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REVIEW ARTICLE

Opioid Receptors and Opioid Use Disorder: Implications for Treatment

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ABSTRACT: The global opioid crisis has raised the critical need for effective, safe treatment for opioid use disorder (OUD) with minimal side effects. Central to this research are opioid receptors and signaling mechanisms that influence pain relief, reward, and addiction. This review examines the connection between opioid receptors and OUD, focusing on the mu-opioid receptor (MOR), the delta-opioid receptor (DOR), and the kappa-opioid receptor (KOR). This review also evaluates current medication treatments for OUD (methadone, buprenorphine, naltrexone), highlighting their successes and challenges. Exploring how opioid receptors and their functions contribute to OUD and treatment options can provide insight into mitigating the opioid crisis, guiding the development of safer and more effective OUD therapies.

KEYWORDS: Cellular and Molecular Biology, Neurobiology, Opioid Receptor, Opioid Use Disorder (OUD), Endogenous Opioid System (EOS), Medication-Assisted Treatment (MAT).

Introduction

Opioids are a class of natural or synthetic drugs that derive from or mimic alkaloids found in opium poppies (*Papaver somniferum*). The medicinal and recreational use of naturally occurring opiates for pain relief or to cause euphoria dates back thousands of years. However, it was only in the early 1800s that morphine was isolated as the most active component of opium, making it the first alkaloid to be isolated from a natural product.[1,2] Since then, many more opioids have been isolated and developed to be used clinically as treatment for moderate to severe pain, often prescribed after surgery, injury, or for health conditions like cancer.[3] Since the 1990s, opioid prescription rates have risen significantly. This surge stemmed from the recognition of pain undertreatment as a major clinical issue and the misconception that patients were not at risk of developing opioid use disorder (OUD).[4,5] Despite their side effects, including dependence, euphoria, addiction, respiratory depression, constipation, nausea, and vomiting,[6] opioid use persists today, in part due to the critical need for effective pain management. With estimates suggesting that pain affects 20% of adults globally,[7] opioids are a primary treatment option for acute and cancer pain.

In recent decades, a global public health crisis has emerged, known as the "opioid epidemic" or "opioid crisis." Leading factors of this crisis include the role of pharmaceutical companies, poor regulation, overprescription, and the rise in illegal drug use. A primary reason for the widespread use and misuse of opioids is their high addictive potential. For example, heroin, an illegal opioid made from morphine, is one of the most addictive drugs on the planet.[8] Opioids are so addictive because they interact with the brain's reward system, triggering euphoria and the release of endorphins and dopamine.[9] Consequently, 60 million people worldwide face the addictive effects of opioids,[8] and the crisis is particularly serious in North America. In 2023, pharmacies in the United States dispensed around 125 million opioid prescriptions.[3] Furthermore, in the last two decades, the United States and Canada have had nearly 600,000 deaths caused by opioid overdose. By 2029, this number is estimated to reach 1.2 million.[10] A significant portion of these numbers are linked to OUD, with over 16 million affected by it globally and 2.1 million in the United States.[11]

Characterized by chronic compulsive or harmful use of opioids, OUD is driven by the effects of drugs on the brain, mediated by mu (MOR), kappa (KOR), and delta (DOR) opioid receptors. These receptors were discovered in the early 1970s as the binding site of opioids.[12] They belong to the G protein-coupled receptors (GPCRs) family, the largest class of membrane proteins in the human genome, and some of the most common drug targets. When activated by opioids, these receptors can affect pain perception, mood, and stress, leading to widespread clinical and recreational use.[13] MORs are the most researched out of the three main receptors, as they have been shown to be responsible for the analgesic, rewarding, tolerance-inducing, and withdrawal effects of morphine, a mu receptor agonist. This was demonstrated by a study involving the deletion of OPRM1, the gene encoding MORs, in mice, which subsequently eliminated these effects.[14]

