An Insight about Opioid Use Disorder; Pathophysiology, Stages and Neurocircuitry Effects

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Abstract
Accurate estimation of the population-based prevalence of OUD is challenging. The availability and quality of data on OUD varies geographically. The types of opioids used and the typical routes of administration vary between countries and have changed over time. The likelihood of OUD following opioid use is high compared with most other drugs. Some individuals are highly vulnerable to OUD following opioid use, whereas others do not develop OUD and cease within a year of first use. A complex interplay of structural, social, developmental and behavioral risk factors is likely to have a role in the development of OUD. OUD has a moderate to high heritability. Several consequences of prescribed and non-medical opioid use cause substantial burden to the individual, families, and the broader community. Building on conceptual frameworks derived from neurobiology from animal models, clinical brain imaging studies and social psychology, a three-stage cycle of OUD has been hypothesized, consisting of binge/intoxication, withdrawal/negative affect and preoccupation/ anticipation stages. Dramatic tolerance (that is, a lower response to a drug following repeated administration of the drug or the need for larger doses to produce the same effect) develops to the analgesic, euphorigenic, sedative and other effects of opioids, including their lethal effects, and can develop after a single administration. Symptoms of physical withdrawal in humans include piloerection, chills, insomnia, diarrhea, nausea, vomiting and aches, and the severity and duration vary based on the dose and duration of opioid exposure and the pharmacological properties of the opioid used, including efficacy and pharmacokinetics.

Keywords: Opioid Use Disorder

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Introduction:

Accurate estimation of the population-based prevalence of OUD is challenging. The availability and quality of data on OUD varies geographically, making prevalence estimates uncertain for many countries. In the 2016 Global Burden of Disease study, 26.8 million people were estimated to be living with OUD worldwide **(1).**, with the highest estimated prevalence observed in the USA **(1).**

Types of drug use

The types of opioids used and the typical routes of administration vary between countries and have changed over time. For example, opium (by smoking or ingestion) was historically the most common opioid consumed in countries in the Middle East, such as in Iran, although injection of opioids has become a more prominent feature of illicit opioid use in Iran in recent decades **(2,3)**

By contrast, prescription opioid use is more common in North America; in the USA, prescriptions for opioid analgesics quadrupled between 1999 and 2010, with a sharp increase in deaths over the same period. Population surveys suggest that the prevalence of lifetime heroin use in the USA increased from 0.33% in 2001–2002 to 1.6% in 2012–2013. Additionally, there is evidence of dramatic increases in the use of synthetic opioids (including illicit fentanyl) in the USA, with an estimated more than six times increase in overdose deaths caused by synthetic opioids from 2013 (~3,105 deaths) to 2016 (~20,000) **(4).**

Course

The likelihood of OUD following opioid use is high compared with most other drugs. Some individuals are highly vulnerable to OUD following opioid use, whereas others do not develop OUD and cease within a year of first use **(5).**

There are anecdotal accounts of individuals who manage to use opioids infrequently, although they remain at risk of acquiring blood-borne virus infections (and the subsequent morbidity and mortality), even if other health and social problems associated with OUD do not develop. Many people who develop OUD have a chronic remitting course of the disorder. Data from cohorts of individuals with heroin dependency suggests that they can cycle in and out of active OUD over years or decades, interspersed with periods of exposure to treatment, incarceration and abstinence **(6).**

Risk factors for OUD

A complex interplay of structural, social, developmental and behavioral risk factors is likely to have a role in the development of OUD. OUD has a moderate to high heritability; An important risk factor for OUD and for overdose deaths is the availability and volume of prescriptions of opioid pain medication **(7)**

The availability of opioids for analgesic purposes varies substantially across the globe and it is not surprising that countries that have much higher prescribing rates for opioids have greater

rates of non-medical use and opioid overdose deaths such as in North America, Western Europe and Australia Indeed, the USA and Canada have experienced an epidemic of opioid prescribing, which has been a driver of the current public health emergency of OUD. For example, in 2012, there were enough opioid prescriptions in the USA (~259 million) for "every adult in the United States to have a bottle of pills" **(8).**

The consequences of this over-prescribing have been severe. Prescription sales of opioids for pain management have increased alongside increases in opioid-related deaths, with >165,000 deaths in the USA between 1999 and 2014. Several family factors increase risk of illicit drug use during adolescence such as poor quality of parent–child interactions (neglect) and relationships, parental conflict, childhood maltreatment (abuse), parent incarceration, and parental and sibling drug use **(9).**

