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CURRENT AND EMERGING PHARMACOTHERAPIES IN OPIOID USE DISORDER: A NARRATIVE REVIEW

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ABSTRACT

Background

Opioid use disorder (OUD) represents a major global health crisis, characterized by high relapse rates, overdose risk, mortality, and socioeconomic burden. While naloxone has been the cornerstone of opioid overdose reversal, limitations such as its short half-life, need for repeated dosing, inability to alleviate withdrawal symptoms, and lack of efficacy in long-term relapse prevention highlight the need for adjunctive or alternative pharmacotherapies. Ongoing research into novel pharmacological strategies offers opportunities to improve long-term outcomes in OUD management.

Methods

A narrative review was conducted using recent literature from PubMed, Embase, and the Cochrane Library. The review included clinical trials, systematic reviews, and guideline documents focusing on current pharmacotherapies for OUD (methadone, buprenorphine, naloxone) and emerging agents such as nalmefene, methocinnamox, compound 368, mitragynine, and non-opioid adjuncts like clonidine and lofexidine.

Results and Conclusion

Methadone and buprenorphine remain first-line therapies, with intranasal nalmefene formulations offering new avenues for rapid overdose reversal. However, limited access, stigma, and underutilization remain major barriers. Expanding availability of proven therapies, particularly methadone with its strong evidence base, alongside further large scale, clinical research into implementation in primary care and correctional settings, represents a critical step in addressing the opioid epidemic. Given the genetic, immunological, and microbiome influences in OUD, a one-size-fits-all approach is insufficient. Future management must integrate precision medicine, novel pharmacological strategies, and community support to achieve sustainable recovery.

Keywords: *Opioid use disorder; Naloxone; Opiate overdose; Opioid related disorders; Methadone; Buprenorphine; Naltrexone; Nalmefene; Compound 368; Withdrawal symptoms; Methocinnamox; Clonidine; Lofexidine.*

1. INTRODUCTION

Drugs that activate the opioid receptors are considered opioids [Carley et al., 2021]. Opioid use disorder (OUD) can be defined as chronic and often relapsing use of opioids, marked by clinically apparent symptoms that range from dependence to addiction [Dydyk et al., 2025, Bell et al., 2020].Some global estimates place its prevalence at 40.5 million people, with an estimated 125,000 yearly deaths due to overdose, with an annual trend of increase in this number every year [Degenhardt et al., 2019, World Health Organization, 2023]. Thus, it contributes significantly to mortality and therefore, is an economic burden among individuals and communities worldwide [Carley et al., 2021, Barkus et al., 2024]. Managing OUD involves various therapeutic modalities, including screening, engagement, proper assessment, diagnosis, consideration of level of care, acute management of overdose or withdrawal, medication treatment, psychotherapeutic approaches, and community support [Brady et al., 2021].

Medication-assisted treatment is considered the most effective approach for treating OUD [Hart et al., 2024]. The chronic, relapsing, and remitting nature of OUD has led to the implementation of long-term treatments and medications like methadone, buprenorphine, and naloxone [Wolfgang et al., 2023]. Hence, initiation of Medication treatment following diagnosis and acute management is the standard chronological pipeline followed [Brady et al., 2021].

Opioids have held a critical role in clinical medicine, predominantly recognized for being the oldest and most potent analgesics used in pain management [Stein et al., 2016]. Simultaneously, their potential for abuse and addiction has triggered a global public health emergency. To overcome these adverse consequences, opiod reversal drugs and techniques must be studied in detail. Bridging the gap between the clinical pharmacology of opiods and their antagonists is essential for developing effective, long-term interventions.

2. PATHOPHYSIOLOGY OF OPIOID USE DISORDER

G-protein-coupled receptors (GPCR), such as μ, δ, and κ opioid receptors, are the sites of binding for the majority of the opioid drugs. **Figure 1** illustrates how μ-opioid receptors (MORs) block adenylyl cyclase, limit Ca2+ channel activity, and/or activate inwardly rectifying K+ (GIRK) channels through Gi/o-dependent signalling pathways [Montandon et al., 2022], all of which decrease neuronal activity. The Oprm1 gene encodes the MOR, which is widely expressed in the respiratory network centres that regulate breathing as well as in the central and peripheral neural systems of mammals [Baldo et al., 2024]. The pathophysiology of opioids in hyperalgesia is yet unknown, although it seems to be associated with an imbalance between the pronociceptive and antinociceptive systems in the body [Mitra et al., 2008]. Similar links between dopamine dysregulation and schizophrenia have been found in neuropsychiatric literature. Many of the central side effects have been linked to the mesolimbic dopaminergic system in particular [Spanagel et al., 1992]. Buprenorphine has a significant affinity for opioid receptors. It functions as a partial agonist of the MOR and opioid receptor-like 1 (ORL-1) and as an antagonist of the δ- and κ-opioid receptors [Tabanelli et al., 2023]. Toll-like receptor 4 (TLR4), a crucial component in the pathogenesis of neonatal opioid withdrawal syndrome, is similarly not widely expressed in the midbrain neural progenitors that resulted from a prolonged iPSC neural induction [Sullivan et al., 2025].

