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The Changing Opioid Crisis: development, challenges and opportunities

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Abstract

The current opioid epidemic is one of the most severe public health crisis in US history. Responding to it has been difficult due to its rapidly changing nature and the severity of its associated outcomes. This review examines the origin and evolution of the crisis, the pharmacological properties of opioids, the neurobiology of opioid use and opioid use disorder (OUD), medications for opioid use disorder (MOUD), and existing and promising approaches to prevention. The results of the review indicate that the opioid epidemic is a complex, evolving phenomenon that involves neurobiological vulnerabilities and social determinants of health. Successfully addressing the epidemic will require advances in basic science, development of more acceptable and effective treatments, and implementation of public health approaches, including prevention. The advances achieved in addressing the current crisis should also serve to advance the science and treatment of other substance use disorders.

Origins and Evolution of the Crisis

The current opioid epidemic is one of the most severe public health crisis in US history. Providing an effective response has been difficult because of its changing nature, geographic and demographic diversity, multiplicity of its causes, and the severity of adverse outcomes associated with opioid use and opioid use disorder (OUD). Furthermore, opioid analgesics, which fueled the origins of the opioid epidemic, are therapeutically beneficial when used properly. This, compounds the difficulties of regulating their availability because they cannot be banned, in contrast with illicit drugs. While earlier phases (i.e., first wave) of the crisis were predominantly driven by non-medical use and addiction to prescription opioid analgesics, heroin (second wave) and subsequently illicit synthetic opioids (third wave) have become progressively important as the crisis progressed and more recently there is emerging evidence of increasing fatalities associated with the combination of psychostimulant drugs with opioids (fourth wave). These changes explain why despite the decreases in the number of opioid prescription dispensed, the number of opioid fatalities has continued to rise unabated.¹ Although the opioid crisis is often seen through the prism of fatal overdoses, its

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most dramatic manifestation, the misuse of opioids and OUD also lead to death, disease and suffering from many other causes with devastating medical, social and economic consequences.²⁻⁵

Like most complex problems, the opioid crisis has multiple roots,⁵ including changing social and economic conditions, limited availability of safe and effective analgesics, insufficient treatment capacity for OUD and legal approaches that criminalize OUD rather than fostering treatment. The two major driving factors of the crisis, however, were the steady increase in the rate of opioid prescriptions, particularly in the early stages of the crisis, and the decrease in price and the increase in availability of heroin and synthetic opioids.

Increases in the rate of opioid prescribing followed the identification of undertreatment of pain in the 1990s as an important clinical problem⁶ and the mistaken belief, based on anecdotal evidence, that patients in pain were not at risk for OUD.⁷ Although less than 10% of individuals to whom opioids are prescribed develop OUD,⁸ large increases in the rates of opioid prescriptions inevitably led to more individuals being exposed to opioids and subsequent increases in OUD prevalence. More importantly, increased availability of opioids generated an enormous surplus of medication that was diverted for non-medical use.⁹ From 1991 to 2013, the prevalence of non-medical use of prescription opioids in the US more than doubled, from 1.5% to 4.1%, and the prevalence of prescription OUD tripled, from 0.3% to 0.9%.^{10, 11} At the same time, the severity of nonmedical use, as measured by the frequency of use, also increased among nonmedical users.¹²

A second major factor in the crisis was the increased accessibility and purity of heroin coupled with reduced price partly due to increases in the efficiency of its distribution channels, which led to increases in heroin use and heroin use disorder. From 2001-2002 and 2012-2013 the prevalence of lifetime heroin use in the US increased from 0.33% to 1.6% and the lifetime prevalence of heroin use disorder increased from 0.21% to 0.69%.^{13, 14} There is controversy regarding whether efforts to decrease use of prescription opioids led to increases in heroin use and use disorder. Although individuals who use prescription opioids are more likely than those who don't to use heroin, only 3%-5% of individuals who used prescription drugs non-medically in the previous year also reported using heroin during the same year.¹⁵ Furthermore, increases in heroin use among nonmedical prescription opioids users preceded the development of policies to address misuse of prescription opioids. Thus, it may be the case that efforts to improve prescription of opioids have played a more limited role in the increases in heroin use than that ascribed to them.¹⁶

A more recent entrant has been fentanyl and other very potent synthetic fentanyl analogues. From 2010 to 2017, deaths from fentanyl and other synthetic opioids increased nearly ten - fold, from around 3,000 (14.3% of opioid-related deaths) to over 28,466 (59.8%).^{17, 18} Synthetic opioids are now almost twice as commonly involved in overdose deaths as prescription opioids or heroin.¹⁷ The low production costs of fentanyl and its potency (50-fold compared to heroin) make it an attractive option to mix ("lace") with heroin and illicit manufactured prescription opioids.¹⁹ At present, it is not known how many users actively seek fentanyl, but regardless of intent, heroin users are being exposed to fentanyl or other analogues without realizing it, increasing their risk of overdosing. Overdoses from fentanyl

by itself or combined with heroin appear to be harder to reverse with naloxone than overdoses due to prescription opioids or pure heroin, contributing to the lethality of fentanyl or drugs laced with it. The reasons for the decreased efficacy of naloxone for reversing fentanyl overdoses are unclear and might reflect, its very high potency at the mu opioid receptor (MOR), its very fast pharmacokinetics (entering the brain very rapidly minimizing time for intervention), longer duration of its respiratory depressing effects (that might explain re-narcotization after a temporary reversal of an overdose by naloxone) and/or an additive effects when fentanyl is combined with other drugs including heroin.²⁰

