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Prevention and Treatment of Opioid Misuse and Addiction
A Review

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IMPORTANCE More than 42 000 Americans died of opioid overdoses in 2016, and the fatalities continue to increase. This review analyzes the factors that triggered the opioid crisis and its further evolution, along with the interventions to manage and prevent opioid use disorder (OUD), which are fundamental for curtailing the opioid crisis.

OBSERVATIONS Opioid drugs are among the most powerful analgesics but also among the most addictive. The current opioid crisis, initially triggered by overprescription of opioid analgesics, which facilitated their diversion and misuse, has now expanded to heroin and illicit synthetic opioids (fentanyl and its analogues), the potency of which further increases their addictiveness and lethality. Although there are effective medications to treat OUD (methadone hydrochloride, buprenorphine, and naltrexone hydrochloride), these medications are underused, and the risk of relapse is still high. Strategies to expand medication use and treatment retention include greater involvement of health care professionals (including psychiatrists) and approaches to address comorbidities. In particular, the high prevalence of depression and suicidality among patients with OUD, if untreated, contributes to relapse and increases the risk of overdose fatalities. Prevention interventions include screening and early detection of psychiatric disorders, which increase the risk of substance use disorders, including OUD.

CONCLUSIONS AND RELEVANCE Although overprescription of opioid medications triggered the opioid crisis, improving opioid prescription practices for pain management, although important for addressing the opioid crisis, is no longer sufficient. In parallel, strategies to expand access to medication for OUD and improve treatment retention, including a more active involvement of psychiatrists who are optimally trained to address psychiatric comorbidities, are fundamental to preventing fatalities and achieving recovery. Research into new treatments for OUD, models of care for OUD management that include health care, and interventions to prevent OUD may further help resolve the opioid crisis and prevent it from happening again.

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Supplemental content

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More than 2 million Americans have an opioid use disorder (OUD), and in 2016, more than 42 000 Americans died of opioid overdoses.[1,2] Although in the first years of the opioid crisis, most overdose-associated deaths were caused by misuse of prescription analgesics, heroin and synthetic opioids (fentanyl and its analogues) currently account for most of the fatalities, a scenario that reflects the changing nature of the opioid crisis (**Figure 1**). We reviewed the pharmacology of opioids because it is relevant to their rewarding and analgesic effects that lead to their misuse, the epidemiology of the crisis and its transformations in the past 2 decades, and the interventions to treat and prevent OUD that must be implemented to overcome the current crisis and prevent it from happening again.

Opioid Pharmacology

Opioid drugs—prescription analgesics and illicit drugs—exert their pharmacologic effects by engaging the endogenous opioid system, where they act as agonists at the μ-opioid receptor (MOR). The agonist action at the MOR is responsible for the rewarding effects of opioids and analgesia. In the brain, these receptors are highly concentrated in regions that are part of the pain and reward networks. They are also located in regions that regulate emotions, which is why long-term opioid exposure is frequently associated with depression and anxiety.[4] In addition, MORs are located in brainstem regions that regulate breathing; there,

agonists inhibit neuronal firing, which results in respiratory depression, which is the main cause of death from opioid overdoses.[5] The various types of opioid analgesics (morphine, hydrocodone, and oxycodone hydrochloride), illicit opioids (heroin and fentanyl and its analogues), and medications to treat OUD (methadone hydrochloride, buprenorphine, and naltrexone hydrochloride) or to reverse overdose (naloxone hydrochloride) differ in terms of their affinities to MOR, their functional effects at the MOR (agonists, partial agonists, or antagonists), and their selectivity for MOR compared with that for κ- or Δ-opioid receptors (eTable in the Supplement).

Physical Dependence on Opioids

Physical dependence on opioids is distinct from addiction, and although they reflect different neuroadaptation processes, they are frequently confused because the term dependence is frequently used to connote addiction. This confusion leads to misunderstanding by patients and physicians on the appropriate use of these medications. It has also led to misestimation of the risk of addiction when opioids are used for the treatment of pain.

Physical dependence manifests with the emergence of withdrawal symptoms when use of opioids is abruptly discontinued (or even sometimes when tapered) after long-term administration. Symptoms include insomnia, cramps, diarrhea, nausea, vomiting, and body aches, as well as dysphoria, anxiety, and irritability. The severity of these symptoms varies, depending on chronicity, the opioid drug in question (symptoms are stronger for more potent and shorter-acting drugs), and individual variability.