Opioid abuse can lead to the potentially fatal disease known as opioid withdrawal syndrome [Shah et al., 2023]. Detoxification alone has a poor success rate for treating OUD, a chronic illness that is curable but recurring [Kosten et al., 2019]. Withdrawal before starting opioids could be severe or interfere with treatment. The locus coeruleus, located at the base of the brain, is the main location where opioid withdrawal symptoms begin. Noradrenergic neurones with more opioid receptors are found in the locus coeruleus. The limbic system, as well as the cerebral and cerebellar cortices, are primarily innervated by norepinephrine (NE) from the locus coeruleus region. One of the main causes of opioid withdrawal symptoms is the NE activity in locus coeruleus neurones, which is a process connected to opioid receptors [Shah et al., 2023]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth

Edition (DSM-5), different degrees of problematic opioid abuse indicate the severity of OUD [Kosten et al., 2019]. When patients are being introduced to the MOUDs buprenorphine and naltrexone in therapeutic settings after recent exposure to opioid agonists, it is critical to distinguish between spontaneous and triggered withdrawal [Dunn et al., 2023]. Methadone or buprenorphine are used to replace opioids over the long term [Shah et al., 2023]. OUD may be avoided by identifying physical opioid dependence very early on, before psychological dependence develops [Kosten et al., 2019].

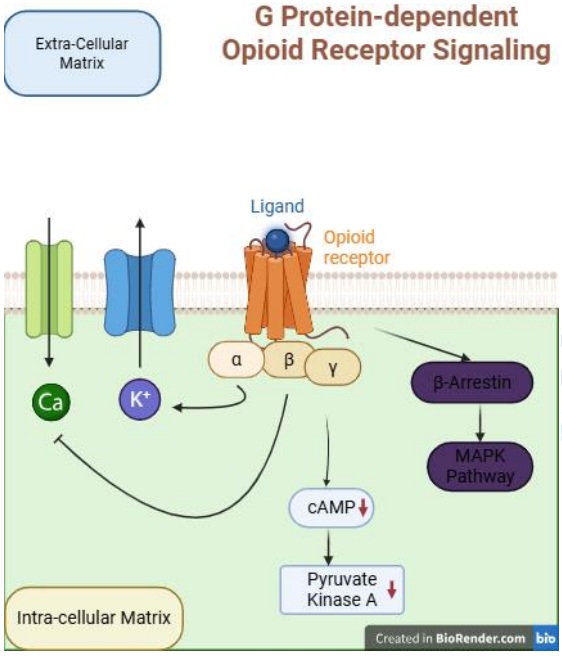

Figure 2: Agents used in the treatment of opioid OUD and withdrawal (MOA).

Legend: Binding of Opioid Agonist on opioid receptor, leads to activation of alpha, beta and gamma unit. Which leads to decrease in influx of Calcium, increase in efflux of Potassium, and decrease in cAMP levels. All of this cumulatively contributes to decrease in neuroexcitability, thus contributing to analgesia a favourable effect of opioid. Secondly β-Arrestin is also stimulated, which elicits the unfavourable effects of opioids, including tolerance, and respiratory depression.

3. AN OVERVIEW OF OPIOID RECEPTORS

Opioid receptors belong to the GPCR family and have extensive distribution along the central and peripheral nervous system, with normal physiological functions extending from pain modulation, mood and reward regulation, and toning down of central nervous stress. These receptors are categorized into four main types: mu (μ), kappa (κ), delta (δ), andORL-1, also known as nociception/orphanin FQ peptide receptor, zeta receptors which have been further discussed in detail in **Table 1** at the bottom.

4. PHARMACEUTICAL AGENTS FOR OPIOID USE DISORDER

4.1 Naloxone

Mechanism of Action

Naloxone is a semisynthetic, lipophilic, competitive, and non-selective opioid receptor antagonist with binding capacity to μ-, κ-, and δ-opioid receptors. However, its clinical efficacy is most pronounced at MORs, due to its greater affinity coupled with inverse agonism, which competitively displaces opioids and thereby rapidly reverses the ventilatory and CNS effects of opioids [Adapt Pharma Operations Limited, 2019, National Library of Medicine, 2021b, Kim et al., 2015]. Its action spans both central and peripheral effects, as well as both endogenous and exogenous opioids [, National Library of Medicine, 2021b]. Unlike earlier opioid antagonists like nalorphine and levallorphan, naloxone lacks intrinsic agonist activity at mu-opioid receptors, making it safer for reversing overdoses without inducing respiratory depression [Foldes et al., 1969, Thomas et al., 1955].

Efficacy and Benefits

Naloxone administration has shown a return of spontaneous circulation following cardiac arrest when administered before the establishment of intravenous or intra-osseous access. This property has yielded contrasting results in different studies; however, sufficient clinical evidence suggests that conducting further placebo-based, randomized controlled trials could be helpful to shed light on this area [Quinn et al., 2024]. Naloxone improves heart rate, cardiac output, and blood pressure [Wampler et al., 2024]. On a molecular level, naloxone has been shown to inhibit sodium and potassium channels, leading to anti-arrhythmic activity [Wampler et al., 2024]. Community-based administration has proven benefits in the

prevention of opioid-related deaths, even when handled by non-doctor professionals [Fischer et al., 2025]. Prompting the need for further study in this area, this can eventually help in tackling the opioid crisis at a community level. A step that could significantly reduce the healthcare and economic burden of the ongoing opioid crisis.

