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Opioid use disorder: current trends and potential treatments

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Opioid use disorder (OUD) is a major public health threat, contributing to morbidity and mortality from addiction, overdose, and related medical conditions. Despite our increasing knowledge about the pathophysiology and existing medical treatments of OUD, it has remained a relapsing and remitting disorder for decades, with rising deaths from overdoses, rather than declining. The COVID-19 pandemic has accelerated the increase in overall substance use and interrupted access to treatment. If increased naloxone access, more buprenorphine prescribers, greater access to treatment, enhanced reimbursement, less stigma and various harm reduction strategies were effective for OUD, overdose deaths would not be at an all-time high. Different prevention and treatment approaches are needed to reverse the concerning trend in OUD. This article will review the recent trends and limitations on existing medications for OUD and briefly review novel approaches to treatment that have the potential to be more durable and effective than existing medications. The focus will be on promising interventional treatments, psychedelics, neuroimmune, neutraceutical, and electromagnetic therapies. At different phases of investigation and FDA approval, these novel approaches have the potential to not just reduce overdoses and deaths, but attenuate OUD, as well as address existing comorbid disorders.

KEYWORDS

opioid-related disorders, public health, therapeutics, electrical stimulation of the brain, hallucinogens, neuroimmunomodulation, pro-dopamine-regulation, homeostasis

Introduction

Opioid use disorder (OUD) is a complex physical and emotional disease with important mood and anhedonic impacts. It also contributes to comorbid medical and infectious diseases that require evaluation and treatment (1). Drug use changes the brain, behavior, and motivational hierarchy via induction of neuroplasticity; the patient with OUD acquires a chronic, progressive neurodysregulation that shortens life, reduces career opportunities and earning potential, increases the risks of other diseases, and often ends in death. Fentanyl is becoming increasingly common. Fentanyl is highly effective at producing OUD and contributing to anhedonia and overdose. Many with OUD also use methamphetamine and cocaine for their euphoric mood effects, but when used regularly, these drugs can lead to alterations in brain function to trigger negative effects, such as dysphoria, anhedonia, and

depression (2). Unfortunately, polysubstance use and relapses are the norm rather than the exception (3, 4). OUD is part of the substance use disorder (SUD) spectrum but is unique among other SUDs in that there is a solid understanding of its neurobiology and there are Food and Drug Administration (FDA) approved treatments (5). Medical management of OUD has not changed much since the 1970s, with agonists like methadone and antagonists like naltrexone. The addition of the partial agonist buprenorphine and extended-release naltrexone (XR-NTX) were important milestones.

Opioid use in the context of worsening substance use

Substance use disorder (SUD) is one of the nation's most pressing public health challenges. According to the 2021 World Drug Report by the United Nations Office on Drugs and Crime (UNODC), at least 275 million people worldwide used controlled substances in the previous year, with more than 36 million meeting the criteria for a substance use disorder (6). Among controlled substances contributing to the burden of disease, opioids stand out as the primary driver of drug-related fatalities, comprising 69% of deaths directly associated with drug use.

Recent data show the evidence-based and FDA-approved treatments for OUD reduce stigma and improve treatment access. Although more people are currently being treated with medications for opioid use disorder (MOUD), deaths continue to increase. Nationally, over the past 15 years, at least 500,000 deaths have been attributed to opioid overdoses, contributing to the decrease in US life expectancy. This concerning trend has worsened during the COVID-19 pandemic (7, 8). Those with SUDs are highly dependent on traditional in-person and often emergent care (9). However, pandemic policies--such as the quarantine--to save lives from the COVID-19 virus, have led to disruptions in such care, leading to worsening opioid overdoses and deaths during the lockdown (10, 11). The Centers for Disease Control and Prevention estimated that for the first time ever, over 100,000 deaths occurred due to overdoses during a 12-month period, and the current Director of the Office of National Drug Control Policy suggested that annual opioid-induced deaths could reach 165,000 by 2025 (12).