All patients treated with opioids or misusing them will develop physical dependence, and withdrawal symptoms usually resolve promptly within a few days but can sometimes last weeks after use is discontinued. Dependence can lead to opioid seeking as individuals attempt to avoid withdrawal symptoms, contributing to addiction by perpetuating repeated exposures.

Opioid Misuse

Opioids are misused for their analgesic effects and rewarding properties; people with physical dependence or addiction to opioids may also misuse opioids to avoid withdrawal symptoms. The use of opioids for their rewarding effects reflects their ability to increase the activity of dopamine neurons in the ventral tegmental area and to increase dopamine release in the nucleus accumbens.[6] In the context of prescription opioids, misuse refers to use other than as prescribed. When misused for their rewarding effects, prescription opioids are frequently snorted or injected, which leads to faster uptake in the brain, enhancing their rewarding effects; when misused via oral administration, opioids tend to be taken at higher doses and/or in combination with other drugs (eg, alcohol). Although opioid misuse does not necessarily result in addiction, opioids are highly addictive, and the risks increase with repeated use, higher doses, and when injected. According to the National Comorbidity Survey, the proportion of users becoming addicted to heroin after using opioids (23%) was higher than for alcohol (15%) and cocaine (17%).[7]

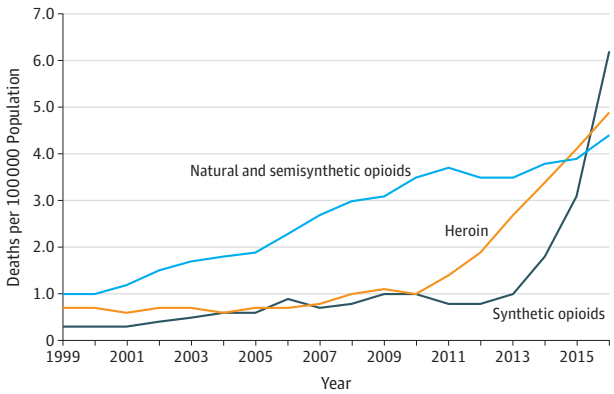
Opioid Addiction

Addiction is distinct from physical dependence and occurs in a smaller subset of opioid users, developing much more gradually. The changes are longer lasting and often require long-term treatment to achieve recovery. Until recently, it was mistakenly believed that pain protected against addiction to opioid medications. A study[8] assessing *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) criteria for OUD in a cohort of patients receiving opioids for chronic pain found that 28.1% had mild OUD, 9.7% had moderate OUD, and 3.5% had severe OUD. Multiple factors have been associated with vulnerability to opioid addiction (term used here to refer to moderate or severe OUD), including genetics, age at initiation, adverse social environments, and psychiatric comorbidities (eg, anxiety, depression).

Addiction to opioids (or other drugs) involves molecular processes associated with learning, which help consolidate automatic behaviors in response to the drug and the stimuli associated with the drug; this is referred to as conditioning. People can become conditioned to opioids because of their rewarding effects or because of their relief of pain, withdrawal symptoms, or dysphoria. With repeated exposures, conditioning is strengthened, energizing the desire and motivation to consume the drug.

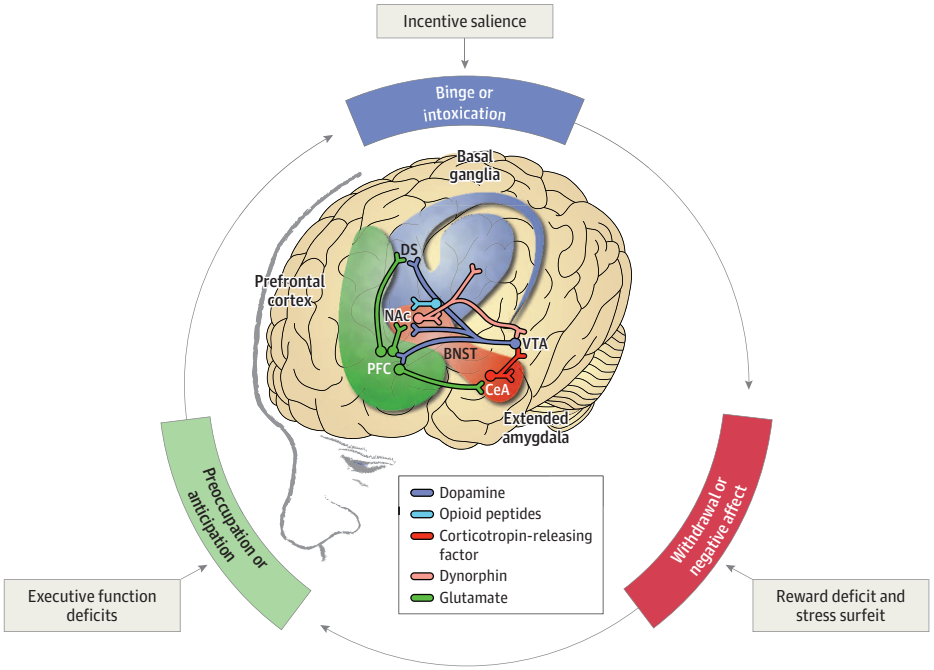
Repeated drug exposures also disrupt striatocortical circuits that are necessary for the proper functioning of the prefrontal cortex, which is needed for self-regulation. Disruption of these circuits underlies the impulsiveness and compulsivity characteristic of addiction. In addition, disruption of circuits in the extended amygdala that regulate emotions and stress renders the person with addiction vulnerable to dysphoria or depression, anxiety, and irritability.[9] These neurocircuitry changes are mutually reinforcing (**Figure 2**), contributing to addiction's relapsing nature. Changes to the dopaminergic circuits of the basal ganglia, the extended amygdala, and the prefrontal cortex correspond to the sequential stages of binge or intoxication, withdrawal, and craving that are characteristic of all substance use disorders. In people addicted to opioids, these changes also persist long after drug use discontinuation, which is why the