Naloxone has been the standard treatment for opioid overdose due to its pharmacokinetic properties, which allow for a speedy onset of action and exhibit significant variability across all routes of administration [Saari et al., 2024]. Bioavailability on oral intake is less than one percent. Considering most overdose patients have difficulty swallowing, this is not a route worth taking with naloxone. Intravenous (IV) administration achieves a peak plasma concentration within 2 minutes (median T_{max}), followed by a rapid decline in 10 minutes [McDonald et al., 2018]. The majority of the current usage of the intravenous route is in a hospital setting (dosage 0.04-0.08 mg), for post-operative reversal of respiratory depression [Saari et al., 2024].

Clinical studies confirm naloxone's efficacy, with 72–77% of patients responding within 10 minutes of IN or IM administration in pre-hospital settings [Kerr et al., 2009]. Intranasal administration results in approximately 50% bioavailability, has a slower onset of action, and adequate bioavailability after 5-20 minutes [Saari et al., 2024, Dietze et al., 2019]. While the intramuscular (IM) route takes 15–30 minutes, to achieve maximum effect, with the most preferred dosage of 0.4 to 0.8 mg [McDonald et al., 2018]. It has a slower, but more extended period of action against opioids compared to the intranasal route at the same dosage. The IN route is ideal when working with populations at higher risk for blood-borne infections and is the preferred non-invasive method if laypersons are administering the drug [Kerr et al., 2009]. However, naloxone's short half-life (30-90 minutes) can be shorter than the long half-life of many potent synthetic opioids like methadone or fentanyl, where rapid onset of respiratory depression requires prompt intervention [Somerville et al., 2017, Chaturbedi et al., 2025]. This necessitates repeated dosing or continuous infusion to prevent the recurrence of overdose symptoms [Somerville et al., 2017]. Further studies comparing the efficacy of larger doses of intranasal naloxone to intramuscular naloxone can help enhance naloxone's current usage profile.

Compound 368 increases the efficacy of naloxone against morphine and fentanyl. The compound binds to an orthosteric site near the site of naloxone binding, interacting indirectly and increasing the duration of action of naloxone [Foley, 2024]. However, the poor blood-brain barrier penetration by compound 368 could bar its effectiveness against fentanyl-induced respiratory depression, presenting a knowledge gap, for further elucidation of its actual effectiveness in a real-world patient setting [Ramos-Gonzalez et al., 2025]. The drug's rapid action, safety profile, and lack of agonist effects solidify its role as the gold standard for opioid overdose reversal despite ongoing debates about optimal dosing for synthetic opioids like fentanyl [Britch et al, 2022, France et al, 2021].

4.2 Buprenorphine

Mechanism of Action

Buprenorphine constitutes an interesting profile with a wide range of actions, initially developed as a synthetic alternative agonist/antagonist to oxycodone and morphine. Its unique drug properties have been a matter of debate over time [Davis, 2025]. Its partial agonistic activity at MORs and antagonist at the δ-opioid reduces analgesia tolerance, and κ-opioid receptors reduce craving associated with addiction [Davis, 2025]. It binds to ORL-1 as well, however it's unclear what this receptor means therapeutically. Since buprenorphine only partially activates the MOR and remains in the central nervous system for an extended duration of time, it differs from full agonists like heroin, codeine, and oxycodone. Furthermore, buprenorphine is a viable opioid option for cancer patients because of this characteristic [Ng et al., 2025].

In the context of opioid reversal, buprenorphine's mechanism of action is complex. Buprenorphine's partial MOR agonism enables it to displace full opioid agonists (e.g., heroin, methadone) from receptors as depicted in **Figure 2**, producing weaker activation thereby partially reversing respiratory depression and sedation [Zamani et al., 2020]. In a clinical trial, buprenorphine

demonstrated efficacy in reversing methadone-induced respiratory depression with fewer withdrawal symptoms compared to high-dose naloxone. However, its utility is limited in severe overdoses or highly opioid-tolerant individuals [Zamani et al., 2020, Mégarbane et al., 2020].

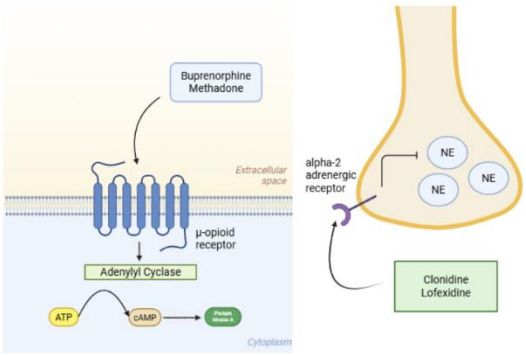

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Figure 2: Agents used in the treatment of opioid OUD and withdrawal (MOA).