Current pharmacological treatments for OUD focus on reducing withdrawal symptoms, cravings, and the risk of relapse while promoting long-term recovery. So far, three medications have been approved by the FDA for OUD treatment: methadone, buprenorphine, and naltrexone.[15,16] Methadone is a long-acting full MOR agonist that activates the receptor similarly to illicit drugs, but more gradually. Buprenorphine is a long-acting partial MOR agonist, meaning it binds to receptors like full agonists, but with less efficacy. It also displaces other full agonists from binding to the receptor.[17] These two medications are based on a treatment approach known as opioid substitution therapy (OST).[18] When taken correctly, they can reduce withdrawal symptoms and cravings without pro-

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ducing euphoria. On the other hand, naltrexone is an MOR antagonist, which inhibits the activation of receptors and their effects. It has been used to prolong sobriety, blocking receptors and the euphoric effects of opioids and lowering the chance of relapse.[19,20] However, these current treatments have notable limitations. For example, the high potency and efficacy of methadone increase the risk of overdose, and being a MOR agonist, it may be misused. More importantly, the treatments are accompanied by significant adverse effects, including nausea, vomiting, constipation, and potentially fatal respiratory depression and QT prolongation.[15] These limitations highlight the need for opioid treatments with fewer side effects and greater efficacy in managing OUD.

This review discusses the neurobiological basis in which opioid receptors and their signaling mechanisms contribute to OUD, focusing on their role in reward systems, tolerance, dependence, and other mechanisms underlying addiction. It will explore the benefits and limitations of current treatments of OUD, particularly medication-assisted treatment (MAT). By examining these topics, this review aims to provide a deeper understanding of how advancements in opioid research can address the ongoing opioid crisis.

The Endogenous Opioid System and OUD:

The endogenous opioid system (EOS) is widely distributed throughout the central nervous system (CNS) and peripheral nervous system (PNS), particularly in neural circuits related to pain, reward, emotion, and autonomic control.[21] It comprises three families of receptors (mu, kappa, delta) and opioid peptides acting at these receptors. There are >20 different identified opioid peptides, all of which are processed from three protein precursors: proopiomelanocortin (POMC), prodynorphin (PDYN), and proenkephalin (PENK).[22] All opioid peptides share a common NH2-terminal Tyr-Gly-Gly-Phe signature tetrapeptide sequence known as the "opioid motif",[23] which interacts with the receptors.[24] However, only three main peptides are generally considered to be part of the EOS: β-endorphins, dynorphins, and enkephalins produced through proteolytic cleavage of POMC, PDYN, and PENK, respectively.[24,25] Each peptide binds to all three receptors, albeit while exhibiting different affinities. β-endorphins act primarily on MORs, while dynorphins act on KORs, and enkephalins act on DORs.[26–28]

Opioid Receptor Activation and G-Protein Signaling:

As GPCRs, the three main opioid receptors share a seven-transmembrane (7TM) helical structure in the form of intracellular and extracellular loops.[29] Receptors contain ligand-binding pockets, where ligands—such as endogenous peptides or synthetic drugs—bind to and activate the receptor (see Figure 1). Ligand binding induces conformational changes that enable intracellular coupling of heterotrimeric Gi/o proteins to the receptor's C terminus.[30] The receptor then promotes the exchange of GDP for GTP on the α subunit of the G protein, and the trimeric G protein complex dissociates into Gα and Gβγ. The Gα component inhibits adenylyl cyclase activation, lowering cAMP production, while the Gβγ component interacts with various ion channels.[31,32] Calcium channels are closed, decreasing Ca^{2+} influx, and G protein-coupled inwardly rectifying K+ (GIRK) channels are opened, increasing K+ efflux. These combined actions result in analgesia by causing hyperpolarization and reduced neuronal excitability, as well as diminished nociceptive stimuli and pain perception. Opioid receptor cellular signaling generally occurs through intracellular G proteins and GPCR kinases (GRKs) and β-arrestins.[33] GRKs can phosphorylate an active receptor's C-terminal tail or intracellular loops, promoting β-arrestin recruitment. This leads to receptor desensitization and internalization, which regulates receptor signaling and prevents excessive cellular responses.[1] Repeated opioid use and receptor activation can lead to receptor down-regulation, which, when paired with desensitization and internalization, can contribute to tolerance.