By necessity, the opioid crisis has shifted the focus to addressing overdose deaths rather than treatment and recovery. A considerable proportion of opioid overdose fatalities are now linked to synthetic opioids, particularly fentanyl. The opioid epidemic has transitioned from being primarily of prescription opioids to heroin and now subsequently fentanyl. Concerningly, with the increase in synthetic opioid use, the trend shows that more and more individuals are also consuming other substances, sometimes inadvertently from contamination and others from co-ingestion of other prescription or psychostimulant drugs. Although SUDs are often discussed in isolation, the reality is that many individuals are combining multiple drugs, often in fatal combinations. For example, in more than half of all methamphetamine-related deaths and about three-quarters of all cocaine-related deaths in 2019, there were co-ingestion of opioids (7). Illicitly manufactured fentanyl is implicated in the increase in overdose deaths in cocaine use, and co-ingestion of fentanyl and other substances, such as methamphetamine, cocaine, and ecstasy, have been shown in postmortem examinations of overdose deaths (13, 14). Patients in the psychiatric emergency rooms often test positive for fentanyl while testing positive for other psychostimulants; unknown contamination with fentanyl puts opioid-naïve psychostimulant users at an increased risk of overdose (15, 16). While the public attention remains on opioid-related deaths, a concerning upsurge in fatalities linked to stimulant drugs suggests that the opioid crisis may be entering a new phase. The ongoing substance use crisis is constantly evolving, marked by changing patterns of substance use and availability, as well as concurrent use of multiple drugs across drug classes.

OUD overdose reversal starts with naloxone

Among all potential interventions, increasing the access to naloxone would have the most significant effect in reducing opioid-use related deaths, according to Pitt et al. (17). While important to implement other strategies, no other harm reduction approach has had as significant of an impact. Naloxone is classified as a "pure" antagonist, meaning it lacks opioid agonistic traits seen in other opioid antagonists, and it displaces other full and/or partial opioid agonists that engage opioid receptors to reverse the effects of euphoria, analgesia, as well as respiratory depression, sedation, and bradycardia. Naloxone is a rapid-acting, easy-to-administer agent that can be given in the setting of opioid intoxication and overdose, to provide swift, life-saving reversal (18). Within minutes, naloxone can fully reverse the effects of opioids. Regardless of the substance use history, naloxone offers substantial potential benefits and minimal risk when overdose is suspected. Thus, the importance of promoting access to naloxone in those who use opioids as well as in potential bystanders who can intervene in an overdose setting cannot be understated. However, it is also important to note that naloxone serves as an intervention rather than a remedy for the underlying condition. Naloxone can treat the overdose acutely, but it does not treat the OUD. Existing evidence does not indicate that experiencing an overdose and subsequent reversal with naloxone alters the trajectory of those with OUD; patients must be connected to subsequent treatment services that include MOUDs for improved outcomes (1). Thus, access to both is critical to reduce OUD related deaths.

Transition with urgency: from overdose reversal to treatment of the whole patient with OUD

It is difficult to accurately estimate the total economic burden associated with substance use, encompassing factors from the cost of treatment as well as reduced productivity, loss of life, and the emotional toll on those left behind (19). Although it has been suggested that mortality can be reduced by evidenced-based treatment approaches, OUD is characterized by a chronic and relapsing course—initially driven by activation of the brain's reward system, but later increasingly dominated by anti-reward neural circuits that trigger negative emotional states and relapses (3, 20). It is noteworthy that one important anti-reward neurocircuit phenomena is the subsequent opioid-induced reduction of functional connectivity (21).

No single treatment approach has proven to be universally effective, as many have other medical and psychiatric comorbidities that often hinder successful treatment. Furthermore, racial and economic disparities in morbidity and mortality point to inequalities that must be addressed and rectified (22). Even harm reduction strategy of naloxone is a limited strategy in that it often requires someone else other than the patient to help administer the reversal agent (23).

The current mainstay of treatment for OUD is MOUDs. Buprenorphine, extended-release naltrexone (XR-NTX), and methadone are all FDA-approved and have been shown to be effective in reducing the number of overdoses in those who remain adherent to treatment—which remains a challenge in access and retention (24–26). Buprenorphine is the most prescribed of the MOUDs and it may help mitigate anhedonia and withdrawal symptoms associated with fentanyl use (27, 28). However, treatment dropouts are common, and patients are often re-initiated on the same buprenorphine (29). Once an overdose is reversed, the patient remains at high risk for overdose, which has led to initiation of buprenorphine in hospitals, emergency rooms, and immediately after rescue. This has not decreased the overall number of deaths, but provides another opportunity to successfully treat the patient.

XR-NTX is a monthly injectable opioid antagonist that acts to block other opioids from activating receptors. Despite the monthly injectable formulation of the drug, transition and compliance to treatment remain an issue, as patients need to go through detoxification to start the medication. Therefore, despite similar efficacy of XR-NTX to buprenorphine shown in the XBOT trial, buprenorphine is more often initiated (30). Augmentation of naltrexone therapy with other agents such as clonidine, lofexidine, and buprenorphine are often tried in outpatient detoxification settings. With augmentation of non-opioid agents like clonidine, patients are able to successful initiate and maintain an opioid antagonist, rather than a partial agonist. This is particularly important for those in occupations related to public for whom methadone or buprenorphine is not prescribed and for those who may be mandated to treatment for their OUD (26, 31).