Legend: Long term opioid dependence and further increases in withdrawal cause the downstream of cAMP, to shift from acute opioid binding to the μ-opioid binding, which in turn results in excess NE discharge from the noradrenergic neurons in the locus coeruleus. Ultimately, treatment for withdrawal leads to either inhibiting excessive NE discharge from locus coeruleus neurons by presynaptic alpha-2 receptor agonism or attenuating the cAMP pathway through μ-opioid receptor agonism.

Efficacy and Benefits

Buprenorphine has poor oral bioavailability due to high first-pass metabolism, which is why it is administered trans-dermally, which improves its bioavailability [Infantino et al., 2021] Additionally, buprenorphine's unique pharmacological profile allows it to provide pain relief while reducing the risk of respiratory depression, making it a valuable alternative in certain clinical situations [White et al., 2017]. Overall, adding buprenorphine to pain management plans could help with both safety and effectiveness issues, especially during the current opioid crisis.

Clinical studies show buprenorphine has a favorable safety profile compared to full μ-opioid receptor agonists. Moreover, buprenorphine's partial agonist properties may lower the risk of overdose and dependence, making it a safer option for patients needing long-term pain management. Although challenges remain in its adoption, the high amount of evidence supports buprenorphine as a superior choice for chronic pain treatment, leading to better outcomes for patients [Davis, 2025, White et al., 2017]. Although naloxone remains the gold standard for rapid overdose reversal, several case reports and clinical studies show buprenorphine's potential when in the absence of naloxone for long-acting opioids [Zamani et al., 2020, Zamani et al., 2017]. In emergency department settings, buprenorphine reversed multi-substance overdoses, though apnoea often required subsequent naloxone administration [Zamani et al., 2017]. Studies also show that buprenorphine decreases opioid-positive tests by 14.2% and doubles treatment retention compared to placebo. Effective treatment generally requires doses of 16 mg/day or higher [MacDonald et al., 2016]. While buprenorphine may not match naloxone's antagonism, its partial agonist activity and longer receptor attachment provides an independent mechanism for reducing opioid toxicity.

4.3 Nalmefene

Mechanism of Action

Nalmefene is a synthetic opioid antagonist used as a riveting treatment for OUD due to its distinctive receptor-binding profile and long-lasting effects [Peppin et al., 2021]. Nalmefene is a competitive MOR antagonist responsible for mediating opioid-induced analgesia, euphoria, and respiratory depression [Glass et al., 1994]. Nalmefene acts as an antagonist at μ, and δ-opioid receptors and is a partial agonist at κ receptors [Zamani et al., 2020]. It has a higher binding affinity for MORs than naloxone, indicating a potentially stronger antagonistic effect [Zamani et al., 2017]. Nalmefene's ability to block these receptors effectively prevents the euphoric and analgesic effects of opioids, thereby decreasing the reinforcing properties that contribute to addiction [Kennedy et al., 2018]. Nalmefene's long-lasting effect comes from its slower rate of dissociation from opioid receptors, which means it blocks those receptors for a much longer time. When given intramuscularly, the drug is almost completely absorbed, making it easy to use in emergency

rooms or even as a take-home option [Zamani et al., 2017]. In the liver, nalmefene is mainly broken down by glucuronidation, and its half-life of 8 to 11 hours is notably better than naloxone's 30 to 90 minutes [Prekupec et al., 2017]. Intranasal (IN) formulations, such as OPNT003, enhanced with dodecyl maltoside, improve bioavailability and reduce time to peak plasma concentration (T_{max}) to 15 minutes, addressing earlier limitations of slow absorption [Krieter et al., 2019]. This prolonged duration is especially beneficial in cases involving long-acting opioids like methadone or extended-release formulations, reducing the need for repeated doses. Additionally, nalmefene has been shown to inhibit the subjective and respiratory effects of fentanyl for up to 8–48 hours, depending on the route of administration [Glass et al., 1994, Krieter et al., 2019].

Efficacy and Benefits

In some clinical situations, nalmefene's pharmacokinetic profile is superior to that of naloxone. Although both drugs effectively reverse acute overdoses, nalmefene's slower clearance (2.5 times less than naloxone), higher oral bioavailability, and lack of dose-dependent liver toxicity make it advantageous for treating synthetic opioid overdoses with extended durations [Glass et al., 1994, Konieczko et al., 1988, Windisch et al., 2021]. Its features, along with partial agonist activity at the κ receptor, suggest it may benefit cocaine use disorder [Windisch et al., 2021]. This partial agonist also blocks cocaine's rewarding effects without causing additional adverse effects like full agonists. Additionally, it might be useful for dystrophin-mediated stress disorders [Windisch et al., 2021]. With a median T-max of two hours, intranasal (IN) nalmefene alone has low bioavailability, limiting emergency use. However, new formulations with absorption enhancers such as dodecyl maltoside lower T-max to 15 minutes and raise plasma concentrations 12-fold, making its pharmacokinetic profile (IN 3 mg) comparable to IM nalmefene (1.5 mg) and acting as a viable rescue option [Krieter et al., 2019]. Although it was removed from the market in 2008 due to non-safety concerns like nausea, meta-analyses support its safety for emergency use, showing no increased risk of serious adverse events. The risk of withdrawal due to adverse effects remains higher than with placebo [Johansen et al., 2017]. Approved as an injectable (Revex®) and under development for intranasal delivery, nalmefene remains a promising alternative to naloxone, particularly in scenarios requiring prolonged receptor blockade [Abram et al., 2017, Purdue Pharma, 2019].