Figure 1. Three Waves of the Increase in Deaths Due to Opioid Overdose



Wave 1 was from 1990 to 2004, wave 2 from 2005 to 2010, and wave 3 from 2011 to 2016. Data are from the National Vital Statistics System Mortality File. Adapted from the Centers for Disease Control and Prevention.[3]

Figure 2. Three Stages of the Addiction Cycle and Associated Neural Circuits



People with substance use disorders cycle through 3 stages in rates that vary with the drug and the severity of their disorder: binge or intoxication, negative affect or withdrawal, and preoccupation or anticipation (craving); these stages are associated with activity in the basal ganglia (nucleus accumbens [NAc] and dorsal striatum [DS]), extended amygdala, and prefrontal cortex (PFC), respectively. BNST indicates bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; and VTA, ventral tegmental area. Adapted from Koob GF and Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;38:760-773.[10]

treatment of opioid addiction requires continuous care to achieve recovery.

Opioid Analgesia

Opioids are effective for treating severe acute pain, but their effectiveness in treating chronic pain is less clear.[11] Tolerance rapidly develops to their analgesic effects; thus, patients require increasingly higher doses, thereby increasing the risk of addiction, respiratory depression, and fatal overdose. Furthermore, opioids can result in hyperalgesia, exacerbating instead of alleviating pain.[12] The opioid crisis has led to various measures that encourage greater caution in opioid prescribing, including new Centers for Disease Control and Prevention guidelines for management of chronic pain.[13] Prescription drug monitoring programs are intended to reduce "doctor shopping" (receiving prescriptions for controlled substances from several physicians) by patients and harmful prescribing by physicians.

Shifting Patterns of Opioid Misuse

The opioid crisis was sparked initially by the overreliance on opioids to treat pain. The overprescription of opioid analgesics facilitated their diversion and misuse, while also exposing patients with chronic pain to the risk of addiction and overdose without necessarily improving their pain conditions.

Beginning in the early 2000s, some of those addicted to prescription opioids (particularly young adults) began transitioning to heroin because the latter was cheaper and easier to obtain. Three quarters of treatment-seeking heroin users who had begun their drug use in the 2000s began with prescription opioids.[14] Increased availability of inexpensive, high-purity heroin has made it easier for new opioid users to initiate drug use with heroin, possibly in part because high-quality heroin can be administered through other routes than injection. Between 2005 and 2015, the percentage of new opioid users initiating drug use with heroin increased from 8.7% to 33.3%.[15]

The shift toward heroin use contributed to the escalation of opioid-associated fatalities, now further exacerbated by adulteration of heroin with fentanyl or fentanyl analogues. As of 2016, fentanyl and other synthetic opioids accounted for more overdose deaths than prescription opioids or heroin (Figure 1). The high potency of fentanyl (50 times more potent than heroin) increases the risk of overdosing; this risk is further exacerbated by its combination with other drugs and the impossibility of controlling the dose administered.

