. Unfortunately, in many areas, there can be a significant delay in outpatient clinic appointments to continue buprenorphine treatment.

Other considerations with buprenorphine products include limits imposed on the number of patients a provider can treat at one time, typically 30 the first year and then a provider can apply to increase that number to 100 [14]. Additionally, the fact that physicians are required to take an 8-h waiver course to be able to prescribe the medication and NP and PAs were not allowed until recently to become waivered has limited availability of this treatment option.

Naltrexone

In October 2010, the Food and Drug Administration (FDA) approved extended-release naltrexone based primarily on findings from a trial conducted in Russia, where agonist treatment is illegal [18]. Naltrexone administration requires a complete opioid detoxification period, typically 7–10 days; otherwise, it may precipitate withdrawal [19•]. Naltrexone is available in several

formulations including oral as well as in an extended-release injection. One intramuscular injection of extended-release naltrexone can block an individual's response to opioids for up to 28 days [18].

The advantages of naltrexone are that it can be given in a wide variety of settings, including primary care settings and criminal justice settings along with specialty clinics. The depot formulation allows patients to only see their provider monthly as opposed to daily as with some of the other OUD medication treatment plans. Extensive research has shown that patients treated with extended-release naltrexone have lower rates of treatment dropout, less opioid use, and reduced cravings [19•]. Unlike methadone and buprenorphine, there is no known diversion potential for extended-release naltrexone, increasing its appeal to providers and the criminal justice system.

However, barriers to extended-release naltrexone utilization also exist. It is relatively expensive. A study by Jackson et al. [18] in 2015 found that extended-release naltrexone had a state-average per-diem price of $48.36, compared with $13.31 and $21.16 for methadone and sublingual buprenorphine treatment, respectively. Also, adherence tends to be lower in naltrexone-treated patients compared to agonist therapy; however, a recent study found that if patients could tolerate opioid detoxification, then depot naltrexone showed non-inferiority to sublingual buprenorphine for treatment retention and drug-free urine tests [20]. Naltrexone can be an excellent choice for those patients who have a high motivation to abstain, particularly those who have been in the criminal justice system or health care providers whose drug use is carefully monitored and face sanctions if they resume their drug use. [21]. See Table 1 for a list of pros and cons.

Novel treatments for opioid use disorder

Lorcaserin

There is a clear need to develop new treatments for opioid use disorders that have less abuse potential and fewer side effects and are cost effective. Methadone has the potential for abuse and can cause QT prolongation, which can be further worsened by drug interaction. Non-compliance and misuse is a concern during buprenorphine treatment. Extended-release naltrexone does not have the potential for abuse; however, treatment can be expensive and it requires complete a complete opioid detoxification period. New areas of research are exploring pharmacologic treatments in several different areas. One of the new areas of focus is how cue reactivity is engaged in substance use. Cue reactivity is a conditioned (learned) response to specific stimuli, occurring within the context of specific environmental surroundings that includes both subjective and physiological components. The limbic-corticalstriatial circuitry mediates development of cue reactivity and drug reward and is regulated by dopamine and serotonin (5-HT) neurotransmission, particularly the 5-HT_{2C} receptor (5-HT_{2C}R). Lorcaserin (Belviq) is a selective 5-HT_{2C}R agonist that is FDA-approved for the treatment of obesity. Selective 5-HT_{2C}R agonists have been shown to reduce cue reactivity for nicotine and cocaine. In a phase II clinical trial, lorcaserin along with counseling, demonstrated increased smoking cessation among participants [22]. In preclinical trials, lorcaserin has been shown to reduce self-administration of cocaine and other psychostimulants [23].

Table 1. Pros and cons of treatment options for opioid use disorder

Treatment	Pros	Cons
Methadone	Less relapse Extensive research on effectiveness Reduction in infectious diseases Long half-life	Abuse potential Interactions with other medications QT prolongation Long-term side effects Treatment must be in a federally approved opioid treatment center Risk of overdose to methadone itself (treatment with methadone reduces risk of overdose to other opioids)
Buprenorphine	Less medication interactions than methadone Low risk of overdose unless combined with other drugs (benzodiazepines)	Misuse and diversion risk (with sublingual formulations) Can precipitate withdrawal in patients taking opioids Waiver needed to prescribe buprenorphine for opioid use disorder
Naltrexone	No abuse or diversion risk No need for special clinic or DEA waiver to prescribe	Cost of depot formulation Requires a complete opioid detoxification period Historically lower patient acceptance than agonist/partial agonist treatment, although patients who can undergo opioid detoxification can do well in treatment
Lorcaserin	No documented abuse potential Limited side effects Addresses cue reactivity and impulsivity in preclinical models May have effects on more than one drug based on preclinical models	Human data limited Potential risk of serotonin syndrome if combined with other serotonergic agents
Medicinal Cannabis	Safety profile for overdose risk significantly better than full agonist opioid treatments Potential effects on pain reduction	Abuse potential More human data needed Schedule 1 drug Risk of psychosis Cardiovascular risks

Prescription painkillers, such as oxycodone, are the most commonly used illicit drugs in the USA, second only to marijuana [24]. This increase in opioid misuse has led to research examining the efficacy of lorcaserin on self-administration and cue reactivity in opioid use. In a study in rodents, lorcaserin suppressed not only self-administration of oxycodone but also cue reactivity in both abstinence and extinction-reinstatement models [25••]. In another study with heroin-treated mice, when pretreated with lorcaserin, there was a decrease in behavioral sensitization and naloxone-precipitated withdrawal [26••].