While MOUDs are highly effective and FDA approved, they are not a "magic bullet", and the entire scientific community should continue their pursuit to develop alternative non-addictive and safe treatments (32, 33). Despite best efforts, the existing strategies for preventing and treating OUD will still result in more than 700,000 deaths in the US between 2016 and 2025, from both prescription and non-prescription opioids such as fentanyl (34).

The most favorable outcomes are associated with extended duration of MOUD therapy. However, treatment drop out and relapses are common. When OUD treatment with a MOUD ends or is discontinued by the patient, they often relapse, overdose, and rarely have the disease remitted. Risk of overdose appears to persist even after completion of buprenorphine treatment, and stopping MOUD is associated with an elevated overdose risk, raising a controversial question about whether opioid agonist treatment can lead to opioid deficiency or opioid system dysregulation (3, 35). This risk of relapse and overdose persists even several years of recovery; thus, recovery can be akin to a "remission" of OUD symptoms rather than a complete cure or elimination. While it may be true that prolonged MOUD is the most effective in preventing relapse, it is also true that the quality of life on MOUD treatment can be negatively impacted and most patients do not remain on lifelong treatment for OUD. One study revealed that patients on long-term Suboxone exhibited significantly flat affect ($p < 0.01$) and reported diminished sense of feelings of happiness, sadness, and anxiety compared to both the general population and Alcoholics Anonymous (AA) groups (36). Despite the limitations, treatment of OUD is still linked to improved outcomes in morbidity and mortality, and integration of MOUD with effective, evidence-based therapy and contingency management lead to enhanced outcomes (37). It is thought that achieving successful treatment of OUD requires not just medications but a comprehensive approach that addresses the psychosocial factors that predispose and perpetuate individuals toward opioid use disorder.

Brain and behavioral recovery take hope, patience, time, and effort. No one knows if or when the brain will return to its pre-morbid function. Interestingly, research from China revealed that even after 10 months of heroin abstinence, there were changes in resting state of functional connectivity (RSFC) patterns between the midbrain and various cortical regions, such as diminished RSFC of the medial orbitofrontal cortex (mOFC) and anterior cingulate cortex compared to non-heroin using controls. Persistent reward circuitry abnormalities were present after 16 months, but enhancement of RSFC in certain circuits were seen in long-term abstinence compared with short-term (38, 39). Abstinence from substance use, as well as adopting a healthy diet, and other regenerative treatments, including exercise and transcranial magnetic stimulation may all help expedite brain recovery (40, 41).

Pro-dopamine regulation and assessment of preaddiction

At the population health level, a "preaddiction" model, like prediabetes, has been suggested to ring the alarm bell for an early intervention before the addiction progresses to cause more severe symptoms and engender chronic changes in the brain's neural circuitry. SUD is currently defined by the DSM-5 based on 11 symptoms of impaired control, and severity is determined by the number of symptoms patients endorse. The term addiction specifically refers to severe SUD, which is defined as having six or more symptoms. This occurs in about 4–5% of adults, compared to 13% of the adult population who have mild to moderate SUD, defined as having 2–5 symptoms (42). Although larger proportion of the population suffer from mild to moderate SUD, public health policies and treatment focus on those with severe, often chronic addictions, to prevent overdoses and deaths, rather than the much larger population grappling with early-stage SUDs. By focusing on those with early-stage addiction, McLellan et al. argue that a preaddiction model that looks for early signs of addiction increases public awareness and allows early intervention that can increase disease detection, shorten delays to treatment, and prevent progression (42, 43). Directors of the National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism have also advocated for the integration of "preaddiction" to the conceptualization of addiction in the DSM.

Although the term preaddiction borrows from the advances made in diabetes, but it is best conceptualized as dopamine or reward dysregulation, where there is a net hypodopaminergia within the meso-limbic reward circuitry from inappropriate or dysregulated neurotransmitter systems (44, 45). Therefore, the terms "reward

deficiency" or "reward dysregulation" have also been proposed (46, 47). Reward deficiency syndrome (RDS) refers to behavioral dysfunctions resulting from the disruption of the reward circuitry, due to both genetic and epigenetic factors, and can describe a wide spectrum of psychiatric disorders, from various addictions to obsessive and compulsive disorders and other behavioral conditions (47).