Pharmacological properties of opioids

In addition to their effect on MOR, opioid drugs also bind to kappa- (KOR) and delta-opioid (DOR) receptors, although their affinity, intrinsic efficacy, pharmacokinetics and bioavailability vary by drug. In particular opioid drugs with fast uptake into the brain and full agonist effects at MOR such as heroin and fentanyl are particularly rewarding.²⁰ A strategy for developing opioid medications with lower abuse liability entails opioids formulations with slower entry into the brain and/or formulations that cannot be injected, since this is the route of administration that results in the faster rate of drug uptake in brain. The intrinsic efficacy of full agonist drugs such as heroin and fentanyl leads to greater rewarding effects than for partial agonists such as buprenorphine. Additionally, the rate of clearance of opioid drugs from the brain determines their duration of action and the severity of withdrawal symptoms upon their discontinuation. For that reason, heroin is associated with a much more severe withdrawal than a drug such as buprenorphine, which clears the brain more slowly. Opioids drugs with longer half-lives, slower clearance rates and slower brain uptake are favored for the treatment of OUD. By binding to MOR they decrease craving and prevent the emergence of withdrawal symptoms. Methadone enters the brain rapidly, which is why it is given orally when used for OUD treatment, for this will slow its entry into the brain. Also while it is a full MOR agonist, it has agonist effects at galanin receptors, which are co-expressed with MOR in brain reward regions antagonizing them, and thus reducing methadone's rewarding effects.³¹

The positive (increase reward) and negative (avoid pain) reinforcing effects of opioids, trigger learned associations between the receipt of the drug and these experiences resulting in conditioning. In parallel, the repeated administration of opioids triggers physiological adaptations that result in tolerance and in physical dependence. Tolerance necessitates increasing opioid doses in order to achieve the same levels of analgesia and when misusing them increasing the doses or shifting to more potent opioids such as fentanyl in order to experience their rewarding effects. The development of tolerance does not occur at the same rate for the various pharmacological effects of opioids. In general, tolerance to the analgesic and hedonic effects develops faster than to respiratory depression, whereas tolerance to constipation might never develop.³² This explains why increases in dose to maintain analgesia (or reward) or doses injected to get high can markedly increase the risk of overdose.

Physical dependence to opioids also occurs rapidly and is responsible for the emergence of withdrawal symptoms when opioids are abruptly discontinued, which creates a negative

reinforcement mechanism that can contribute to the maintenance of opioid use. The severity of withdrawal symptoms varies as a function of the opioid drug used; greater for higher potency short acting opioids than for longer lasting opioids as well as the chronicity of exposure. The symptoms from acute withdrawal usually resolve within days and are rarely lethal, but are extremely uncomfortable and are a powerful trigger for relapse in those with an OUD and for continued opioid use among those being treated with opioid analgesics. The risk of withdrawal is minimized or prevented by tapering opioids gradually.

Repeated use of opioids often results in physical dependence as a result of multiple neuroadaptations including desensitization and internalization of the MOR, impaired MOR signaling with intracellular effectors, and adaptations in glial signaling and in neuropeptide systems that interact with MOR-sensitive neurons, among others^{33, 34}. In contrast to physical dependence, OUD develops only in a minority of individuals exposed to opioids. It is characterized by a pattern of maladaptive opioid use that leads to clinically significant impairment or distress and is manifested as intense craving for opioids, erosion of inhibitory control over efforts to refrain from using them, persistent thinking about procuring the drug, and impaired control over opioid use. Because of their repeated opioid use, those with OUD also suffer from physical dependence and tolerance, unless they have undergone supervised medical withdrawal (formerly known as detoxification) in which case they can have OUD without having physical dependence or tolerance. This is clinically relevant in that patients undergoing medically supervised withdrawal without subsequent treatment for OUD are at an extremely high risk of relapse and of overdosing since they crave the drug as intensely as prior to their withdrawal but have lost their tolerance to the opioids. The behavioral manifestations of OUD are associated with structural and functional changes in the brain's reward, executive control, emotion and interoceptive circuits.^{58,59}

Biological factors contributing to OUD

In addition to the environmental contributions to the crisis, multiple biological factors modulate an individuals' vulnerability for opioid use, non-medical use and OUD, including genetic predisposition, brain development, mental illness and social factors.

Genetics

Studies of genetic epidemiology indicate that genes contribute about 50% of the vulnerability to SUD, including OUD. Yet identifying specific genetic variants for increased OUD risk has been difficult, which is likely to reflect in part the fact that OUD, like other psychiatric disorders is a polygenic disease. Genes influence brain development and function of brain circuits and neurotransmitter systems that mediate the reactivity to the environment including drug responses. Furthermore, genes can intervene at different stages of OUD development, including propensity to use (i.e. genes that modulate personality traits) risk of transition from use to OUD (i.e. gene involved in conditioning and neuroplasticity), and vulnerability to relapse (i.e. genes that modulate severity of withdrawal symptoms, sensitivity to stress or other potential triggers). Because OUD often co-occurs with other psychiatric disorders, genes that increase the risk for those co-occurring disorders can also

indirectly increase OUD risk. The effects of genes are also moderated by environmental influences.

Despite these complexities, studies have been able to identify genes that appear to contribute to OUD risk (Table 1). For example, *OPRM1* the gene that encodes for MOR has been implicated in increased vulnerability to OUD.³⁵ Similarly, converging evidence of genome-wide association, neuroimaging and rodent studies support a role in OUD for *CNIH3*, a gene that encodes for the Cornichon Family AMPA Receptor Auxiliary Protein that regulates trafficking and gating properties of AMPA receptors.³⁶ Preliminary results also suggest that the *BDNF* Val(66) Met genotype, which has been associated with neurobehavioral deficits, may promote drug-seeking in individuals with OUD.³⁷

Other genes, though not directly linked to OUD, relate to risk factors, such as personality traits, or brain regions implicated in the circuitry of addiction. For example, polymorphisms associated with low activity in *MAOA*, the gene for monoamine oxidase A, have been linked to a predisposition to externalizing behaviors and disorders that is moderated by environmental exposures.^{38, 39} Similarly, the catecholamine-O-methyltransferase (COMT) gene variant V(108/158)M, leads to greater dopamine degradation and impaired modulation of prefrontal cortex⁴⁰, and has been associated with increased amygdalar reactivity⁴¹ and with disrupted modulation of cortical and striatal activation during anticipation or receipt of a reward.^{42, 43} Numerous animal and human studies have also demonstrated the role of dopamine receptors in reward related behaviors,⁴⁴⁻⁴⁶ but to date, no study has directly linked any dopamine-related gene to the risk of OUD.