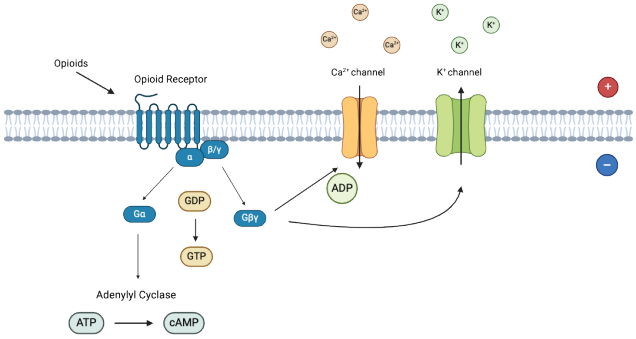

Figure 1: Signal transduction pathway of Gi/o-coupled opioid receptors. The figure illustrates how opioid receptor signaling forms the molecular basis for opioid-induced analgesia and many of their central effects. Upon ligand binding, the receptor undergoes a conformational change that activates the associated Gi/o heterotrimeric G protein. This activation promotes GDP–GTP exchange on the Gα subunit, leading to its dissociation from the Gβγ dimer. The Gα subunit inhibits adenylyl cyclase, reducing cAMP production and downstream intracellular signaling. Simultaneously, the Gβγ subunit modulates ion channel activity by inhibiting voltage-gated calcium (Ca^{2+}) channels and activating G protein-gated inwardly rectifying potassium (GIRK) channels. Created in BioRender. Cui, E. (2025) https://BioRender.com/4d7fnl1

Differential Receptor Function:

Opioid receptors can mediate the effects of endogenous ligands, such as endorphins, as well as exogenous ligands, including morphine and fentanyl.[34] As discussed earlier, these receptors are classified into three main types: the mu-opioid receptor (MOR), kappa-opioid receptor (KOR), and delta-opioid receptor (DOR), each encoded by distinct genes (OPRM1, OPRK1, OPRD1, respectively).[13] While MORs, KORs, and DORs are all implicated in analgesia, studies have shown that they each contribute to further distinct physiological and behavioral effects. In OPRM1 knockout (KO) mice (mice in which the OPRM1 gene has been removed), the effects of morphine on analgesia, reward, withdrawal, dependence development, and respiratory depression were undetected.[14,35] Meanwhile, in OPRK1 KO and OPRD1 KO mice, these effects remained detectable.[36,37] Due to these findings placing the MOR as the responsible receptor for both the therapeutic and the adverse effects of morphine, MORs are the main target for opioid analgesics. On the other hand, DORs have been shown to contribute to mood-related, anxiolytic, and

antidepressant effects,[38] and KORs have been associated with dysphoria, as well as aversive and psychotomimetic effects.[39,40]

Anatomic Distribution of the EOS:

The wide anatomic distribution of the EOS contributes to the analgesic and other physiological effects of opioids on the human body. For example, opioid receptors can be expressed in the lungs, heart, kidneys, pancreas, and small intestine, as well as in neuroendocrine, immune, and ectodermal cells.[41] As a result, they can affect organ function, inflammation, and homeostasis.[42] Opioid receptors are also concentrated in areas of the brain and spinal cord (periaqueductal grey (PAG), locus coeruleus (LC), rostral ventral medulla (RVM), and the spinal dorsal horn (SDH)) that help process and manage pain.[34] In the midbrain, when an opioid binds to the MOR, it triggers signals that inhibit certain neurons, leading to a reduction in pain transmission from the body to the brain. This effect is part of the pain relief system that works through the PAG, which communicates with the SDH, controlling pain signals as they reach the thalamus. In addition, opioid receptors in the dorsal root ganglion (DRG) can help modulate the initial pain signals and suppress DRG activity to reduce pain perception.