Ways to improve on existing treatment approaches

Public health solutions proposed to address the worsening opioid epidemic include: relaxing the restrictions for physicians to be able to prescribe MOUD; increasing insurance coverage to increase access to treatment for patients (48–51); inducting patients on high-dose buprenorphine in the emergency department (52, 53); and implementing contingency management along with medical treatment to address other key issues of patients undergoing treatment, such as other concurrent substance use (50). Widespread adoption of these practices may help improve treatment retention and reduce overdoses and deaths, to address critical gaps in delivery of existing treatments (37, 54–56).

All these measures would be helpful to curb damage of the OUD at the population level, but still does not address the intrinsic limitations of existing treatments. Limited effectiveness of existing pharmacologic treatments and harm reduction approaches leaves a desire for more durable, novel treatment approaches especially as they relate to the required induction of "dopamine homeostasis" (57–59).

Novel treatments for SUDs are being investigated, most notably interventional neuromodulatory interventions such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), as well as psychedelics and neuroimmune therapies. Rather than working at modulating specific opioid receptors as existing MOUDs do, these proposed treatments target other aspects of substance use pathophysiology, such as the mesolimbic neural circuitry modulating reward and dorsolateral prefrontal and orbitofrontal cortex involved in craving, or the neuroimmune and epigenetic modulations that occur in response to substances (60, 61).

Developments in interventional neuromodulation treatments for OUD

Interventional neuromodulational treatments such as TMS and DBS work by modulating neural circuits and synaptic plasticity, and several neuromodulating modalities have been investigated for use in various neurologic and psychiatric conditions (62). TMS is a noninvasive treatment that utilizes an extracranial magnetic coil to induce a magnetic field that can stimulate or inhibit targeted cortical and subcortical structures. It is currently FDA-approved for treatment of psychiatric conditions including major depressive disorder and obsessive-compulsive disorder. Clinical trials have shown its effectiveness in reducing substance craving via targeting of the dorsolateral prefrontal cortex, with effects on curbing substance use lasting greater than the immediate treatment period, with various substances such as cocaine, methamphetamine, alcohol, heroin, and cigarette use (63–70). A meta-analysis of repetitive TMS (rTMS) on addiction has found a small, persistent effect on stimulant and behavioral addiction, but not on depressants such as alcohol, opioids, and cannabis (71). However, currently multiple randomized controlled trials are being conducted for various TMS protocols to treat patients with opioid use as well as uncover mechanisms (72–83). Further understanding of the exact mechanism and optimization is needed to implement TMS as treatment for OUD (84). One important aspect regarding TMS relates to the concept of utilizing QEEG to determine individualized or personalized signatures termed PRTMS, first coined and developed by Kevin T. Murphy (85).

Similarly, DBS is a neuromodulatory treatment method that can directly stimulate targeted brain regions, but unlike TMS, it typically relies on surgically implanted electrodes. It has FDA approval for various neurologic conditions, such as Parkinson's disease, tremors, dystonia, as well as epilepsy and OCD. With its ability to reach deeper subcortical structures, DBS is also being investigated for other psychiatric conditions, such as treatment-resistant depression, pain, multiple sclerosis, and addiction. Specifically for addiction, animal models have shown that modulation of nucleus accumbens (NAc) can reverse synaptic changes from cocaine and alcohol use (60, 62), and small case studies in humans have shown effectiveness in treating alcohol use and heroin use (86). More registered clinical trials are examining DBS's effect in various substance use, including both randomized and non-randomized clinical trials on DBS of NAc of the mesolimbic system as well as DBS specifically for the treatment for severe OUD (87–94).

Beyond TMS and DBS, other similar modalities such as vagus nerve stimulation (VNS), focused ultrasound (FUS), and transcranial direct current stimulation (tDCS) are being investigated, with varying degrees of invasiveness and spatial resolution. VNS is FDA-approved for treatment-resistant depression and epilepsy, and FUS is approved for use in treatment-resistant Parkinson's disease as well as essential tremor (95, 96), while tDCS does not have any FDA-approved indications. A small randomized clinical trial on transcutaneous VNS has found significant improvement in behavioral and physiologic opioid withdrawal symptoms, indicating potential utility as adjunct treatment for OUD (93). Although not FDA-approved, tDCS has some evidence for utility in depression and addiction, and multiple clinical trials are ongoing for its use in neuropsychiatric conditions (81, 97–101). FUS is also being investigated in a small, open-label clinical trial for feasibility in treatment for OUD (102).

Overall, more evidence is needed before neuromodulatory modalities are adopted in OUD treatment, but the strength of these proposed therapies is that they work via modulating neural circuitries and synaptic plasticity, rather than maintaining patients on opioid maintenance treatments, as well as treat other comorbid neuropsychiatric conditions, such as other SUDs and mood disorders.