Genes whose product influence synaptic plasticity can also contribute to OUD risk, such as Homer proteins, which regulate the level and activity of glutamate receptors,⁴⁷ and matrix metalloproteinase 9 (MMP-9), which in animal models increases motivation for drug-seeking.^{48, 49} Genes that influence response to stress by modulating the glucocorticoid receptor's affinity for cortisol such as the FKBP5 chaperone protein⁵⁰ may also increase risk of OUD.

Brain Development

Drug experimentation is commonly initiated during adolescence and the risk to addiction is increased with early drug use. The greater vulnerability of adolescents to drug use and experimentation is driven by multiple factors including genetics that are associated with the developmental trajectories of the human brain. At the same time the social environments during childhood will influence brain development in ways that can increase its vulnerability to drugs or provide with resilience. Notably, the development of the human brain has a greater sensitivity to environmental factor during the first than second decades of life whereas genes influence brain development throughout the first and second decades.⁵¹ This explain why social stressors are particularly harmful during early childhood. However while it is heuristically useful to distinguish environmental from genetic factors, it is likely that it is their interactions that ultimately determine how the brain will develop.

A better characterization of human neurodevelopment has allowed us to start to understand the role of the environment at critical moments of brain development and how differences in

the rate of development of neuronal circuits influence vulnerability for drug use. For example, during adolescence reward and emotion circuits develop faster than those related to executive function, creating an imbalance between systems that favor experimentation, reward-seeking and drug use and systems underpinning self-regulation. Early exposure to drugs of abuse may further impair the development of the prefrontal cortex, decreasing self-regulating capabilities and increasing the long-term risk for SUD.⁵²

Several brain imaging studies have started or will soon start to generate data to inform the development of the brain and the influence of substance use in this development. The Adolescent Brain Cognitive Development Study (ABCD) is a longitudinal study of children 9-10 years old who will be assessed with brain imaging, genotyping, and deep phenotyping and followed for 10 years. It recently completed the baseline assessment of 11,875 children and has started to provide valuable data on normal variability in brain development and its influence by environmental factors.⁵³ The Baby Connectome Project is a four-year study of children from birth through five years of age, intended to provide a better understanding of how the brain develops from infancy through early childhood and the factors that contribute to healthy brain development.⁵⁴ It will help characterize human brain connectivity and map patterns of structural and functional connectivity to important behavioral skills. Additional biological (e.g., genetic markers) and environmental measures (e.g., family demographics) will be collected and examined to provide a more comprehensive picture of the factors that affect brain development. Finally, the planned HEALthy Brain and Child Development (HBCD) study aims to prospectively follow 7,500 infants through childhood (e.g., age 9-10) to assess structural and functional brain development as well as cognitive, behavioral, social, and emotional development and the long-term impacts of pre/postnatal drug (expected oversampling for opioid prenatal exposures) and adverse environmental exposures on brain and behavioral health and risk for substance use and mental disorders.

Social determinants

Epigenetics are implicated in the persistent neuroplastic changes associated with exposure to environmental factors that increase vulnerability to addiction such as social stressors or drug exposures.⁵⁵ For example, the environment's ability to shape the circuits of emotion, particularly those impacted during critical periods of prenatal, postnatal, and adolescent brain development,⁵⁶ taps heavily on epigenetic mechanisms.^{46, 57} Studies have also started to assess the effects of social stressors on the development of the human brain, and these studies are relevant for understanding why social stressors increase the risk for SUD and other psychiatric disorders. Studies evaluating the effects of social deprivation during infancy and early childhood have reported delayed maturation that results in impaired brain connectivity, which could underlie increased impulsivity in these children.⁵⁸ Fortunately, preliminary studies suggest that interventions that provide social support may help reverse some of these impairments.⁵⁹ Nevertheless, stressful events at any age can increase vulnerability to opioid use and OUD.

Though the developing brain is the most sensitive to adverse social environments, these can also negatively influence the adult brain in ways that increase the vulnerability to drugs use and addiction. This is apparent in the current opioid epidemic and the other “deaths of

despair” (overdoses, suicide and alcohol-driven cirrhosis) that have prominently affected adult white Americans from economically impoverished environments. There is a scarcity of research on the effects of adverse social environments on adult brain function.^{60, 61}

Neurocircuitry of addiction

Reward Circuitry

Although much remains to be learned, our growing knowledge of the brain’s reward circuitry (originating in the dopamine neurons in the ventral tegmental area projecting to the nucleus accumbens, ventral prefrontal cortex and amygdala) and its changes have been fundamental for understanding drug taking and addiction. Reward (more precisely, reinforcement) can be defined as any event that increases the probability of repeating the action. Animal^{62,63} and human studies consistently indicate that drugs release dopamine (DA) in the nucleus accumbens (NAc), which is fundamental to their rewarding effects. Additionally, increases in endogenous opioids and cannabinoids are also associated with the rewarding effects of various drugs.^{64, 65} It is thought that the rapid release of DA and its binding to D₁ receptors (D₁R) in the ventral (location of NAc) and dorsal striatum, which stimulates cyclic AMP (cAMP) signaling is associated with euphoria and pleasure (so-called “high”) and triggers conditioning (learned association between the drug effects and situation where it occurred). By contrast, stimulation of D₂ receptors (D₂R), which inhibit cAMP signaling, does not appear to be associated with rewarding effects per se but blocks the aversive effects when D₂R-expressing medium spiny neurons (D₂R-MSN) are not inhibited by DA.⁶⁶ Individuals with SUD often have decreased baseline DA release in the striatum (including in nucleus accumbens) and experience an attenuated DA increase and less intense reward from drug use (i.e., tolerance), which is interpreted to reflect a hypofunction of their reward circuit. It is unknown to what extent this hypofunction reflects a predisposition of the individual versus consequences from chronic drug exposures.