4.4 Methocinnamox (MCAM)

Mechanism of Action

Methocinnamox (MCAM), chemically knownas14β-(4′-methylcinnamoylamido)-7,8-dihydro-N-cyclopropylmethyl-normorphinone) is a pseudo-irreversible MOR antagonist, meaning it binds non-covalently but remains functionally bound for prolonged periods, rendering the receptors ineffective for a period of two weeks [Jordan et al., 2022]. MCAM also exhibits reversible competitive antagonism at δ and κ opioid receptors at higher concentrations. In HEK (human embryonic kidney) cells expressing human MOR, MCAM demonstrated time-dependent, non-surmountable, and non-reversible antagonism of μ-agonist inhibition of cAMP production, confirming pseudo-irreversible binding. Unlike its reversible competitive antagonism at δ and κ opioid receptors, MCAM's interaction with MORs involves not only pseudo-irreversible orthosteric binding but also allosteric modulation, evidenced by its ability to shift DAMGO concentration-response curves in a naloxone-insensitive manner. This dual mechanism alters both the affinity and intrinsic efficacy of opioid agonists, making MCAM a non-surmountable antagonist and a promising alternative to naloxone in opioid overdose management, [Zamora et al., 2021, Gerak et al., 2019] as shown in **Table 2** at the bottom.

Efficacy and Benefits

Animal studies reveal that MCAM demonstrates robust and sustained efficacy in reversing and preventing opioid-induced effects, with pseudo-irreversible, insurmountable antagonism at the MOR, unlike naloxone and naltrexone which bind competitively. Repeated administration of MCAM 0.32 mg/kg every 12 days in animal models-maintained effectiveness for over two months without adverse reactions or tolerance development, indicating its potential for long-

term OUD management [Maguire et al., 2020]. In rhesus macaques, MCAM attenuated heroin-induced respiratory depression for at least four days, effects far exceeding the duration of naloxone or naltrexone. Importantly, MCAM blocks morphine's behavioral effects and physiological effects of opioids, such as respiratory depression, analgesia, gastrointestinal motility, and mechanical sensitivity for at least 7 days without impairing memory or natural reward processing, suggesting a favorable safety profile [Minervini et al., 2020, Gerak et al., 2020], referring to **Table 3** at the bottom. Its prolonged duration of action (up to two weeks) could improve compliance in outpatient treatment compared to daily or implantable options like naltrexone, and its effectiveness remains intact whether delivered subcutaneously (longer effect) or intravenously (shorter effect), offering flexibility in clinical use [Jimenez et al., 2021]. These characteristics make MCAM a promising alternative or adjunct to current therapies, particularly in high-risk patients requiring both immediate reversal and sustained protection from opioid effects, including relapse and overdose. While human trials are still pending, major funding is underway to advance MCAM toward clinical testing.

4.5 Methadone

Mechanism of Action

Methadone is a synthetic opioid that functions primarily as a full agonist at the MOR producing sustained G-protein mediated inhibition of adenylate cyclase, enhanced K^+ conductance and reduced neuronal excitability; thereby suppressing pain transmission and opioid withdrawal symptoms [Durrani et al., 2025]. Methadone also exhibits NMDA-receptor antagonism (primarily attributed to the S-enantiomer), which may reduce development of opioid tolerance, and opioid-induced hyperalgesia [Sunilkumar et al., 2018]. In addition to NMDA receptor antagonism, methadone interacts with other targets, including modulation of monoamine reuptake, which may enhance its effectiveness in OUD by contributing to mood stabilization and reduction of withdrawal-related dysphoria [80]. Methadone is metabolized mainly via CYP450 enzymes (notably CYP3A4, with contributions from CYP2B6 and CYP2D6) and has a long and variable half-life (reported roughly 8–60 hours), a pharmacokinetic profile that underpins once-daily maintenance dosing but also requires careful titration because of accumulation and drug–drug interactions [Sunilkumar et al., 2018].

Efficacy and Benefits

Robust evidence and international guidance support methadone maintenance, an opioid agonist maintenance therapy (OAMT) as an effective treatment for OUD: methadone treatment is associated with large reductions in illicit opioid use, improved retention in care, and substantial decreases in opioid-related mortality compared with no pharmacotherapy [Klimas et al., 2021]. Cohort and guideline-level data show that people started on methadone after a nonfatal overdose have markedly lower subsequent opioid-related mortality, and meta-analyses/systematic reviews report improved treatment retention and lower all-cause and overdose mortality during opioid agonist treatment [Ma et al., 2019, Russolillo et al., 2018]. Methadone is typically initiated at 15–30 mg once daily, with dose adjustments made every 3–5 days based on symptom control and tolerability. After the initial stabilization maintenance therapy generally requires 80–100 mg per day to achieve optimal effectiveness [Toce et al., 2018]. Rapid dose escalation during the early phase of treatment, particularly at doses exceeding 100 mg/day, can increase the risk of QT interval prolongation on electrocardiography, which may predispose patients to cardiac arrhythmia [Schuckit et al., 2016]. As a cornerstone of medication-assisted treatment, methadone is FDA-approved for both detoxification and the management of OUD. It has been shown to improve retention in treatment and detoxification programs, which in turn is associated with reductions in mortality among individuals with OUD [Durrani et al., 2025].