Renewed interest in psychedelics for SUD

Psychedelic medicine has seen a resurgence of interest in recent years as potential therapeutics, including for SUDs (103, 104). Prior to the passage of the Controlled Substance Act of 1970, psychedelics had been studied and utilized as potential therapeutic adjuncts, with anecdotal evidence and small clinical trials showing positive impact on mood and decreased substance use, with effect appearing to last

longer than the duration of use. Many psychedelic agents are derivatives of natural substances that had traditional medicinal and spiritual uses, and they are generally considered to have low potential for dependence and low risk of serious adverse effects, even at high doses. Classic psychedelics are agents that have serotonergic activity via 5-hydroxytryptamine 2A receptors, whereas non-classic agents have lesser-known neuropharmacology. But overall, psychedelic agents appear to increase neuroplasticity, demonstrating increased synapses in key brain areas involved in emotion processing and social cognition (105–109). Being classified as schedule I controlled substances had hindered subsequent research on psychedelics, until the need for better treatments of psychiatric conditions such as treatment resistant mood, anxiety, and SUDs led to renewed interest in these agents.

Of the psychedelic agents, only esketamine—the S enantiomer of ketamine, an anesthetic that acts as an NMDA receptor antagonist—currently has FDA approval for use in treatment-resistant depression, with durable effects on depression symptoms, including suicidality (110, 111). Ketamine enhances connections between the brain regions involved in dopamine production and regulation, which may help explain its antidepressant effects (112). Interests in ketamine for other uses are expanding, and ketamine is currently being investigated with plans for a phase 3 clinical trial for use in alcohol use disorder after a phase 2 trial showed on average 86% of days abstinent in the 6 months after treatment, compared to 2% before the trial (113).

Psilocybin, an active ingredient in mushrooms, and MDMA, a synthetic drug also known as ecstasy, are also next in the pipelines for FDA approval, with mounting evidence in phase 2 clinical trials leading to phase 3 trials. Psilocybin completed its largest randomized controlled trial on treatment-resistant depression to date, with phase 2 study evidence showing about 36% of patients with improved depression symptoms by at least 50% at 3 weeks and 24% experiencing sustained effect at 3 months after treatment, compared to control (114). Currently, a phase 3 trial for psilocybin for cancer-associated anxiety, depression, and distress is planned (115). Similar to psilocybin, MDMA has shown promising results for treating neuropsychiatric disorders in phase 2 trials (116), and in 2021, a phase 3 trial showed that MDMA-assisted therapy led to significant reduction in severe PTSD symptoms, even when patients had comorbidities such as SUDs; 88% of patients saw more than 50% reduction in symptoms and 67% no longer qualifying for a PTSD diagnosis (117). The second phase 3 trial is ongoing (118).

With mounting evidence of potential therapeutic use of these agents, FDA approval of MDMA, psilocybin, and ketamine can pave the way for greater exploration and application of psychedelics as therapy for SUDs, including opioid use. Existing evidence on psychedelics on SUDs are anecdotally reported reduction in substance use and small clinical cases or trials (119). Previous open label studies on psilocybin have shown improved abstinence in cigarette and alcohol use (120–122), and a meta-analysis on ketamine's effect on substance use showed reduced craving and increased abstinence (123). Multiple open-label as well as randomized clinical trials are investigating psilocybin, ketamine, and MDMA-assisted treatment for patients who also have opioid dependence (124–130). Other psychedelic agents, such as LSD, ibogaine, kratom, and mescaline are also of interest as a potential therapeutic for OUD, for their role in reducing craving and substance use (104, 131–140).

Potential neuroimmune modulatory approaches to treating OUD

Changes to brain's synaptic plasticity via neuroimmune modulation seen in addiction suggest the role of agents that can disrupt and/or mitigate the changes from substance use and addiction as potential therapeutics (141, 142). Existing medications may be applicable to OUD and substance use treatment in this manner, by modulating or reversing synaptic plasticity. For example, N-Acetylcysteine, an antioxidant medication with multiple clinical applications, has shown to reverse cocaine-induced metaplasticity in in rats (143), and ceftriaxone, a third generation cephalosporine antibiotic, has shown to downregulate glutamate transporter 1 (EEAT2) and reduce drug seeking behavior (144, 145). Similarly, spironolactone, a mineralocorticoid receptor antagonist, has been shown to reduce alcohol consumption in both mice and humans, but to a greater degree in humans (146). Novel immune-modulating agents can also be developed to target known signaling pathways involved in addiction and OUD, such as TLR4, a transmembrane protein that plays a role in rewarding effects of substances, leading to reinforcement of use (147–149).