With repeated drug use, conditioning strengthens and drives the motivation to procure the drug reinforcers. Exposure to conditioned stimuli (referred to as cues) by themselves triggers firing of DA neurons and DA release, energizing the motivation to obtain the drug. When previously neutral stimuli become conditioned to the drug they acquire incentive salience, becoming desirable⁶⁷. Conditioning and the associated DA increases in the striatum are hypothesized to underlie the intense desire for drugs that addicted individuals experience upon exposure to environments or situations where they have taken drugs that frequently leads them to relapse.

The drug-induced stimulation of D₁R signaling involved with conditioning triggers synaptic changes in N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors that enhance glutamatergic signaling in the affected synapses.^{68, 69} At the circuit levels these neuroplastic changes strengthen striatal-pallidal-thalamo-cortical loops that include the ventral and the dorsal striatum, resulting in habit formation⁷⁰ and compulsive response for drugs. As SUD progresses, a prominent hypothesis is that these circuits become increasingly sensitized to drug-cues, environmental stressors or negative emotional states, which can then more readily trigger compulsive drug consumption. In more advanced stages, substance use behaviors are more driven by a

growing importance of dorsal striatum and habits and a decreasing role of positive drug reward. In parallel, as drug-procuring and taking becomes increasingly salient in the addicted individual, non-drug related activities become less motivating and rewarding.^{71, 72}

Although DA and glutamate remain central to our understanding of the reward circuits, these circuits are also modulated by γ -aminobutyric acid (GABA), serotonin, acetylcholine, and the endogenous opioid and cannabinoid systems. Similarly, it is important to realize that, like any other, the reward circuit (as well as the executive control circuit) interact and overlap with circuitry involved in the perception of internal bodily states or interoception (including primary sensory cortex, insula, anterior cingulate cortex and precuneus), homeostasis (hypothalamus), stress (amygdala, hypothalamus, and habenula), salience attribution (orbitofrontal cortex) and learning and memory (amygdala, hippocampus and dorsal striatum) and that the interplay with these circuits modulates the responses to rewards and to conditioned cues (Figure 1).⁷³

Emotion Circuitry

Although positive reinforcers play a major role in the initial phases of drug taking and the development of OUD, in more advanced stages negative emotional experiences such as withdrawal symptoms, craving and enhanced sensitivity to stress become increasingly important and drive drug taking. The increased role of negative reinforcement in drug taking (as a means to escape the negative emotional state) is a considerable barrier to abstinence and a formidable obstacle to successful treatment.

The negative emotional state can be understood as enhancement of processes that are the inverse of those involved in reward (i.e., “anti-reward processes”) ⁷⁴ that are derived from neuroadaptions to drug-induced stimulation.⁶² In the case of opioids most of the physical manifestations of withdrawal, which emerge with drug discontinuation are caused by decreased MOR-triggered intracellular signaling and by enhanced autonomic reactivity.⁷⁵ Early signs of withdrawal, appearing generally in the first 8-36 hours of heroin discontinuation include mydriasis, piloerection, muscle twitching, lacrimation, rhinorrhea, diaphoresis, yawning, restlessness, myalgia, abdominal pain, nausea/vomiting, tremor and insomnia. Individuals with fully developed opioid withdrawal can also experience tachycardia, tachypnea, hypertension or hypotension, dehydration, hyperglycemia, fever, anorexia and diarrhea.

In addition to these physiological manifestations, opioid withdrawal is often associated with neuropsychological symptoms that include, irritability, emotional pain, dysphoria, insomnia and subjective distress that can last several months. The subjective aspects of the negative emotional state are associated with disrupted dopaminergic, serotonergic, noradrenergic, glutamatergic, GABAergic neurotransmission in reward and emotion networks (including NAc).⁶⁷ Stress-related neurotransmitters, such as CRF, norepinephrine, and dynorphin, are also recruited in the extended amygdala and contribute to the distress and increased irritability often present in withdrawal and protracted abstinence.⁷⁶ The lateral habenula, which decreases DA neuronal firing in VTA when expected rewards do not materialize⁷⁷⁻⁷⁹ and is a target of serotonin neurons from the dorsal raphe that modulate mood, also plays a crucial role in triggering and maintaining negative emotional states.⁸⁰ Similarly, the insula,

which is reciprocally connected to several limbic regions and to the default mode network (DMN) has an interoceptive function that integrates autonomic and visceral information with emotion and motivation⁸¹, plays a key role in the self-awareness of negative emotional states and of craving.⁸²⁻⁸⁴

Executive Control Circuitry

Impairments in executive function (including self-regulation), which can precede as a vulnerability factor for SUD or develop secondary to chronic drug exposures, are important contributors to impulsive and compulsive drug taking.⁶⁷

During withdrawal the emergence of the preoccupation/anticipation phase along with mounting craving for the drug results from the interplay of two opposing systems: a Go and a Stop system. The Go system includes most of the circuitry described in the two previous sections, which underlies the hedonic, habitual and emotional aversive aspects that leads to continued drug taking.^{85, 86} The Stop system seeks to control the incentive value of choices, regulate habitual behavior, maintain goal-directed behavior and suppress affective responses to negative emotional signals.⁸⁷⁻⁸⁹ In this framework, the Stop system seeks to inhibit signals generated by the Go system.