Individual risk factors for OUD include male sex, externalizing disorders in childhood (such as conduct disorder), poor school performance, low commitment to education and non-completion of secondary education. Of the externalizing disorders, conduct problems in childhood and early adolescence are a key pathway to substance use in young people and are a feature of the onset of OUD **(10).**

Indeed, in one case–control study, people who inject opioids were over four times more likely to have experienced early conduct problems that were severe enough to become known to local government social services. In addition, there is consistent evidence that the prevalence of childhood physical and sexual abuse is increased in people with a history of opioid use; however, the quality of the evidence is not strong **(11).**

Burden of disease and sequelae of OUD

Several consequences of prescribed and non-medical opioid use cause substantial burden to the individual, families, and the broader community. For example, OUD itself carries a substantial health burden owing to the disability associated with OUD and the risk of overdose. The health burden from OUD varies dramatically across countries, with the highest burden observed in the USA **(1).**

The shifts in the types of opioids consumed in some countries have dramatically increased the risk of opioid overdose and opioid-related mortality. For example, since 2010 in the USA, deaths due to prescribed opioids have stayed relatively constant, whereas illicit opioid-related overdose deaths have increased substantially; this effect was first attributable to heroin but has more recently been due to fentanyl **(12).**

People who have developed OUD have an increased risk of a range of other social and health-related harms, including incarceration, injuries, suicide, homicide, and blood-borne virus infections, compared with the general population. In the USA, the number of reported cases of acute HCV infection doubled between 2011 and 2015. Similarly, the number of cases of opioid neonatal abstinence syndrome increased from 1.20 per 1,000 live births in the year 2000 to 3.39

in 2009, whereas the percentage of days spent in intensive care because of neonatal abstinence syndrome increased from 0.6% to 4.0% between 2004 and 2014 **(13).**

Mechanisms/Pathophysiology

Stages of the addiction cycle

Building on conceptual frameworks derived from neurobiology from animal models, clinical brain imaging studies and social psychology, a three-stage cycle of OUD has been hypothesized, consisting of binge/intoxication, withdrawal/negative affect and preoccupation/ anticipation stages **(14).**

These three stages represent dysregulation in three functional domains that are mediated by three major neurocircuits: the binge/intoxication stage represents dysfunction with incentive salience/pathological habits and is mediated by the basal ganglia; the withdrawal/negative affect stage represents negative emotional states and is mediated by the extended amygdala; and the preoccupation/anticipation stage represents dysfunction in executive function, which is mediated by the prefrontal cortex (PFC) **(14).**

Endogenous opioid peptides

Opioid addiction involves the hijacking of the endogenous opioid system; a complex neuromodulatory system composed of a family of endogenous opioid peptides (β-endorphins, enkephalins and dynorphins) and receptors. Endogenous opioids have a distinct polypeptide precursor and a differential but overlapping distribution throughout the brain and undergo preferential binding to the three opioid receptors: μ-opioid receptors (endorphins), δ-opioid receptors (enkephalins) and κ-opioid receptors (dynorphins) receptors. **(15).**

Opioid peptides and their receptors are expressed throughout the peripheral and central nervous systems. These peptides regulate many aspects of physiology, including pain processing, stress reactivity, reward sensitivity, mood, respiration, and gastrointestinal, endocrine and immune functions **(16).**

Neurocircuitry of opioid addiction

Binge/intoxication stage: opioid intoxication and incentive salience

μ-Opioid agonist drugs are profoundly rewarding to both animals and humans, independent of pain or discomfort. As such, the reward induced by opioids leads to the association of the reward with drug-associated stimuli, such as a smell, a visual cue, any white powder or a specific context (for example, a street corner), triggering drug craving (conditioned reinforcement/incentive salience). In humans, incentive salience has been studied in laboratory settings that measured craving and drug-like urges with exposure to drug-related cues (historically termed 'needle freak' behavior) **(17).**

Opioid drugs, such as heroin, are self-administered intravenously by mice, rats, monkeys and humans. When provided under restricted conditions, animals maintain stable levels of opioid

intake without major signs of physical dependence; however, when given under unlimited-access conditions, animals rapidly escalate their opioid intake (18).