Epidemiology of Opioid Misuse and OUD

In 2016, almost 11 million American adults (age ≥18 years) misused opioids in the past year, with males (6.4 million [4.9%]) misusing opioids more frequently than females (5.4 million [3.9%]).[1] Misuse of opioids by adolescents remains low, whereas the highest rates of misuse are among young adults aged 18 to 25 years. In 2016, a total of 392 000 individuals aged 18 to 25 years (1.1%) had OUD compared with 153 00 (0.6%) of adolescents and 1 599 000 (0.8%) of adults 26 years and older.[1]

The rates of fatalities due to OUD and overdose and the types of opioids triggering overdoses vary markedly by state. In 2016, there were 43.4 opioid overdose fatalities per 100 000 persons in West Virginia compared with 29.7 in Massachusetts and 5.9 in Arkansas.[16] The geographic diversity correlates to a certain extent with socio-

economic factors, such as poverty. Among those under the poverty level, 5.9% were reported to have OUD compared with 4.8% of those between 100% and 199% of the poverty level and 3.9% of those at twice or more than the poverty level.[1] There is also variability among races/ethnicities, with opioid misuse being most prevalent among non-Hispanic white individuals (4.6% vs 4.0% among African American individuals and 1.8% among Asian individuals).[1] These prevalence rates are changing, however, as prescription opioids are being replaced by heroin and synthetic opioids.

The increase in the exposure to opioids among females has translated into a 4-fold increase in the number of neonates born with neonatal abstinence syndrome between 1999 and 2013 (from 1.5 to 6.0 per 1000 hospital births).[17] As in other populations, opioid exposure in pregnant women reflects prescription of opioids for pain management, medication-assisted treatment for OUD, and opioid misuse. On the basis of data through 2007, a total of 23% of pregnant women enrolled in Medicaid filled an opioid prescription during pregnancy.[18] Although severity of neonatal abstinence syndrome has been shown to be substantially milder when women are treated with methadone or buprenorphine, their newborns still require care for neonatal abstinence syndrome.[19]

Comorbidity of OUD

Pain is frequently comorbid with OUD, reflecting that opioid exposure was initially intended to alleviate pain and that hyperalgesia is associated with repeated exposure to prescription and illicit opioids.[20] Chronic pain might increase the risk of an OUD in part by dysregulating the brain's stress circuitry and by increasing risk of tolerance to the analgesic effects of opioids. Increased conditioning to high doses of morphine was reported in an animal model of chronic pain.[21]

In addition, OUD is highly comorbid with other mental illnesses, especially mood disorders, likely because individuals with mental illness, particularly a mood disorder, are more apt to be prescribed an opioid analgesic. A recent article[22] reported that approximately 50% of opioid prescriptions are written for individuals with a mental illness, even though they represent only 16% of the population. This finding reflected the higher prevalence of chronic pain among those with a mood disorder. Even after controlling for severity and type of pain condition, those with a mood disorder were more likely to receive a prescription and to receive a higher opioid dose than those without a mood disorder. Patients with mood disorders might also be at greater risk of misusing opioids because of their antidepressant properties.[23,24]

Some of the opioid overdose fatalities could also reflect intentional suicide because suicide risk is higher in patients with OUD, chronic pain, or a mood disorder.[25] Moreover, among patients with chronic pain and suicidal ideation, 75% reported that they planned to do so through overdose, and risk of successful suicide was doubled in patients with chronic pain compared with control individuals without pain.[26] A previous report[27] tried to estimate the risk of suicide among veterans with OUD. In female veterans with OUD, suicide risk was more than 8 times greater than for those without OUD; in male veterans, the risk was more than twice that for those without OUD. Estimating the exact proportion of suicides among fatalities classified as being due to overdose is difficult, but this incidence might be between 20% and 30%.[28]

Frequently, OUDs are comorbid with infectious diseases because injecting drugs increases the risk of blood-transmitted infections, including HIV infection, hepatitis C virus infection, and endocarditis. In 2015, injection drug use accounted for 9.1% of the 39 513 new diagnoses of HIV infection in the United States,[29] and the incidence of hepatitis C virus infection increased 2.9-fold from 2010 to 2015.[30]

Prevention

The misuse of and addiction to prescription analgesics, heroin, and synthetics (fentanyl and analogues) require universal and targeted prevention strategies. An important intervention to decrease prescription opioid misuse is reducing inappropriate prescribing. New federal guidelines and improved physician education in opioid prescribing and pain management are already having an influence on reducing overprescribing, although prescription rates in the United States are still high, with prescriptions of 178 billion morphine milligram equivalents in 2017.[31] Prescription drug monitoring programs have been implemented in all states, although their effectiveness has been mixed depending on their ease of operability and how they are regulated.