The Stop system involves a widely distributed and complex prefrontal cortex–subcortical circuitry. It is mediated through glutamatergic projections from prefrontal cortex to the caudate and ventral striatum to modulate the striatal-pallidal-thalamocortical direct (D₁ receptor-mediated) and indirect (D₂ receptor-mediated) pathways, and to modulate the mesocortical dopamine neurons in the ventral tegmental area, which exert control over DA release in the prefrontal cortex.⁷³ Deficits in prefrontal cortex in individuals with SUD are associated in impairments in executive function that can interfere with decision making, self-regulation, inhibitory control, and working memory.⁹⁰ Reduced activity in the prefrontal cortex (including dorsolateral prefrontal cortex, anterior cingulate gyrus, and medial orbitofrontal cortex) is also associated with downregulation of D2R in the striatum,⁹¹⁻⁹³ and disrupted GABAergic activity in striatum and prefrontal cortex.^{94, 95}

The orbital frontal cortex, anterior cingulate cortex and dorsolateral prefrontal cortex are involved with incentive salience, emotional regulation, and decision making, respectively. Deficits in striatal D2R-mediated DA signaling, which modulates them, may underlie the enhanced motivational value of drugs and the loss of control over drug intake in SUD.⁹⁶ Furthermore, because dysfunction of the orbital frontal cortex and the anterior cingulate cortex are associated with compulsive behaviors and impulsivity,⁹⁷ DA's impaired modulation of these regions may contribute to compulsive and impulsive drug taking in SUD.⁹⁶

Several pathways can encode signals that increase the risk of relapse with exposure to cues, which can activate the ventral prefrontal cortex, including ventral anterior cingulate, and medial and lateral orbitofrontal cortices.⁹⁸⁻¹⁰¹ Cue-induced reinstatement involves glutamatergic projections from the prefrontal cortex, basolateral amygdala, and ventral subiculum to the NAc, and DA projections to the basolateral amygdala and dorsal striatum.¹⁰²⁻¹⁰⁴

In contrast to cue-induced relapse, stress-induced reinstatement depends on the activation of both CRF and norepinephrine in parts of the extended amygdala (i.e., central nucleus of the amygdala and bed nucleus of the stria terminalis) and the VTA.¹⁰⁵ Protracted abstinence, mostly described for alcohol, appears to involve overactive glutamatergic and CRF systems.^{106, 107} A third pathway to relapse is through interoceptive stimuli related to the insula⁸²⁻⁸⁴ and its activation during craving has been associated with relapse.¹⁰⁸

Pharmacological treatment of opioids

A range of pharmacological treatments exists to treat different components of OUD. Information on these medications was recently reviewed by the U.S. Substance Abuse and Mental Health Administration¹⁰⁹ and by the National Academy of Medicine.¹¹⁰

Withdrawal

Medically supervised withdrawal (formerly referred to as detoxification) is the gradual taper of opioid agonist medications (methadone or buprenorphine) guided by a clinician to alleviate withdrawal symptoms. The use of α_2 -agonists such as lofexidine (recently approved by the FDA for the treatment of opioid withdrawal) or clonidine can also help attenuate symptoms of withdrawal,¹¹¹ though subsequent initiation of medications for OUD (MOUD) is required to prevent relapse into drug taking. Indeed, medically supervised withdrawal is not recommended as an isolated strategy, as most patients without subsequent MOUD initiation relapse shortly thereafter¹¹²⁻¹¹⁴ and are at increased risk for overdosing due to the loss of tolerance.¹¹⁵ Medically supervised withdrawal is required, though, for patients starting naltrexone, as described in the next section.

Maintenance

Ongoing outpatient treatment with MOUD leads to better retention and outcomes for OUD¹¹⁶ and reduced risk of HIV and HCV infection and overdose death.¹¹⁷⁻¹²¹ At present, MOUD constitutes the standard of care for most patients with OUD. There are three FDA-approved MOUD: methadone, buprenorphine and naltrexone. In deciding on a specific medication the clinician should evaluate the patient's responses to prior MOUD treatment, tolerance to opioids and patient preferences. Patients, in turn, should be informed of the efficacy, risks, benefits and relative advantages of each of these medications.

Methadone has been available the longest and has the largest evidence of efficacy.^{119, 121} Higher doses of methadone are associated with better retention in treatment, less heroin use during treatment and lower withdrawal symptoms, until around 100 mg/day, after which the reliability of evidence is lower.¹²² Because methadone is a full MOR agonist, it has no ceiling effect. It can lead to overdoses if it is used at doses above the patient's tolerance or combined with other central nervous depressants such as alcohol, benzodiazepines or other opioids. To minimize the risk of intoxication or overdose, methadone should be started at low doses and increased gradually with daily monitoring over several weeks. An important barrier to the use of methadone, particularly in rural settings is that, with a few exceptions, in the US methadone has to be administered in a licensed opioid treatment programs (methadone clinics) and cannot be prescribed by office-based clinicians.

The use of buprenorphine^{123, 124} has certain advantages over methadone, which explains its growing use for OUD treatment. First, although it can still be lethal when combined with other central nervous depressant substances, as a partial agonist, buprenorphine has lower lethality than methadone.¹²⁴ Second, its antagonist effects at the KOR may contribute to its efficacy for OUD.^{125, 126} Its KOR antagonist properties may also have antidepressant effects, which could help improve the depressive symptoms that are common in OUD. Buprenorphine is also an agonist at the nociceptin receptor, which is also implicated on its therapeutic benefits. To deter the injection of buprenorphine, which would enhance its rewarding effects, it is often prescribed in a formulation that includes naloxone, a short-acting opioid antagonist that has poor bioavailability when sublingually administered, but blocks buprenorphine effects if injected. Currently, in the US, prescribers of buprenorphine for the treatment of OUD need to obtain a waiver from the Drug Enforcement Administration (DEA) after completing an 8-hour training.

Extended-release (XR) formulations of buprenorphine have been developed to improve patient adherence. Although, 6-months buprenorphine implants were shown to be as effective as low-dose sublingual buprenorphine,¹²⁷ its benefits are restricted to patients who respond to low doses of buprenorphine (8mg). In 2017, the FDA approved a 1-month XR buprenorphine injection for patients with OUD who have been treated with sublingual buprenorphine for at least one week. Another 1-month and a 1-week XR buprenorphine are currently under FDA review. It would be important to know whether those new formulations can increase treatment retention.