4.6 Compound 368

Mechanism of Action

MORis a primary target for analgesia. Negative allosteric modulators (NAMs) of MOR, such as compound 368, bind to an extracellular vestibule [O'Brein et al., 2024] distinct from the

orthosteric ligand-binding site where traditional opioids bind [Che et al., 2024]. All MOR agonists and antagonists share key interactions at this orthosteric site. Cryogenic electron microscopy (cryo-EM) reveals that 368 stabilises an inactive receptor conformation by altering the orientation of the second (TM2) and seventh (TM7) transmembrane helices, which hinders agonist-induced G protein signalling when forming direct contacts with naloxone [89, 90]. The compound's selectivity for MOR, over δ and κ opioid receptor further underscores its targeted mechanism [Thompson et al., 2015, Wang et al., 2023].

Efficacy and Benefits

Unlike naloxone, which directly displaces opioids from the orthosteric site, 368 acts cooperatively with naloxone by increasing its binding affinity. This synergy enhances naloxone's ability to reverse opioid-induced signalling cascades, including inhibition of adenylyl cyclase activity, decreased G-protein activation, and attenuation of β-arrestin recruitment, which collectively mitigate opioid-induced respiratory depression while preserving some analgesic effects. In vivo studies confirm that 368 markedly potentiates naloxone's efficacy [O'Brein et al., 2024]. When combined with low-dose naloxone (0.1 mg/kg), 368 potentiates naloxone's efficacy by 7.6-fold in vivo, effectively reversing morphine and fentanyl-induced behaviors in mice while minimizing withdrawal symptoms. This synergy allows for reduced naloxone dosing, addressing limitations in reversing overdoses of long-acting opioids and mitigating the risk of withdrawal [Abdelal et al., 2022].

4.7 Mitragynine (Kratom)

Mechanism of Action

Kratom (Mitragyna speciosa) is a tropical plant native to Southeast Asia and has recently gathered considerable popularity in Western cultures as an opioid-like herbal supplement, for pain management and opioid withdrawal symptoms. Mitragynine, the principal active alkaloid in kratom, is responsible for its primary pharmacological effects and comprises up to 66% of the plant's total alkaloid content [Harun et al., 2022, Ramachandram et al., 2019]. This psychoactive alkaloid acts through multiple mechanisms, including interaction with opioid receptors by functioning as partial agonists at MORs and as competitive antagonists at δ and κ **opioid** receptors [Kruegel et al., 2018]. It is also reported that mitragynine and its analogues were potent agonists in the [National Library of Medicine, 2021b]GTPγS assays at the MORs, indicating efficient activation of G-proteins, though it failed to recruit β-arrestin-2, that initiates many opioid side-effect pathways [Váradi et al., 2016]. Mitragynine agonist activity at α_2-adrenergic receptors may further enhance its overall analgesic effect by reducing sympathetic nervous system responses [98]. Additionally, it exhibits anti-inflammatory effects by selectively inhibiting COX-2 mRNA and protein expression, leading to reduced PGE2 production in LPS-stimulated macrophages, while sparing COX-1 at lower concentrations [Annuar et al., 2024, Green et al., 2025]. A study conducted on rats concluded that the administration of 10, 20 and 40 mg/kg mitragynine, produces anxiolytic-like effects due to the interaction with dopaminergic, γ-amino-butyric acid (GABA)ergic, and opioidergic systems in the brain, thereby reducing anxiety and promoting a calming effect [Annuar et al., 2024], enhancing its therapeutic potential in OUD.

Efficacy and Benefits

The efficacy of kratom in managing OUD has been widely reported in literature. Recent preclinical studies have demonstrated that kratom and its constituent alkaloids exhibit therapeutic potential in animal models of pain, anxiety, depression, and opioid dependence [Green et al., 2025]. Among kratom alkaloids, 7-hydroxymitragynine shows the highest in vitro affinity for opioid receptors, whereas mitragynine exhibits low-efficacy agonist activity at the μ-opioid receptor, contributing to milder opioid-like effects [Li, 2022]. Naloxone is a MOR antagonist used to reverse opioid overdose, but not for managing withdrawal or OUD maintenance. Mitragynine, by contrast, acts as a partial MOR agonist, with less severity of dependence, making it ideal for withdrawal symptom relief [Harun et al., 2022, Obeng et al., 2020]. It could therefore complement or, in some settings, serve as an alternative to medications like buprenorphine or methadone,