Withdrawal/negative affect stage: opioid tolerance and withdrawal

Dramatic tolerance (that is, a lower response to a drug following repeated administration of the drug or the need for larger doses to produce the same effect) develops to the analgesic, euphorigenic, sedative and other effects of opioids, including their lethal effects, and can develop after a single administration (19).

The lethal effects of μ-opioid agonists are primarily due to respiratory depression via their actions in brainstem respiratory nuclei, specifically the pre-Bötzinger complex and the parabrachial nucleus. Interestingly, clinical studies have revealed differential tolerance levels for the different opioid effects, such that individuals become very tolerant to the rewarding, analgesic or respiratory depressant effects, whilst still showing sedation, miosis (constriction of pupil) and constipation (20).

Most opioid tolerance is thought to be pharmacodynamic and not dispositional, meaning that tolerance involves neuronal adaptations rather than increased opioid metabolism (20).

Neurobiological mechanisms of tolerance range from opioid receptor desensitization and downregulation to cellular and circuitry allostasis. In the descending pain processing pathways, G proteins that are activated by μ-opioid receptors following opioid peptide binding can modulate the activity of several second messengers and cellular effectors, triggering μ-opioid receptor desensitization, μ-opioid receptor internalization, transcriptional changes in the expression of both opioid receptors and other proteins, and structural changes (such as dendritic spine remodeling), all of which collectively lead to cellular tolerance (21).

Dissecting the role of one of the major non-G protein signal transduction pathways for μ-opioid receptors has revealed a key role for the β-arrestin pathway in opioid receptor desensitization and resensitization. μ-Opioid agonists typically cause activation of the arrestin 3 pathway downstream from the G-protein cascade. Indeed, mice deficient in arrestin 3 (also known as β-arrestin 2) have greater analgesia, but significantly less antinociceptive tolerance, dependence, constipation and respiratory suppression compared with wild-type mice, suggesting that drugs that activate μ-opioid receptors without activating the β-arrestin pathway (such as biased opioid agonists) may have high analgesic potential and lower adverse effects (22).

Withdrawal symptoms have a major role in relapse and can also be conditioned to cues and context in the environment. Indeed, negative emotional symptoms associated with acute withdrawal, protracted abstinence and conditioned withdrawal significantly improve with the use of MOUD. Studies of the neurobiological substrates of physical withdrawal in animal models have revealed the involvement of multiple regions, including the periaqueductal grey, dorsal thalamus and locus coeruleus (4).

Brain regions that are responsible for affective (motivational and emotional) withdrawal have a focal point in the extended amygdala. Two neuroadaptations hypothesized to produce the

negative emotional state (such as malaise) that contributes to the negative reinforcement associated with opioid withdrawal: a loss of function in reward systems (in the VTA and NAc) that mediate the acute reinforcing effects of opioids and a gain of function in the extended amygdala, which mediates stress-like responses (23).

Chronic morphine use in animals is also associated with a smaller dopaminergic neuron size in the VTA and a greater sensitivity to dopamine D2 receptor antagonists; PET studies of people with opioid dependence have revealed lower levels of D2 receptors across the entire striatum compared with controls, which was associated with years of opioid use. However, a decrease in dopamine release in the striatum was not observed after naloxone-precipitated withdrawal; instead, a trend for dopamine increases in the dorsal striatum was noted (24).

Gain of function of the brain stress systems during opioid withdrawal is mediated by neurochemicals in the extended amygdala that are involved in the aversive effects that act in opposition to the acute effects of opioids to reduce stress (for example, corticotropin-releasing factor (CRF), dynorphin and noradrenaline). The blockade of CRF receptors in the central nucleus of the amygdala blocks compulsive opioid seeking in animals that were allowed extended access to the drug (known as the long-access model) (25).

In addition, administration of a κ-opioid receptor antagonist into the shell of the NAc blocked the stress-induced potentiation of opioid reward and reinstatement of opioid-seeking behavior and prohibited the escalation of drug consumption in long-access models. Dynorphin–κ-opioid receptor activation may also explain the hypodopaminergic state that is driven by excessive opioid administration, either of a single, large dose or chronic administration (26).

The activation of neuropeptide Y and the endocannabinoid systems and other anti-stress systems in the extended amygdala may modulate the increase in stress reactivity associated with opioid withdrawal and, as such, could buffer endogenous pro-stress systems (27).