Other strategies include developing new, safer pain medications and abuse-deterrent formulations (ADFs) of existing opioid medications. The ADFs contain properties intended to make intentional misuse more difficult or less rewarding, and evidence suggests that they can decrease misuse of that specific formulation. However, even though ADFs have been clinically available for several years, they represent a small percentage of the total opioid prescriptions. The restricted penetration of ADF opioids is likely to reflect their higher costs, which limit their reimbursement.[32] In some instances, as was the case for the original oxycodone hydrochloride formulation, ADFs may encourage a shift to misuse of other opioids or to unexpected routes of administration.[33,34] A Risk Evaluation and Mitigation Strategy can be required by the US Food and Drug Administration for medications with serious safety concerns. The Risk Evaluation and Mitigation Strategy for opioid medications includes training in acute and chronic pain management, including pharmacologic and nonpharmacologic treatments.[35]

Strategies that would have an influence on all forms of opioid misuse involve implementing evidence-based prevention interventions for substance use disorders in family, school, and/or community settings. Universal prevention interventions initiated in childhood and adolescence decrease later drug use, including prescription opioid misuse.[36-38] These interventions share common elements intended to strengthen protective factors in individuals and their families, schools, and communities while decreasing factors associated with risk (**Box 1**). For children or adolescents who are at high risk because of adverse social environments or psychiatric disorders, tailored interventions can prevent future drug misuse.[40]

Socioeconomic factors continue to influence the opioid crisis. Restricted job opportunities, erosion of communities, and loss of purpose have been linked to the psychological pain and stress fueling the demand for opioids.[41] Initially, opioid misuse was mostly concentrated in rural areas and among poor white Americans, but as misuse of heroin and synthetics has expanded, it is now affecting urban areas and minority groups. Thus, strategies that provide access to educa-

Box 1. Risk and Protective Factors for Adolescent and Young Adult Substance Use

Risk Factors

Individual
- Genetic factors
- Starting substance use early
- Perceiving little risk in substance use
- Peers who use substances
- Emotional distress or aggressiveness that starts early and is persistent
- Psychiatric disorder

Family
- Substance misuse in the family
- Family conflict, abuse, or neglect
- Parents who favorably view or approve of substance use

School
- Poor academic performance
- Student does not view school as rewarding or meaningful and lacks commitment to school
- Perception that use of drugs among classmates is high
- Poor control over school drug consumption

Community
- Lower socioeconomic status
- Availability and cost of drugs and alcohol
- Community norms favorable toward alcohol and drugs

Protective Factors

Individual
- Resiliency
- Self-efficacy
- Spirituality
- Interpersonal skills, including social, emotional, and cognitive skills
- Treatment of psychiatric disorder

Family, school, and community
- Attachment to family, school, and community
- Meaningful involvement with family, school, or community
- Positive behavior is recognized
- Norms in the family, school, and community that drug misuse is not acceptable
- Being in a committed relationship or marriage with a partner who does not misuse drugs
- Opportunity for fulfilling extracurricular activities

Adapted and modified from US Department of Health.[39]

tion to all citizens and sustainable work opportunities are long-term interventions for preventing OUD and associated problems.

Treatment

The strong evidence for the effectiveness of medications for OUD (frequently also referred to as medication-assisted treatment) has made medications for OUD the criterion standard of treatment for OUD. Currently, 3 medications are approved by the US Food and Drug Administration to treat OUD: methadone (a full agonist at the MOR), buprenorphine (a partial agonist at the MOR), and extended-release naltrexone (an antagonist at the MOR). Details on doses, dispensing, and clinical effects for medications for OUD are provided in **Box 2**. Medications for OUD are ordinarily given in conjunction with behavioral treatment, and studies[49,50] have generally shown strong benefits of medications for OUD compared with behavioral treatments alone. Medications for OUD increase social functioning while reducing illicit opioid use, risk of overdose, transmission of infectious disease, criminality, and treatment retention. Unfortunately, stigma toward methadone and buprenorphine because of their agonist actions at the MOR has limited their use because of the belief by many that their use substitutes one addictive drug for another.

Treatment with agonists and partial agonists is pharmacodynamically distinct from sustaining an addiction to a prescription or illicit opioid.[51] The slow rate of entry of methadone and buprenorphine into the brain (Box 2) limits their rewarding effects. This limitation is because drug reward is accentuated when drugs enter the brain rapidly and have fast-binding properties, which explains why methadone and buprenorphine, although providing relief from craving and withdrawal, do not produce the intense euphoria achieved with heroin or other opioids when they are injected or taken at high doses. In addition, their slow dissociation and clearance from MOR prevent emergence of craving and withdrawal symptoms during treatment. The physiologic stability provided by medications for OUD facilitates the reentry and integration of patients to their communities.