Neuroadaptations and OUD:

The EOS is crucial in regulating behaviors related to important survival mechanisms like reward and pain aversion. Thus, when the system's function is compromised, these behaviors are as well. For example, one of the main consequences of such impairment is the risk of developing OUD. Continuous drug use can lead to neuroadaptations, which are changes in the brain's structure and function. This includes the process in which the main initial cellular responses of the brain to a drug adapt to diminish the drug's effects.[43] This means the brain requires more frequent or higher doses of the drug to achieve the same effects, leading to tolerance. Neuroadaptations also include individuals becoming used to the presence of the drug, meaning that in its absence, users will experience withdrawal symptoms like pain, anxiety, and cravings, which encourage continued use.[44] Long-term use can also lead to neuroadaptations in areas of the brain involved in motivation, reward processing, habit formation, and motor control, such as the ventral tegmental area (VTA) and the striatum. An example of a brain alteration caused by a drug of abuse is the expression of stable forms of the ΔFosB protein. In a study done with mice, repeated substance exposure resulted in accumulating levels of ΔFosB in the nucleus accumbens, leading to increased sensitivity to the rewarding effects of the drug. This study suggests that ΔFosB may play a role in developing and maintaining addiction.[45] To conclude, the dysfunction of the EOS in conditions like OUD is linked to its role in modulating the reward-and pain-related effects of substances. These adaptations, occurring in key reward and motivation centers, are critical in the transition from controlled use to addiction and eventually full-blown OUD.

■ Current Pharmacological Treatments for Opioid Use Disorder:

OUD is defined as chronic opioid use despite significant harm or distress and is characterized by neuroadaptation and changes in neuronal circuits.[11] It involves dependence, in which the body adapts to the presence of opioids, which can manifest through withdrawal symptoms (e.g., cravings, sweating, anxiety), prompting one to continue taking opioids. It also involves tolerance, requiring higher or more frequent doses to maintain effects, whether analgesic or euphoric.[46] Treatments of OUD include rehabilitation, cognitive behavioral therapy, and medication-assisted treatment (MAT), which have proved to be particularly effective.[47] Currently, three medications have been approved by the FDA for OUD treatment: methadone, buprenorphine, and naltrexone.[15,16] The first two medications are based on OST and work by replacing the problematic opioid with a safer one.

Table 1: Overview of FDA-approved medications to treat opioid use disorder. The table includes the mechanism of action, effectiveness, benefits, adverse effects, and clinical considerations of methadone, buprenorphine, and naltrexone. While each drug has distinct clinical profiles, methadone and buprenorphine are more strongly associated with reduced mortality and higher treatment retention, whereas naltrexone may be useful for abstinence prolongation but is limited by poor adherence and initiation challenges.[48–57]

Medication	Mechanism of Action	Effectiveness	Benefits	Adverse Effects	Clinical Considerations
Methadone	Full mu-opioid agonist	Associated with decreases in all-cause mortality Higher treatment retention rates than low-dose buprenorphine, comparable to high-dose buprenorphine Effective at reducing opioid-associated transmission of infectious disease,and crime Long-term results (6+ months) more favorable for individuals receiving methadone	Long-acting Reduces withdrawal symptoms and cravings Does not produce euphoria	QTc interval prolongation Risk of respiratory depression Risk of sedation Nausea Constipation Diaphoresis	Patients should be seen daily prior to and during initiation Initial dose: 20-30 mg orally for first dose. In patients with low opioid tolerance, start with 10-15 mg. May give additional 5-10 mg if after 2-4 hours symptoms have not been suppressed or reappear Daily dose: Increase the dose by 10 mg every 5 days as needed, no more than 20 mg a week, to address cravings or withdrawal symptoms More effective at higher daily dosages (80 to 120 mg) than at moderate dosages (40 to 50 mg) Can be administered daily for most patients
Buprenorphine	Partial mu-opioid agonist	All-cause mortality reduced by %50 Must be given at a sufficiently high dose (roughly>16 mg/day) to be effective Patients on doses of buprenorphine of >16 mg/day 1.82 times more likely to stay in treatment than placebo-treated patients	Displays ceiling effect for respiratory depression, euphoria, sedation, and intoxication Reduces cravings Mitigates withdrawal symptoms	May precipitate withdrawal Low risk of respiratory depression Nausea Headache Insomnia Vomiting Constipation	Patients must be in mild to moderate withdrawal before initiating treatment Initial dose: 4-8 mg, depending on patient requirement Daily dose: 4-24 mg, should not exceed 32 mg Overtime, dose should be titrated up to eliminate withdrawal symptoms and reduce cravings Higher doses associated with improved treatment retention and reduced illicit opioid use May initially need to be seen 1-2 times a week, and monthly further on
Naltrexone	Antagonist	Has not been associated with decreased mortality Limited by poor treatment adherence Monthly injections improve adherence; clinical trial showed 90% abstinent weeks vs. 35% with placebo, higher retention (58% vs. 42%) Treatment initiation harder due to required detoxification Extended release naltrexone formulation similar in effectiveness at treating OUD to buprenorphine/naloxone combination	Blocks effect of opioid agonists Does not produce tolerance or withdrawal Not addictive Not at risk of abuse or diversion Suppresses cravings	Headache Lowered tolerance (therefore, increased risk of overdose) Injection site reactions Insomnia Increased alanine transaminase Increased creatine phosphokinase	Patient must be completely detoxicated for 7-14 days before taking naltrexone Initial dose: 25 mg Daily dose: 50 mg Intramuscular naltrexone is administered in doses of 380 mg every four weeks