The third FDA-approved MOUD is naltrexone, which is a MOR antagonist that can be prescribed by clinicians in outpatient practice. The efficacy of its immediate release formulation was limited by poor adherence, but the development of a monthly extended release formulation (XR-NTX) significantly improved outcomes.¹²⁸⁻¹³¹ It has been particularly useful in justice system settings reluctant to use agonist therapies,¹³⁰ although there is need to assess whether it would be superior to XR-buprenorphine in those settings. Naltrexone is also a KOR antagonist, and while its affinity is lower than that for MOR, a recent brain imaging study reported KOR occupancies > 80% in patients with alcohol use disorder treated with naltrexone.¹³² Antagonism of KOR by naltrexone could contribute to the mood improvements reported in OUD patients treated with naltrexone.¹³³ A potential barrier for the use of XR-NTX is the need for medically supervised withdrawal. Patients cannot use short-acting opioids for at least 7 days and long-acting opioids for 10-14 days preceding induction onto naltrexone to avoid triggering a withdrawal syndrome. A rapid taper consisting of a single day of buprenorphine followed by ascending doses of oral naltrexone along with clonidine and other adjunctive medications (e.g., clonazepam and prochlorperazine) may allow for faster induction protocols for XR-NTX,¹³¹ but requires further study before it can be recommended as standard strategy.

At present, limited data are available regarding the comparative effectiveness of MOUD or about which patients will respond better to each medication.¹⁰⁹ A Cochrane review concluded that flexible-dose methadone leads to greater retention than sublingual buprenorphine,¹¹⁹ but whether the same results would hold when compared with XR-buprenorphine is unknown. There are currently no published Cochrane reviews of XR-NTX

versus buprenorphine, but two studies^{134, 135} have suggested that patients who can be inducted onto XR-NTX have similar outcomes to those treated with sublingual buprenorphine. However, in one of those studies¹³⁴ a substantial proportion of patients were unable to complete XR-NTX induction, mostly due to early relapse, leading to superior outcomes for the buprenorphine group in the intent-to-treat analysis.

As knowledge about MOUDs continues to grow, three priority areas need to be addressed. First, studies suggest that longer time in treatment is associated with better outcomes and that the risk of relapse greatly increases after medication discontinuation, yet rates of MOUD discontinuation in the first 6 months of treatment remain very high. Thus, there is a need to improve retention in MOUD treatment. It is also important to know which patients, when and under what circumstances can safely discontinue MOUD.

Second, current evidence indicates that counseling or psychotherapy do not increase retention in buprenorphine treatment or improve abstinence rates^{116, 136-139} and that methadone treatment¹⁴⁰ and buprenorphine without concomitant counseling is vastly superior to no treatment.¹⁴¹ It is important to determine whether the potential benefits of concurrent psychotherapy outweigh the barrier to treatment created by requiring provision of psychotherapy when delivering buprenorphine treatment (such counseling is at present not required for XR-NTX). This was highlighted in the recent report of the National Academy of Medicine, which emphasized that lack of behavioral treatment support is not a reason for withholding MOUD.¹¹⁰ Nevertheless, evidence-based behavioral interventions can be useful in engaging some patients with OUD in treatment, retaining them in treatment, improving outcomes, and helping them achieve recovery.¹⁴² More research is needed to determine which behavioral interventions provided in conjunction with MOUD are most helpful for which patients, including evidence on the effectiveness peer support. There is also a need to develop models of care that better attract and retain patients in care and can overcome the barriers posed by the limited availability of well-trained clinicians. The use of technology-based approaches (i.e. Telehealth, mHealth) may be a promising avenue to achieve these goals.

Third, research is needed to evaluate whether residential or inpatient treatment is superior to outpatient treatment for initiating MOUD. This question is important to evaluate the optimal allocation of resources for the treatment of OUD.

Preventing Opioid-Related Overdoses

Despite national and local efforts, the number of opioid-related overdoses continue to increase, highlighting the need of clinicians to educate patients and their families about the risk of overdose and how to respond to it. Several medication- and patient-related factors increase the risk of overdose.¹⁴³ Patient-related factors include: 1) Age above 65 years; 2) respiratory problems; 3) long-term opioid use; 4) substance use disorder (including alcohol use disorder); 5) comorbid mood disorders and/or suicidality; 6) use after a period of abstinence (e.g. following medically supervised withdrawal or incarceration); 7) prior overdose. Medication-related factors include: 1) Daily dose above 100 morphine milligram equivalents; 2) use of higher doses than prescribed (or than usually consumed, in the case of

illicit opioids); 3) combination with fentanyl, other high-potency opioids or other substances, such as alcohol or benzodiazepines.

The acute treatment of overdose is administration of naloxone. For many years naloxone, which required injection, could only be administered by health care providers, but the availability of an auto-injectable naloxone device and a naloxone spray now allow laypersons to administer naloxone to revert overdoses.^{144, 145} Nevertheless, increasing the availability of naloxone to ensure that it can reach those who need it on short notice remains a challenge, as there is considerable variability in the availability of naloxone by locality.¹⁴⁶ A 2019 analysis concluded that making naloxone available without prescription (“over the counter”) would substantially increase its availability.¹⁴⁷

In most cases a single dose of naloxone is sufficient to reverse the overdose. However, when high doses or high potency opioids such as fentanyl are used more than one dose is necessary to restore or maintain spontaneous breathing.¹⁴⁸ Furthermore, the fast pharmacokinetics of fentanyl can result in abrupt respiratory depression, which in some instances does not provide sufficient time to administer naloxone. It is believed that the duration of the respiratory depression from fentanyl or other analogues is longer than the duration of its reversal from naloxone. Moreover, thoracic rigidity associated with serotonergic effects from some of the opioids drugs might also interfere with overdose reversals. Naloxone can also fail to reverse overdoses in which opioids are combined with other CNS depressants, such as alcohol or benzodiazepines. First-responders to an overdose should stay with patients until emergency medical services arrive and transport them to an emergency room for a more systematic evaluation. Reversal of the overdose generally triggers an acute withdrawal syndrome,¹¹¹ which can lead patients to leave medical supervision to seek opioids for relieving withdrawal. Upon reversal of an overdose OUD patients should be linked to OUD treatment otherwise their risk of overdosing again is very high. The emergency room offers unique opportunities to start patients on MOUD if they can be linked with ongoing services.¹⁴⁹ Nevertheless, more research is needed to improve the management of patients immediately after reversal of an overdose, to retain them under care and to initiate effective MOUD.