especially when combined with non-opioid pathways. Additionally, Hassan et al. (2020) reported that intraperitoneal administration of mitragynine at doses of 5–30 mg/kg effectively reduced acute morphine dependence in rats, with a significant decrease in withdrawal symptoms observed after four days of mitragynine treatment [Hassan et al., 2020]. Preclinical evidence also suggests that Mitragyna speciosa alkaloid extract significantly reduces naloxone-precipitated withdrawal symptoms like jumping and diarrhea in morphine-dependent mice, suggesting it may serve as an effective adjunct to naloxone [Wilson et al., 2021, Cheaha et al., 2017]. Studies also suggest that by activating both MOR and alpha-2 receptor (α_2R), mitragynine may achieve improved analgesic benefits through synergistic antinociception, allowing for effective pain control at lower doses [Obeng et al., 2022]. Furthermore, Mitragynine does not produce respiratory depression, likely due to its G-protein–biased agonism at the MOR and lack of β-arrestin-2 recruitment [Henningfield et al., 2022, Gutridge et al., 2020]. Clinical studies have shown that mitragynine is generally well-tolerated, with no serious adverse effects reported aside from mild symptoms such as tongue numbness and slight elevations in blood pressure and heart rate following ingestion [Yu et al., 2024]. The highlighted studies provide strong evidence that kratom and its active constituents have the potential to serve as a foundation for developing new therapeutic agents. However, as of 2025, mitragynine has not been approved for medical use by the FDA and there are no clinical trials in humans that define a therapeutic dosage for OUD. Further clinical research is warranted to determine its efficacy, safety, and appropriate dosing parameters.

4.8 α2-Adrenergic Receptor Agonists

Mechanism of Action Binding of an opioid to MORs on noradrenergic neurons in the locus coeruleus suppresses NE release, but abrupt cessation of the opioid leads to a compensatory NE surge that produces characteristic noradrenergic hyperactivity withdrawal symptoms such as chills, anxiety, irritability, tachycardia, insomnia, and gastrointestinal distress [Jones et al., 2021, Srivastava et al., 2020]. Clonidine and Lofexidine mitigate these opioid withdrawal effects by binding to presynaptic α_2A/α_2C receptors on noradrenergic neurons, particularly in the locus coeruleus. This activation inhibits adenylyl cyclase via Gi/o signaling, decreases cAMP levels, and suppresses excessive NE release, thereby calming the autonomic overactivity seen in withdrawal [Motiejunaite et al., 2021]. In 2018, the FDA approved lofexidine, as the first non-opioid medication specifically for managing opioid withdrawal symptoms [Jones et al., 2021]. Lofexidine follows the same pathway yet, owing to its higher α_2: imidazoline selectivity, causes significantly less hypotension and sedation than clonidine at equipotent doses [Raffa et al., 2019, Amanda et al., 2020]. A systematic review analyzing five randomized controlled trials (RCTs) revealed no significant differences between clonidine and lofexidine concerning their efficacy in alleviating withdrawal symptoms.[Amanda et al., 2020] In four of the studies examined, clonidine was associated with a higher incidence of adverse effects, a finding that reached statistical significance, while lofexidine exhibited increased adverse effects in only one of the trials [Amanda et al., 2020].

Efficacy and Benefits

Evidence from the last decade confirms these agentsvalue as nonopioid adjuncts during detoxification. Both agonists function independently of naloxone, as their therapeutic effects stem from α_2-mediated suppression of noradrenergic activity rather than opioid receptor antagonism [Gowing et al., 2016]. A phase 3 randomized trial (n = 602) showed that lofexidine 2.16–2.88 mg day^{-1} reduced opioid withdrawal symptoms over seven days, by ~30 %, as measured by the Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) [Fishman et al., 2019]. Comparative reviews and outpatient cohorts report symptom relief equivalent to clonidine but far lower rates of clinically significant hypotension and markedly better treatment retention with lofexidine [Kuszmaul et al., 2020]. Common adverse effects included orthostatic hypotension, hypotension, and bradycardia, but these were generally manageable and caused few discontinuations

[Fishman et al., 2019]. According to the ASAM 2020 Guideline, lofexidine and clonidine are more effective than placebo for managing opioid withdrawal and improving treatment completion, though methadone and buprenorphine are generally more effective overall. Alpha-2 adrenergic agonists can also support withdrawal during tapering from methadone or buprenorphine and help facilitate a smoother, more rapid initiation of extended-release naltrexone [ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020]. The non-opioid mechanism of alpha-2 adrenergic also makes it suitable for patients who are not yet ready for opioid replacement therapy or who are initiating detoxification [Fishman et al., 2019]. An interesting use case for Clonidine has been reported in improving post-cesarean section analgesic outcome, where the usage of Intrathecal clonidine demonstrated prolonged sensory and motor blockade, reduced 24-hour opioid consumption(Oxycodone 153.5 vs 207 min; $p < 0.001$), and longer time to first analgesic request(153.5 vs 207 min; $p < 0.001$) after cesarean delivery compared to control patients not receiving clonidine.[Cook et al., 2022] Its counterpart, Neuraxial clonidine, has been more extensively studied with a Meta-analysis reporting a reduced 24 h morphine consumption [mean difference (MD): −7.2 mg] and prolonged time to first analgesic request (MD: 135 min) when compared with the control group.[Allen et al., 2018] Neuraxial clonidine increased intraoperative hypotension [odds ratio (OR): 2.849], intraoperative sedation (OR: 2.355), but reduced the need for intraoperative analgesic supplementation (OR: 0.224) [Allen et al., 2018]. The prolonged action time of clonidine along with its properties of extending and enhancing the opioid-related euphoria coupled with reducing the amount of psychoactive drug needed, makes it likely to be abused.[Mitchell et al., 2021] Many case reports have discussed this unfortunate use case. Highlighting the need of awareness and caution among healthcare workers, who regularly prescribe clonidine with opioids. [Mitchell et al., 2021]Clonidine remains an inexpensive option that reliably blunts objective autonomic signs and demonstrates superior efficacy to placebo in easing withdrawal and improving treatment retention, yet guidelines note it is less effective for subjective distress and insomnia and should be paired with other supportive drugs (e.g., benzodiazepines for anxiety, trazodone for insomnia) [Srivastava et al., 2020]. In fact, clonidine is often used with other treatments (e.g., opioid taper or naltrexone) because by itself it does not block opioid effects. Therefore, α2-adrenergic agonists are best utilized as adjunctive agents rather than primary standalone therapies. The summary of indication of potential medications for OUD and withdrawal is shown in **Table 4** at the bottom.