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Methadone:

Methadone works as a full MOR agonist and manages withdrawal symptoms (e.g., tachycardia, sweating, nausea, vomiting, and diarrhea), reduces cravings, and dulls the effects of other opioids.[58,59] At a maintenance dose, it does not produce euphoria. Compared to morphine, methadone produces enhanced analgesia with reduced tolerance.[60] This may be due to its inhibition of serotonin and norepinephrine uptake, as well as its role as an antagonist at the N-methyl-D-aspartate (NMDA) receptor, which is involved in pain modulation and transmission.[61] Methadone also has a longer duration of action and half-life, making it a good substitute for pain treatment and for OUD, as fewer doses are required to maintain analgesia and prevent withdrawal symptoms.[62] The effects of methadone will typically last 24-36 hours, while short-acting opioids taken to manage withdrawal will often need to be taken three to four times a day.[55]

Buprenorphine:

Buprenorphine is a partial MOR agonist, meaning the maximal effect buprenorphine can produce will always be lower than that of a full MOR agonist and is thereby less potent. When taken at the proper dosage, buprenorphine can mitigate withdrawal symptoms and reduce cravings without causing euphoria.[63] Buprenorphine has a high affinity for the MOR but lower intrinsic activity compared to full MOR agonists such as morphine, heroin, oxycodone, and methadone. This means that buprenorphine preferentially binds to and displaces other full agonists with lower affinity from the receptor.[17,64] Additionally, buprenorphine has a very low receptor dissociation rate, as well as a long duration of action and half-life.[18] Buprenorphine also appears to display a "ceiling effect" for respiratory depression, euphoria, sedation, and intoxication. This can be beneficial as these effects will plateau, leading to lower risks and less severe effects of overdose compared to full agonists.[19,65]

Naltrexone:

Naltrexone is an antagonist preferentially of the MOR and, to a lesser extent, of the KOR and DOR.[66] Naltrexone will block the euphoric and sedative effects of opioids. As an antagonist, naltrexone is not addictive and has no abuse or diversion potential. Naltrexone is also reported to reduce and suppress cravings and may also reduce tolerance. However, this lowered tolerance could be dangerous in the case of relapse, as taking previous levels of doses could lead to overdose and serious effects like respiratory arrest and circulatory collapse.[67] To reduce the risk of withdrawal caused by OUD, patients must be opioid-free for at least 7-14 days before starting naltrexone.[68] Individuals taking naltrexone should also refrain from using any other opioids or drugs, consuming alcohol, or taking sedatives or tranquilizers. In this way, naltrexone is primarily used to prolong abstinence and maintain recovery.