Prevention

Because of the urgency of the crisis, most efforts to date have emphasized treatment approaches. There is growing recognition, however, of the need to develop effective preventive interventions for OUD.^{1, 5, 150} Initial preventive approaches in the US focused on improving prescription practices for opioid analgesics and increasing the availability of naloxone to prevent overdoses. The growing role of heroin, fentanyl and other synthetic opioids in the opioid crisis,^{1, 16, 151} has required broadening the scope of preventive interventions. There are no evidence-based primary and secondary prevention for OUD for adults or for youth transitioning into adulthood, but several approaches appear as promising directions.

One approach would be to adapt existing interventions that have been successful for youth. Evidence-supported prevention interventions delivered in community or school settings have

shown effectiveness at reducing substance use and other related problem behaviors, including middle-school interventions that have specifically demonstrated an impact on reducing prescription opioid misuse.¹⁵² However, whether those interventions would work in adults is unknown. An obvious difficulty in adapting these interventions is the lack of a setting similar to school where adults could be easily reached.

A second direction would be the development of conceptual frameworks that articulate the relationship among risk factors for OUD to help guide which interventions might be most effective given the prevalence of the risk factors, how they relate to other relevant risk factors and how modifiable the risk factors are. These models could help examine how risk factors present at birth (e.g., family history of substance use disorders) or childhood (e.g., adverse childhood events) can increase the likelihood of risk factors in adolescence (e.g., early onset of psychiatric disorders, low educational achievement), which in turn increase the risk of OUD in adulthood.¹⁵³ Simulations could help identify which interventions might be most promising at the full population level or for subgroups with specific constellations of risk factors, as well as to identify potential unintended consequences of those interventions.

A third approach would be to increase the focus on populations at risk that can be accessed for screening and treatment. Those include, for example, individuals who receive regular health care and those in the justice system. Improved management of opioid prescriptions and of treatment of OUD for pregnant women is also a high priority, as it could benefit the mother and simultaneously decrease the risk of neonatal abstinence syndrome (NAS) in newborns by decreasing their in-utero exposure to opioids.

Even with wider use of non-opioid analgesics or use of non-pharmacological approaches, opioids will continue to be necessary for the treatment of many patients with severe pain. Efforts to prevent the development of opioid misuse and OUD can be started in clinical settings. This includes assessment of risk of OUD before opioids are prescribed, periodic assessment of the need for opioid use, and use of urine testing to rule out illicit use of other substances. There is evidence that prescribing lower doses/fewer pills in the emergency room/post-surgery is associated with lower rates of long-term use and possibly OUD. There is also a need to assess each patient for licit and illicit use of other substances, particularly benzodiazepines and alcohol, which can increase the lethality of opioids by potentiating their depressing respiratory effects. Individuals who misuse opioids or develop OUD should be treated by their primary physicians if they have the necessary expertise and support or otherwise be referred to an addiction specialist.

Prevention approaches should also consider supply approaches. The most common sources of diverted opioid analgesics are friends or relatives who were legitimately prescribed opioids.¹⁵⁴ As with any other medication, it is important to educate patients who receive legitimate prescriptions about the health hazards they create for others when they give them their medications. Similarly, it is important to educate patients about the health risks they incur when they take medications (including opioids) that were not prescribed to them. Use of Prescription Drug Monitoring Programs (PDMPs) can help reduce doctor shopping and overdoses, but their use to date is inconsistent. This may be due in part to the voluntary

nature of the programs in many states, delays in updating the information, restrictions in data sharing across jurisdictions and the need to access them through a separate computer from the one used to access electronic health records.¹⁵⁰ Approaches that could help decreased the availability of heroin and fentanyl, traditionally in the purview of law enforcement primarily, would also advance prevention, but their development and implementation are challenging in the face of the evolving nature of the epidemic.

Research Gaps and Translational Opportunities

Basic Science

In addition to making progress in clinical and public health approaches, there is a need to advance fundamental science that can provide the foundations of more effective interventions for the current crisis and provide the basis to combat future ones. For example, there is a need to better understand the genes implicated in individual differences in vulnerability to the stages and sequelae along the OUD trajectory, including the development of tolerance, physical dependence, addiction, hyperalgesia, and respiratory depression for they could help identify new medication targets and in the future could serve as biomarkers to predict risk for side effects. Animal models could be used to identify the functions of the relevant genetic variants, epigenetic modifications, and gene networks.

Similarly, technological advances, such as those emerging from the BRAIN initiative could be leveraged to gain a deeper knowledge of endogenous opioids and to identify the consequences of exogenous opioid administration on the endogenous opioid systems and the cells and circuits they modulate across a trajectory of opioid use, ranging from acute administration, tolerance, physical dependence, addiction, and recovery to relapse. This could include studying profile changes in the transcriptome and methylome of opioid-synthesizing neurons, imaging the intracellular signaling cascades following opioid receptor activation (and how those cascades change across the trajectory of opioid use) and using quantitative brain-wide optical imaging combined with computational pipelines for cellular registration to provide unbiased documentation of the stereotyped distributions of cellular activity and cell-types engaged by opioids under different conditions. Post-mortem brains could be used to identify human-specific genes and their proteins, as has been done in the study of other psychiatric disorders. Use of post-mortem brains would enable the discovery and integration of genomic, epigenomic, proteomic, metabolomic, and non-coding RNA features across many brain regions and cell types that distinguish individuals with vulnerabilities to OUD and opioid-induced respiratory depression. This knowledge could be combined to validate findings in animal models (i.e., does the animal model recapitulate the human brain biology?) and to reverse translate from human to test a hypothesis in rodents.

A systematic investigation of developmental trajectories of the human brain is relevant for our understanding of the mechanism through which adverse child experiences as well as drug exposures during fetal development increase risk for drug use and other mental illnesses. To address this question, the HEALthy Brain and Child Development (HBCD) Study, which is part of the HEAL Initiative from the National Institutes of Health,¹⁵⁵ will establish a large cohort of pregnant women from regions of the country significantly affected by the opioid crisis, and follow them and their children for at least 10 years. The study will

help better understand typical brain development, beginning in the prenatal period through early childhood, including variability in development and how it contributes to cognitive, behavioral, social, and emotional function.