Other neuroimmune modulatory agents are of interest, including biologic agents, such as antibodies, and vaccines that block the effect of substances of abuse (150–154), but low immunogenicity remains a major challenge to being effective in humans. Overall, much more evidence is needed to develop novel neuroimmunotherapeutics as effective treatments for SUDs. However, the potential benefit of the proposed approaches is that they may modulate or even reverse the lasting damages substance use imposes on the brain.

Summary

The nation has had a series of drug overdose epidemics, starting with prescription opioids, moving to injectable heroin and then fentanyl. Addiction policy experts have suggested a number of policy changes that increase access and reduce stigma along with many harm reduction strategies that have been enthusiastically adopted. Despite this, the actual effects on OUD & drug overdose rates have been difficult to demonstrate.

The efficacy of OUD treatments is limited by poor adherence and it is unclear if recovery to premorbid levels is even possible. Comorbid psychiatric, addictive, or medical disorders often contribute to recidivism. While expanding access to treatment and adopting harm reduction approaches are important in saving lives, to reverse the concerning trends in OUD, there must also be novel treatments that are more durable, non-addicting, safe, and effective. Promising potential treatments include neuromodulating modalities such as TMS and DBS, which target different areas of the neural circuitry involved in addiction. Some of these modalities are already FDA-approved for other neuropsychiatric conditions and have evidence of effectiveness in reducing substance use, with several clinical trials in progress. In addition to neuromodulation, psychedelics has been gaining much interest in potential for use in various SUD, with mounting evidence for use of psychedelics in psychiatric conditions. If the FDA approves psilocybin and MDMA after successful phase 3 trials, there will be reduced barriers to investigate applications of psychedelics despite their current

classification as Schedule I substances. Like psychedelics, but with less evidence, are neuroimmune modulating approaches to treating addiction. Without new inventions for pain treatment, new treatments for OUD and SUD which might offer the hope of a re-setting of the brain to pre-use functionality and cures we will not make the kind of progress that we need to reverse this crisis.

Conclusion

By using agents that target pathways that lead to changes in synaptic plasticity seen in addiction, this approach can prevent addiction and/or reverse damages caused by addiction. All of these proposed approaches to treating OUD are at various stages in investigation and development. However, the potential benefits of these approaches are their ability to target structural changes that occur in the brain in addiction and treat comorbid conditions, such as other addictions and mood disorders. If successful, they will shift the paradigm of OUD treatment away from the opioid receptor and have the potential to cure, not just manage, OUD.

Author contributions

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National Institute on Drug Abuse

en español

DrugFacts

Naloxone DrugFacts

What is naloxone?

Naloxone is a medicine that rapidly reverses an opioid overdose. It is an opioid antagonist. This means that it attaches to opioid receptors and reverses and blocks the effects of other opioids. Naloxone can quickly restore normal breathing to a person if their breathing has slowed or stopped because of an opioid overdose. But, naloxone has no effect on someone who does not have opioids in their system, and it is not a treatment for opioid use disorder. Examples of opioids include heroin, fentanyl, oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, and morphine.

What are some signs of an opioid overdose?

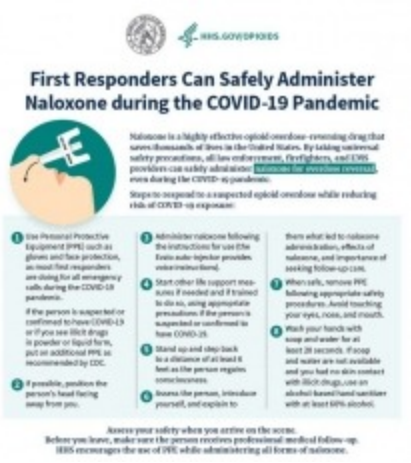
- unconsciousness
- very small pupils
- slow or shallow breathing
- vomiting
- an inability to speak
- faint heartbeat
- limp arms and legs
- pale skin
- purple lips and fingernails

How is naloxone given?

Naloxone should be given to any person who shows signs of an opioid overdose or when an overdose is suspected. Naloxone can be given as a nasal spray or it can be injected into the muscle, under the skin, or into the veins. Steps for responding to an opioid overdose can be found in the Substance Abuse and Mental Health Administration's (SAMHSA) *Opioid Overdose Prevention Toolkit*.

What are the different naloxone delivery systems?

Naloxone comes in two FDA-approved forms: injectable and prepackaged nasal spray. No matter what dosage form you use, it's important to receive training on how and when to use naloxone. You should also read the product instructions and check the expiration date.