Because of their agonist properties, methadone and buprenorphine are only available from opioid treatment programs (methadone) or from prescribers with a special Drug Abuse Treatment Act 2000 waiver (buprenorphine). Extended-release naltrexone, because it is an antagonist, can be prescribed by any physician and presents no abuse liability; because the use of extended-release naltrexone for OUD is relatively new and adherence to the immediate-release naltrexone has historically been a problem, fewer studies[47,48] have reported naltrexone's effectiveness, but evidence is mounting that it may be as effective as buprenorphine for some patients.

Despite their efficacy, medications for OUD are underused. In 2015, between 31% and 37% of patients with OUD in specialty facilities received medications for OUD.[52] A recent study[53] in Massachusetts reported that only 30% of those who survived an opioid overdose received medications for OUD in the year after their overdose. In addition, when they are prescribed, buprenorphine and methadone are frequently given at too low a dose and/or for too short a duration. For example, one study[54] reported that nearly half of patients treated with buprenorphine in opioid treatment facilities receive 90 or fewer days or continuous treatment.

Expanding access to medications for OUD in primary care and specialty settings (psychiatrists, pain clinics, emergency departments, and infectious diseases clinics) will require educating practitioners throughout health care to screen and treat OUD, clearing misconceptions about medications for OUD and how to use them, and removing infrastructural barriers to their use, including loosening restrictions on who can prescribe them.[55-57]

Box 2. Medications for Opioid Use Disorder

Methadone

Full MOR agonist, typically daily oral doses of 80-160 mg methadone hydrochloride, used for more than 4 decades

Dispensing mostly limited to licensed opioid treatment programs or methadone clinics

Reduces cravings and withdrawal symptoms

Does not produce euphoria in opioid-dependent individuals because MOR binding is slower and longer lasting than that of heroin or fentanyl and oral delivery slows its entry into the brain

Normalizes the physiology of the stress-responsive hypothalamic-pituitary-adrenal axis[42]

Produces physical dependence and, if use is abruptly discontinued, results in acute withdrawal; thus, discontinuation of the drug requires slow tapering to avoid withdrawal

Strong evidence that it reduces illicit opioid use and risk of overdose and improves other outcomes (a Cochrane review[43] in 2009 found 33% fewer opioid-positive drug test results for patients taking methadone, who were also 4.4 times more likely to stay in treatment than those not taking medication)

Buprenorphine

Partial MOR agonist

κ-Opioid receptor antagonist

Nociceptin receptor agonist[44]

IR formulation

- Generally taken 3-4 times/wk at daily doses typically between 16 and 24 mg[45]
- Most frequently prescribed as a sublingual film that contains naloxone, which induces withdrawal when drug is injected

ER formulations

- A subdermal implant that delivers the equivalent of 8 mg of buprenorphine was approved in 2016, but use was limited by the restricted doses it delivers
- A once-monthly depot injection was approved in 2017, and additional once-monthly and once-weekly formulations are currently being reviewed for FDA approval

Approved to treat OUD in 2002

Dispensing by physicians or nurses who have a Drug Abuse Treatment Act 2000 waiver

Reduces cravings and withdrawal symptoms

Does not produce euphoria in opioid-dependent patients because its binding to MOR is slow (slower than for methadone) and (as a partial agonist) it has less efficacy to stimulate reward

Because buprenorphine is a partial agonist, its use in patients with OUD with high levels of tolerance might result in acute withdrawal, in which case treatment with methadone, with its full agonist effects, might be more beneficial

ER formulations of buprenorphine will facilitate adherence and OUD management, including for patients living in rural areas

Strong evidence that it reduces illicit opioid use and overdoses and improves other outcomes (a Swedish study found a 100% failure rate within 3 mo when treatment with buprenorphine was tapered after 6 d vs 25% when buprenorphine treatment was maintained and a 20% mortality rate among those who left treatment)[46]

Naltrexone

Antagonist at MOR

Antagonist at κ-opioid receptor

IR formulation: 50 mg once daily

ER formulation: 380 mg delivered intramuscularly every 4 wk

IR formulation approved for OUD in 1984 but had poor adherence

ER formulation approved for OUD in 2010, which has facilitated adherence

Does not require a license or waiver to prescribe

Interferes with the binding of opioid drugs, thus inhibiting their effects, including reward and analgesia