Preoccupation/anticipation stage: opioid craving and relapse

The preoccupation/anticipation stage of the addiction cycle in humans involves dysfunction of executive function. Executive function is mediated by the PFC and impairments in response inhibition, salience attribution and self-regulation were conceptualized as underlying relapse and bingeing in humans (28).

Animal models of craving have historically used paradigms of drug-induced, cue-induced and stress-induced reinstatement of drug-seeking behavior in non-dependent animals that are allowed limited access to opioids. In these models, administering μ-opioid receptor agonists injected systemically or directly in the VTA reinstates opioid-seeking behavior during extinction, and reinstatement of opioid-seeking behavior during extinction is blocked by naloxone (29).

Re-exposure to a previous heroin-paired cue or context after extinction can reinstate heroin-seeking behavior in nondependent rats. In addition, in rodents, cue-induced reinstatement engages neurocircuitry from the medial PFC to the NAc, and context-induced reinstatement engages projections from the ventromedial PFC and subiculum to the NAc shell. One key molecular

mechanism of cue-induced reinstatement of opioid seeking involves the dysregulation of glutamatergic homeostasis and particularly of metabotropic glutamate receptors 2 and 3 **(30).**

In rats, the stress-induced (via foot shock) reinstatement of opioid self-administration can be blocked using CRF receptor antagonists and α2-adrenergic receptor agonists, which inhibit noradrenaline release. Brain regions that are critical for the role of CRF and adrenergic drugs in the foot shock-induced reinstatement of opioid self-administration include parts of the extended amygdala. In humans, individuals with OUD have a dysregulated hypothalamic–pituitary–adrenal stress axis; this dysregulation persists during cycles of addiction and may drive brain stress systems as identified in animal studies. **(31).**

Genetics

OUD, similar to other substance use disorders, has high heritability **(32).**

The A118G (or single-nucleotide polymorphism (SNP) rs1799971-A) polymorphism in OPRM1 (encoding the μ-opioid receptor) might influence the expression of μ-opioid receptors in the brain, the sensitivity to opioid receptor agonist drugs and vulnerability to opioid addiction, although not all studies have demonstrated these associations. Indeed, cis-expression quantitative trait loci analysis has demonstrated that other SNPs, such as rs3778150, and nearby SNPs, may underlie the inconsistent associations between rs1799971 and heroin addiction. Here, SNP rs3778150 was strongly associated with an increased risk of heroin addiction and the functional SNP rs1799971-A was associated with heroin addiction only in those with rs3778150-C. Based largely on case studies, a substantial genetic variation in the metabolism of opioid drugs has been reported, particularly of those that use the cytochrome P450 enzyme system, such as codeine, oxycodone, tramadol and fentanyl **(33).**

This variation leads to extreme cases of poor metabolizers (who have very high drug levels in plasma) or ultra-rapid metabolizers (who need much higher drug doses for therapeutic efficacy). Poor metabolizers could be vulnerable to overdose with ill-founded self-medication attempts and ultra-rapid metabolizers could be vulnerable to excessive intake that makes them vulnerable to addiction. Genome-wide association studies with pathway analyses have identified several loci and gene networks that might account for the heritable vulnerability to OUD, including genes encoding potassium channels, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, calcium channels and glucocorticoid receptors **(34).**

Sex differences

More men misuse and are addicted to opioids than women. Indeed, in the USA in 2017, there were 32,337 opioid overdose deaths in males and 15,263 in females. The prevalence of OUD in the USA also shows sex differences; the 2017 National Survey on Drug Use and Health reported that, of those aged ≥12 years with opioid abuse or dependence, 1,162,090 were men (0.96% of men in this age group in the overall population) and 779,050 were women (0.62% of women in this age group in the overall population) **(35).**

Clinical reports suggest that, for opioids, similar to other drugs of abuse, women progress from initial use to addiction at a faster rate than men. Sex differences in the opioid system have been reported in preclinical studies, which might underlie sex differences in the sensitivity to pain or addiction. In addition, PET studies in humans demonstrated higher levels of μ-opioid receptors in several brain regions (neocortex, caudate, amygdala, thalamus and cerebellum) in women than in men, and that women had less pain-induced activation of μ-opioid receptors than men in the thalamus, basal ganglia and amygdala **(36).**

Preliminary PET studies in humans have also reported significantly higher availability of κ-opioid receptors in the brain of men than women. However, much more preclinical and clinical work is needed to characterize sex differences in the opioid system, which are relevant to both pain and addiction. **(37).**

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