First Responders Can Safely Administer Naloxone during the COVID-19 Pandemic (HHS)

- **Injectable** brands of naloxone are offered by different companies listed in the FDA Orange Book under "naloxone" (look for "injectable"). Typically, the proper dose must be drawn up from a vial. Usually, it is injected with a needle into muscle, although it also may be administered into a vein or under the skin. The FDA recently approved Zimhi™, a single-dose, prefilled syringe that can be injected into the muscle or under the skin.
    - *Note: Some people use an improvised nasal spray emergency kit not approved by the FDA that combines injectable naloxone with an attachment designed to deliver naloxone through the nose. However, this improvised intranasal device is not easy to assemble, especially when under pressure in an emergency, and requires training beforehand. Additionally, the FDA-approved naloxone devices have been shown to produce substantially higher blood levels of naloxone than the improvised nasal spray. These outcomes suggest that the approved prepackaged nasal spray technology is preferable over non-FDA-approved forms.*
- **Prepackaged Nasal Spray (generic naloxone, Narcan®, Kloxxado®),** developed as a result of NIDA-funded research, is an FDA-approved prefilled, needle-free device that requires no assembly and is sprayed into one nostril while the person lays on their back. This device can also be easier for loved ones and bystanders without formal training to use.

Is there a preferable delivery system?

All systems used by first responders deliver the stated dose of naloxone and can be highly effective in reversing an opioid overdose. Study findings released in March 2019 suggests that the FDA-approved naloxone devices deliver higher blood levels of naloxone than the improvised nasal devices.

Is Narcan® the same as naloxone?

When naloxone was first approved to reverse opioid overdoses, its brand name was "Narcan." There are now other formulations and brand names for naloxone, but many people continue to call all of these products "Narcan." However, the proper generic name is "naloxone."

Can I give naloxone to someone who has overdosed?

Yes. Families with loved ones who struggle with opioid addiction should have naloxone nearby; ask their family member to carry it; and let friends know where it is. People should still call 911 immediately in the event of an overdose.

Naloxone is being used more by police officers, emergency medical technicians, and non-emergency first responders than before. In most states, people who are at risk or who know someone at risk for an opioid overdose can be trained on how to give naloxone. Families can ask their pharmacists or health care provider how to use the devices.

What precautions are needed when giving naloxone?

Naloxone works to reverse opioid overdose in the body for only 30 to 90 minutes. But many opioids remain in the body longer than that. Because of this, it is possible for a person to still experience the effects of an overdose after a dose of naloxone wears off. Also, some opioids are stronger and might require multiple doses of

naloxone. Therefore, one of the most important steps to take is to call 911 so the individual can receive immediate medical attention. NIDA is supporting research for stronger formulations for use with potent opioids like fentanyl.

People who are given naloxone should be observed constantly until emergency care arrives. They should be monitored for another 2 hours after the last dose of naloxone is given to make sure breathing does not slow or stop.

People with physical dependence on opioids may have withdrawal symptoms within minutes after they are given naloxone. Withdrawal symptoms might include headaches, changes in blood pressure, rapid heart rate, sweating, nausea, vomiting, and tremors. While this is uncomfortable, it is usually not life threatening. The risk of death for someone overdosing on opioids is worse than the risk of having a bad reaction to naloxone. Clinicians in emergency room settings are being trained to offer patients immediate relief and referral to treatment for opioid use disorder with effective medications after an opioid overdose is reversed. NIDA offers tools for emergency clinicians here.

Side effects from naloxone are rare, but people might have allergic reactions to the medicine. Overall, naloxone is a safe medicine. But it only reverses an overdose in people with opioids in their systems and will not reverse overdoses

Tolerance vs. Dependence vs. Addiction

Long-term use of prescription opioids, even as prescribed by a doctor, can cause some people to develop a **tolerance**, which means that they need higher and/or more frequent doses of the drug to get the desired effects.

Drug **dependence** occurs with repeated use, causing the neurons to adapt so they only function normally in the presence of the drug. The absence of the drug causes several physiological reactions, ranging from mild in the case of caffeine, to potentially life-threatening, such as with heroin. Some chronic pain patients are dependent on opioids and require medical support to stop taking the drug.

Drug **addiction** is a chronic disease characterized by compulsive, or uncontrollable, drug seeking and use despite harmful consequences and long-lasting changes in the brain. The

from other drugs like cocaine or methamphetamine.

> changes can result in harmful behaviors by those who misuse drugs, whether prescription or illicit drugs.

How much does naloxone cost?