Patients need to undergo detoxification before initiating naltrexone treatment to avert withdrawal, which can be challenging, and not all patients succeed

The evidence is still limited, but studies thus far suggest that the ER formulation reduces opioid use, and preliminary data suggest it might prevent overdoses (2 comparative-effectiveness studies[47,48] in 2017 found that, after patients were inducted on treatment with ER naltrexone, it was equally effective as buprenorphine at promoting abstinence and retaining patients in treatment)

Lofexidine

α-Adrenergic receptor agonist, three 0.18-mg tablets taken orally, 4 times daily at 5- to 6-h intervals

Approved in 2018 as the first FDA medication to treat opioid withdrawal, although it has been used to treat opioid withdrawal in the United Kingdom since the 1990s

Dispensing is by physicians

Research is needed to determine whether it might be helpful in facilitating induction into naltrexone or buprenorphine for patients with high levels of tolerance and whether it can improve adherence in patients treated with medications for OUD

Naloxone

Antagonist at MOR

Autoinjection: 2 mg of 0.4 mL of naloxone hydrochloride solution in a prefilled autoinjector for intramuscular or subcutaneous injection

Nasal spray: 4 mg of naloxone hydrochloride in 0.1 mL for intranasal administration

Injection: 0.4 mg/mL, available in 2 pack sizes, containing 0.8 mg of naloxone in 2 mL or 2.0 mg of naloxone hydrochloride in 5 mL

FDA first approved naloxone for overdoses in 1971

The autoinjector was approved in 2014

The intranasal spray was approved in 2015

Increasing access to naloxone is a major component to reverse the overdose epidemic (in Massachusetts communities where overdose education and naloxone distribution were implemented, death due to overdose was reduced 27%-46%)

With the increase in overdoses from fentanyl and other synthetic opioids, multiple naloxone doses are necessary for reversal (reversals might fail when opioids are combined with other respiratory-depressing drugs, eg, alcohol, benzodiazepines; thus, there is a need for longer-lasting naloxone formulations or other overdose-reversal tools)

Abbreviations: ER, extended release; FDA, US Food and Drug Administration; IR, immediate release; MOR, μ-opioid receptor; OUD, opioid use disorder.

Box 3. Research Gaps

Pain Neurobiology

Factors underlying the transition from acute to chronic pain

Risk factors for chronic pain (including sex)

Risk factors for addiction when patients with pain are prescribed an opioid medication

Comorbidity of pain syndromes, mood disorders, and addiction

Pain Treatment

New compounds that target non–opioid pain-modulating systems in the body, such as the endocannabinoid system

New compounds that target the MOR but in a manner that produces fewer adverse effects and less misuse liability (eg, biased agonists, bivalent molecules that concomitantly target μ and galanin or nociceptin receptors)

Strategies to interfere with signaling of molecules that produce pain, such as sodium and calcium channel blockers that modulate excitability of pain fibers

Strategies that block the source of the pain (ie, CGRP)

Nonpharmacologic interventions, such as transcranial magnetic stimulation, peripheral nerve stimulation, mindfulness, biofeedback, and others

OUD Neurobiology

Interactions between pain and rewarding effects of opioids
- Relevant to the high comorbidity between pain and OUD
- Will lead to better ways of preventing OUD in patients with pain

Effects of long-term opioid use on emotion and stress networks
- Relevant to the high risk of dysphoria, suicidality, and social withdrawal in OUD

Neurobiological mechanisms by which adverse social environments influence vulnerability for OUD

OUD Prevention

Prevention strategies in young adults (who are at highest risk of first misusing opioids and then developing an OUD)

Prevention strategies in patients with pain treated with opioids

Improved metrics to assess the results of prevention interventions

Strategies to integrate a comprehensive set of evidence-based prevention and treatment interventions at the community level

Implementation research to increase adoption of effective prevention interventions

OUD Treatment

New treatment options

Comparative effectiveness of existing treatments

Implementation research to increase medication of OUD use

Effectiveness of medications for OUD with specific populations

Appropriate duration of use of medication for OUD

How to better personalize behavioral treatments to the individual

How to determine when a patient is ready to be tapered off medication for OUD

Improved assessment of when inpatient treatment is indicated

Biomarkers or other indicators to determine which medication for OUD is optimal for a given patient

Treatment strategy for individuals who may be misusing opioids but have yet to develop a moderate to severe OUD

Treatment of adolescents with OUD, including the use of medication for OUD

What is the best form of medication for OUD to use for pregnant women (this should include studies to evaluate the benefits from ER naltrexone)?