Naloxone:

Naloxone is a fast-acting antagonist used to rapidly and temporarily reverse overdose rather than directly treat OUD. Naloxone is generally considered to be safe, as there is no risk for misuse or development of dependence. Naloxone has a high affinity for MORs and, acting as an inverse agonist, removes other opioids bound to the receptor.[69] Naloxone is also available commercially in combination with buprenorphine as Suboxone, which is used for maintenance treatment of OUD, dependence, and addiction.[70]

Overall, these medications have proven to be effective in treating OUD and its symptoms, allowing patients to maintain recovery and supporting social reintegration (see Table 1). Substantial evidence has shown that MAT reduces opioid use and OUD-related symptoms, as well as the risk of infectious disease transmission and drug-associated criminal behavior.[20] OST has been associated with considerably lowered all-cause mortality rates[58] and has even been shown to preserve immune and cognitive functions.[71,72] However, they still come with significant limitations (see Table 1). Many patients are still likely to relapse or quit, particularly with naltrexone, as no euphoric or addictive effects are produced. The use of other drugs while taking naltrexone can be incredibly dangerous and carries an increased risk of fatal overdose.[73] Methadone and buprenorphine, as MOR agonists, still have risks of misuse or diversion.[74] Methadone, as a full agonist with high potency and efficacy, has a substantial risk of overdose and pronounced adverse effects, including nausea, vomiting, respiratory depression, pruritus, sedation, hypotension, hypogonadism, constipation, diaphoresis, and QTc interval prolongation.[15,59] Buprenorphine may precipitate withdrawal if taken too soon after a full agonist (e.g., fentanyl, heroin, prescription opioids) by an individual dependent on opioids.[75] This is due to the displacement of other lower-affinity opioids by buprenorphine. Adverse effects of buprenorphine are similar and include nausea, vomiting, memory loss, dizziness, hypotension, CNS depression, constipation, miosis, QTc interval prolongation, respiratory depression, and insomnia.[17,58] Naltrexone can also cause side effects, including nausea, vomiting, anxiety, constipation, insomnia, loss of appetite, dizziness, injection site reactions, increased alanine transaminase (may indicate liver damage or disease), and increased creatine phosphokinase (may indicate muscle, heart, or brain damage).[76,77]

■ Conclusion

Opioid use disorder is closely connected to the interactions of the EOS, particularly through mu, kappa, and delta opioid receptors and their signaling pathways. This review has explored how the EOS and receptors contribute to OUD, particularly through neuroadaptations and their roles in the brain's reward system. This review has also evaluated current treatments—methadone, buprenorphine, and naltrexone—which, while beneficial, have notable limitations. Addressing the opioid crisis requires advancement in two main directions: finding improved analgesics with high efficacy but minimal addictive potential and side effects, and developing new and better treatments for OUD and those facing effects such as dependency, addiction, and withdrawal. In recent years, new promising approaches to treating OUD have emerged, such as neuromodulation and psychedelics. Neuromodulation treatments such as transcranial magnetic stimulation (TMS)

and deep brain stimulation (DBS) target and modulate neural circuits and synaptic plasticity.[78] A systematic review and meta-analysis of neuromodulation therapies for substance use disorders found that TMS produced medium to large effect sizes in reducing substance use and cravings, particularly when multiple stimulation sessions were applied.[79] Additionally, psychedelic medicine, such as psilocybin and LSD, has reemerged as a topic of discussion and possible therapy. They are generally considered to have low potential for dependence and addiction, and several studies have produced results suggesting psychedelic use to be associated with reduced odds of problematic substance use or OUD.[80–83] Other approaches include targeting components of the dopamine-dependent reward circuitry, identifying genetic factors that increase vulnerability to OUD, and modulating gene products accordingly. Vaccines are also being explored as a form of immunotherapy by reducing or slowing drug entry into the brain, thereby reducing effects associated with overdose.[84–87] While further research and trials are necessary to ensure the safety and effectiveness of these treatments, they show promise toward offering new methods to manage opioid use disorder and the larger opioid crisis.

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