The cost varies depending on where you get the naloxone, how you get it, and what type you get. Patients with insurance should check with their insurance company to see if this medicine is covered. Patients without insurance can check the retail costs at their local pharmacies. Some drug companies have cost assistance programs for patients unable to pay for it.

Where can I get naloxone?

Many pharmacies carry naloxone. In some states, you can get naloxone from a pharmacist even if your doctor did not write you a prescription for it. It is also possible to get naloxone from community-based distribution programs, local public health groups, or local health departments, free of charge.

Co-Prescribing Naloxone with Prescription Opioids

Research indicates that clinicians prescribing naloxone along with prescription opioids may reduce the risk of opioid-related emergency room visits and prescription opioid-involved overdose deaths. The U.S. Centers for Disease Control and Prevention recommends co-prescription of naloxone for some patients who take opioids. This recommendation was first outlined in the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain and is still present in the updated 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain.

Points to remember

- Naloxone is a medicine that rapidly reverses an opioid overdose. It attaches to opioid receptors and reverses and blocks the effects of other opioids.
- Naloxone is a safe medicine. It only reverses overdoses in people with opioids in their systems.
- There are two FDA-approved formulations of naloxone: injectable and prepackaged nasal spray.
- Police officers, emergency medical technicians, and first responders are trained on how to give naloxone.
- In some states, friends and family members can be trained on how to give naloxone.
- Naloxone only works in the body for 30 to 90 minutes. It is possible for a person to still experience the effects of an overdose after naloxone wears off or need multiple doses if a potent opioid is in a person's system.
- In some areas, you can get naloxone from pharmacies with or without a personal prescription from community-based distribution programs, or local health departments. The cost varies depending on where and how you get it as well as what type you get.

Learn more

For more information about naloxone and opioid use disorder, visit:

- NIDA's Opioids webpage
- NIDA's Naloxone for Opioid Overdose: Life-Saving Science Policy Brief

January 2022

Overdose Prevention

APRIL 16, 2024

Opioid Use Disorder: Diagnosis

WHAT TO KNOW

- Identification of opioid use disorder (OUD) is an opportunity for clinicians to initiate potentially life-saving interventions.
- Clinicians should collaborate with the patient regarding their safety to increase the likelihood of successful treatment.
- Treatment with opioids for pain is associated with increased risk for OUD, particularly if opioids are prescribed for more than 90 days.

Identifying OUD

If clinicians are concerned and suspect their patient may have OUD, they should discuss the concerns with the patient in a nonjudgmental manner. Clinicians can provide an opportunity for patients to disclose related concerns or problems. Concerns about OUD may be informed by

- Patient stated concerns
- Patient behavior
- Findings in prescription drug monitoring program (PDMP) data
- Results of toxicology testing

Clinicians should assess for the presence of OUD using the following checklist based on the DSM-5 criteria.

Diagnostic criteria

OUD is demonstrated by at least 2 out of the 11 criteria below occurring within a year. Severity of OUD is determined based on the number of criteria met. [A]

- Mild: 2-3 criteria
- Moderate: 4-5 criteria
- Severe: greater than or equal to 6 criteria

Diagnostic Criteria [B]

- Taking opioids in larger amounts or over a longer period of time than intended
- Having a persistent desire or unsuccessful attempts to reduce or control opioid use
- Spending excess time obtaining, using, or recovering from opioids
- Craving opioids
- Continued opioid use causing inability to fulfill work, home, or school responsibilities
- Continuing opioid use despite having persistent social or interpersonal problems
- Lack of involvement in social, occupational, or recreational activities
- Using opioids in physically hazardous situations
- Continuing opioid use in spite of awareness of persistent physical or psychological problems

- a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or
- b. Markedly diminished effect with continued use of the same amount of an opioid.

- Exhibiting withdrawal symptoms, as manifested by either of the following:*
  - a. The characteristic opioid withdrawal syndrome, or
  - b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Tolerance and withdrawal are not considered to be met for those taking opioids solely under appropriate medical supervision.

Resources

There are a variety of resources that can assist with diagnosis and treatment of OUD:

- 2022 *Clinical Practice Guideline for Prescribing Opioids for Pain*
- Prescription drug monitoring programs (PDMPs)
- Naloxone Toolkit
- Medications for Opioid Use Disorder Study
- Addiction Medicine Toolkit
- SAMHSA Treatment Locator sites and Opioid Treatment Program Directory

SOURCES

CONTENT SOURCE:
National Center for Injury Prevention and Control

FOOTNOTES

A. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

B. This the criteria is adapted and has been edited for plain language from the American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.