Improved metrics to assess outcomes of therapeutic interventions

Marijuana and OUD

A few highly publicized studies[64-66] have suggested an association between the availability of medical marijuana in some states and lower-than-expected rates of opioid overdoses or opioid prescriptions in those states, which led to the suggestion that marijuana, as an alternative pain treatment and/or as an alternative recreational substance, may lead to less opioid use

However, longitudinal research shows that marijuana use increases risk for later opioid use, even in people with pain[67]

Research is needed to clarify the association(s), if any, between marijuana use and opioid use and misuse at the individual and population levels

Abbreviations: CGRP, calcitonin gene–related peptide; MOR, μ-opioid receptor; OUD, opioid use disorder.

Access to medications for OUD can also be expanded by engaging criminal justice settings. Approximately 60% of inmates in state and federal prisons have a substance use disorder,[58] often an OUD. Because OUD is mostly untreated during incarceration, inmates face a high risk of overdose after release (mortality is 12 times higher than for the general population within 2 weeks of release).[59] Treating inmates with medications for OUD while they are incarcerated or initiating treatment with medications for OUD before inmates are released can reduce opioid use, increase treatment engagement, and reduce overdoses.[60-62] Another medication fundamental for reversing opioid overdoses is naloxone, a MOR antagonist with fast-binding dynamics that, when used promptly and at adequate doses, quickly reverses an opioid overdose (Box 2). Increasing access to naloxone is a major strategy for decreasing overdose fatalities.[63]

Research Gaps and Conclusion

More research is needed in pain and OUD to further understand the neurobiology of these disorders and to help develop more effective prevention and treatment interventions. The potential therapeutic role of marijuana or its extracts in pain treatment should also be explored because this substance is increasingly available across the United States and Canada (**Box 3**).[64-67]

In the meantime, 4 areas are central to reversing the opioid crisis: (1) improving treatments for pain and improved opioid prescription practices, (2) expanding access to medications for OUD, (3) expanding availability of naloxone and developing models to link patients who experience overdose to OUD treatment, and (4) improving prevention focused on the risk factors for opioid misuse and

OUD. Achieving these goals requires reversing stigma attached to medications for OUD, removing infrastructural barriers to their adoption, and expanding engagement of health care professionals (including psychiatrists) and in criminal justice settings in OUD treatment. Against this background, remediation strategies to address the psychosocial factors that lead people to use opioids and other drugs are necessary to prevent the emergence of another similar crisis in the future.

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Acquisition, analysis, or interpretation of data: Volkow, Jones.
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Supplementary Online Content

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eTable. Types of Opioids and Drugs to Treat Opioid Use Disorder

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Types of Opioids and Drugs to Treat Opioid Use Disorder

Drug	μ affinity (nmol/L)	μ functional profile	κ affinity (nmol/L)	κ functional profile	δ affinity (nmol/L)	δ functional profile	T_{max}	$t_{1/2}$
morphine	1.8[1]	agonist	317[1]	agonist	90[1]	agonist	1.1 hour[2]	1.5-2 hours[3]
oxycodone	8.69[4]	agonist	901[4]	agonist	>1000[4]	agonist	1-2 hours[5]	4 hours[5]
hydrocodone	11.1[4]	agonist	962[4]	agonist	501[4]	agonist	1.3 hours[6]	3.8 hours[6]
heroin	158[7]	agonist	>1000[7]	agonist	>1000[7]	agonist		1.3-7.8mins[8]
fentanyl (i.v.)	7[1]	agonist	470[1]	agonist	151[1]	agonist	1.7 minutes[9]	3.7 hours[9]
carfentanil	0.024[1]	agonist	43[1]	agonist	3.3[1]	agonist		42-51 minutes[10]
methadone (oral concentrate)	4.2[1]	agonist	>1000[1]	agonist	15.1[1]	agonist	1-7.5 hours[11]	8-59 hours[11]
buprenorphine (sublingual)	0.6[1]	partial agonist	1.3[1]	antagonist	2[1]	antagonist	1-2 hours [12]	32-36 hours[12]
XR-naltrexone	0.46[1]	antagonist	6.5[1]	antagonist	9.4[1]	antagonist	2 hours, again at 2-3 days[13]	5-10 days[13]
naloxone (nasal)	1.8[1]	antagonist	17.2[1]	antagonist	27[1]	antagonist	20-30 minutes[14]	2 hours[14]

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