Human studies utilizing lorcaserin for cocaine addiction are underway. Further research on the role of lorcaserin and other serotonergic compounds, as a single or adjunctive treatment for opioid use disorder, is needed.

Medicinal cannabis

Another potential novel treatment for opioid use disorder that has received significant recent notoriety is medicinal cannabis. The use of cannabis for its

medicinal properties is nothing new. The western world was introduced to the medical properties of *C. indica* or "Indian hemp," through Dr. William Brooke O'Shaughnessy after his travels in India in the mid-1800s. He believed that it could be used not only as an analgesic, but also as a muscle relaxant. Various physicians followed his recommendations and began recommending doses of cannabis to treat several ailments. However, as medicinal cannabis began to gain use, other factors came into to play to stall its growth. There was a concern over abuse of marijuana, and in August 1970, Dr. Roger Egeberg wrote a letter recommending that cannabis be labeled as a Schedule I substance until further research was done. As a Schedule I substance, marijuana is categorized as an illegal substance that has the high potential abuse and no current medical use [27•].

Cannabis is made up of phytocannabinoids that target the endocannabinoid receptors CB_1 and CB_2. Although endocannabinoid receptors are numerous throughout the body, CB_1 receptors are mainly located in the nervous system while CB_2 receptors are located mainly in the immune system. Two of the primary phytocannabinoids that have been studied are Δ-THC, a partial agonist at CB1 and CB2 receptors, and cannabidiol (CBD), which has a low affinity at the CB1 and CB2 receptors. The FDA has approved two synthetic versions of Δ-THC, Marinol (dronabinol) and Cesamet (nabilone), for medical purposes. Sativex (nabiximols) is a mouth spray that is used to treat spasticity associated with multiple sclerosis and has been approved for use in 27 countries. Nabiximols are composed of equal amounts THC and CBD and are currently being studied in phase III clinical trials for the treatment of cancer pain [28•].

Currently, physicians are making a push to legalize medicinal marijuana to increase scientific knowledge. Dr. Sanjay Gupta, Chief Medical Correspondent for CNN, is one of those physicians who published an article in 2013 retracting his anti-marijuana stance and urged for more research and understanding on medicinal marijuana, as well as pushing for a schedule reclassification for marijuana [29]. In 2018, Dr. Gupta published an article to Attorney General Jeff Sessions stating that medicinal marijuana could be the answer for alleviating the opioid epidemic. He argued that medicinal cannabis, in place of prescription opioids, could be used to treat pain with fewer side effects [30].

Some uncontrolled evidence supports a reduction in opioid use related to medical marijuana. A preliminary study conducted by Vigil et al. [31••] found that people with chronic pain that were enrolled in a Medical Cannabis Program significantly reduced their dosage of prescription opioid prescriptions compared to those that were not enrolled in the program. Powell et al. [32••] found that states that had medical marijuana laws and had legal access to marijuana dispensaries resulted in the reduction of prescription opioid misuse, deaths due to opioid overdose, and treatment admissions for addiction to pain medication. The problem with these uncontrolled studies is that they cannot determine whether there is an actual causal link between medical marijuana use and reduced opioid use. In addition, the use of cannabis does come with some negatives. Cannabis has been shown to increase the risk of psychosis in adolescents [33] and cardiovascular illness such as stress cardiomyopathy in adults [34]. As with lorcaserin, more clinical research is needed, especially related to the relative effect of THC vs. CBD on opioid misuse.

Conclusion

The increasing misuse of prescription opioids and heroin in the USA has caused a rise in opioid-related overdose, deaths, and emergency room visits. It is therefore more critical than ever to understand the role that current and novel medications play in the treatment of opioid use disorders. Current long-standing treatments such as methadone, buprenorphine, and naltrexone have been studied and are widely used, but have their drawbacks. Methadone can cause interactions with other medications and is associated with QTc prolongation, has an overdose risk, and must be obtained from federally approved dispensaries. Buprenorphine has less of a problem of medication interactions than methadone and has a lower overdose risk and less cardiac effects; however, the number of physicians who have the DEA waiver to prescribe buprenorphine is limited and the sublingual formulation of buprenorphine has a risk of diversion. New depot formulations of buprenorphine should reduce the diversion risk. Novel methods of initiation of buprenorphine, including ED-initiated treatment, show promise to increase buprenorphine accessibility, but access to outpatient clinics where buprenorphine is prescribed as a long-term treatment continues to be a limitation. Depot naltrexone has been shown to be as effective as sublingual buprenorphine in patients who can tolerate detoxification from opioids, but not all patients are willing to undergo detoxification. Novel treatments, such as lorcaserin and medicinal cannabis, may provide additional treatment options, but further human research is needed on the utility of novel treatments for opioid use disorder.

Compliance with Ethical Standards

Conflict of Interest

Dr. Moeller has grant support from Indivior pharmaceuticals. Dr. Johns has nothing to disclose.

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