New Medications

Despite the existence of effective medications for the treatment of OUD, current rates of engagement and retention in treatment suggest that new medications and devices are needed. The introduction of more acceptable and effective medications is crucial to improve the outcomes of individuals with OUD. In turn, improved outcomes could lead to changes in societal attitudes towards OUD, with broader acceptance of OUD as a treatable brain disorder and lower stigmatization of those suffering from it. Because the circuitry and neurotransmitters of the different phases of OUD only partially overlap, several complementary approaches may be necessary to treat the whole spectrum of severity from sporadic to chronic use, withdrawal and relapse.

To help speed the development of novel pharmacotherapies (i.e., excluding already known mechanisms) NIDA recently created a list of medication development priorities based on data from published literature and internal studies with the most direct relevance to OUD.¹⁵⁶ This list, which is not exclusive did not prioritize any of the 10 proposed mechanisms and included: 1) orexin-1 or 1/2 antagonists; 2) Kappa opioid antagonists; 3) GABA-B agonists; 4) Muscarinic M₅ antagonists; 5) AMPA antagonists; 6) nociception opioid peptide receptors/opioid receptor like agonists or antagonists; 7) mGluR2/3 agonists; 8) Ghrelin antagonists; 9) Dopamine D₃ partial agonists; and, 10) Cannabinoid CB-1 antagonists.

In addition to medications that target specific receptors, the development of allosteric modulators of those receptors is also a high priority. Negative allosteric modulators (NAMs) and positive allosteric modulators (PAMs) may provide more physiologically relevant effects compared with agonists and antagonists acting on the same receptor, which may ultimately result in improved clinical outcomes.¹⁵⁷ The development of opioids that selectively activate MOR G-protein intracellular pathways (“biased agonists”) may lead to medication with potent analgesic properties but with lower risk of respiratory depression and addictive liability, which would contribute to decrease the incidence and prevalence of OUD.¹⁵⁸ Other potential directions could include epigenetic, micro RNA and neuroimmune targets.

Better training of health professionals

Despite the severity of the dual crises of chronic pain and OUD, very few medical schools offer adequate training in pain management, and still fewer offer even one course in addiction. Furthermore, surprisingly little is known about how best to train physicians and other health professionals on the management of OUD including the use of medications.¹⁵⁹ There is also evidence that many individuals trained to provide MOUD do not provide that treatment. Some national organizations offer a combination of didactics, supervision and mentoring to provide training beyond residency,¹⁵⁹ and the new subspecialty of addiction medicine is likely to further increase the availability of well-trained professionals that can treat individuals with OUD. However, broader changes, including combating stigma, enhancing institutional support and increasing reimbursement rates may be necessary to

increase rates of treatment among those trained to provide it. Increasing the number of addiction treatment and prevention programs, particularly in low-resource communities is also essential.

Conclusion

The opioid crisis is a complex, evolving phenomenon. It involves neurobiological vulnerabilities and social determinants of health. Successfully addressing the crisis will require advances in basic science, development of more effective treatments, and public health approaches to implement current and emerging knowledge. We hope that this review will alert clinicians and researchers about the current approaches to the crisis and suggest opportunities for future research and for practice improvement. The advances achieved in addressing the current crisis should also serve to expand the science and treatment of other substance use disorders.

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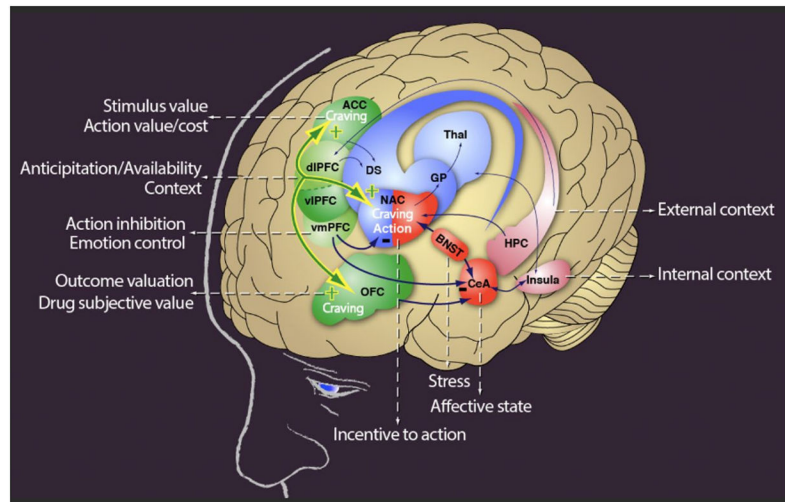


Figure 1.
The circuitry of opioid use disorder (reprinted with permission from: George O, Koob GF. Control of craving by the prefrontal cortex. *Proc Natl Acad Sci U S A.* 2013 Mar 12;110(11):4165-4166

Table 1.

Genes associated with increased vulnerability to opioid use disorder

Gene	Molecular Product or Target	Hypothesized mechanism
<i>OPRM1</i> ³⁵	Mu-opioid receptor	Changes in Mu-receptor expression
<i>CNIH3</i> ³⁶	AMPA receptor auxiliary protein	Influences control over opioid use
<i>BDNF</i> ³⁷	Brain-derived neurotrophic factor	Moderates propensity to drug-seeking
<i>MAOA</i> ^{38, 39}	Monoamine oxidase A	Changes in propensity to externalizing behaviors
<i>COMT</i> ^{40, 41}	Catecholamine-O-methyltransferase	Modulation of prefrontal cortex, amygdalar activity, and reward circuitry
<i>FKBP5</i> ⁵⁰	FK506 binding protein 5	Moderates responsivity to stress
<i>Homer 1-3</i> ⁴⁷	Homer proteins	Influences response to rewards
<i>MMP9</i> ⁴⁸	Matrix metalloproteinase 9	Moderates propensity to drug-seeking

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