5. Future areas for research in Opioid use disorder treatment

Opioid use has been highlighted to be a chronic inflammatory state with studies highlighting a decrease in pro-inflammatory markers with buprenorphine (C-C Chemokine ligand two reduction), and methadone (IL-6, metallopeptidase 9 and tumor necrosis factor-α reduction) [Herlihy et al., 2022]. However, these results have been heterogeneous across studies due to the limited work in this area, for instance, most studies focus on the adult population, and others show a rise in IL-10, an established anti-inflammatory marker [Bryant et al., 2021]. Due to the limited studies combined with their heterogeneous results, more work must be undertaken in this area, because inflammatory pathways could be explored not only for novel treatments but also for biomarker development in the diagnosis and monitoring of treatment.

Opioids are known to cause gut microbial dysbiosis, coupled with a decrease in diversity, essentially promoting a harmful cascade [Herlihy et al., 2022]. Studies on mice have elucidated that restoration of microbiome environment to normal can reinstate tolerance, which is attenuated with microbial depletion [Herlihy et al., 2022]. Essentially there exists a bidirectional relationship between gut microbiome and OUD, providing for a promising area in intervention [Kazemian et al., 2024]. Infact, the close relation between immune system, gut microbiome, and their proven altercation in OUD can be explored for further interventions. CRISPR technology has demonstrated the potential to target genes associated with addiction, thereby providing a pathway for personalized treatment strategies in OUD. The primary enzymes in alcohol metabolism in alcohol addiction are ADH and ALDH, and CRISPR/Cas9 gene editing techniques may be employed to resolve genetic anomalies in alcoholism [Wang et al., 2019]. Changes in the Gabra2 gene can cause drug addiction,

alcoholism, epilepsy, and psychiatric diseases. CRISPR has been utilized to rectify the deletion of the Gabra2 gene in C57BL/6J mice, indicating that Gabra2 gene therapy may be applicable for the treatment of substance misuse. Despite this, CRISPR has its own set of technical constraints and obstacles [Wang et al., 2019].

Artificial intelligence (AI) can be channeled for impactful utilization of resources, which are often limited in the communities currently most impacted by OUD. With the promise of precision medicine, AI can help tackle the intra-individual treatment needs, which are not currently tackled by the conventional system currently in use. [Marques et al., 2024]. In order to develop treatment plans for people with OUD, AI and personalised medicine or individualised treatment can evaluate each patient's unique genetic and environmental traits.

Based only on genetic and gut microbiome factors, OUD susceptibility varies greatly among individuals, adding to the diverse range of possible future areas [Duffy et al., 2024]. Since there is no one-size-fits-all approach to treating OUD, it is crucial that this variety be reflected in the necessary treatment. We're pushing for more exploration in other fields so that additional pharmaceutical substances can be employed either on their own or in combination with current therapies. Moreover, community support is essential for the provision of emotional support, information, and resources to individuals who are coping with OUD. This disorder is multifaceted, necessitating a comprehensive treatment strategy that integrates AI insights, personalized medication, and community support. This method or procedure recognizes the intricate nature of OUD, which includes genetic, environmental, affective, and social factors. By integrating these components, we can more effectively address OUD-related issues and support individuals in their recovery process.

6. CONCLUSION

When used in combination with individualised treatment programs and community assistance, a broad spectrum of pharmacotherapies-including opioid antagonist, partial agonists and antagonists-are an essential part of treating OUD. By lowering cravings and avoiding overdoses, these medications can greatly enhance outcomes for people with OUD. A comprehensive approach is made possible by combination therapies that incorporate holistic support networks, combining psychological and pharmacological techniques to create more successful treatment regimens for high-risk patients.

Author Contributions

Mubashir Raza conceptualized the study. **Jasreen Kaur Sandhu, Maryam Amjad, Eeman Salam, Laiba Sabir, and Sohaib Iqbal** conducted the literature review and drafting while editing and supervision were performed by **Mubashir Raza, Jasreen Kaur Sandhu, Sibtain Ali, and Bushra Jabeen Mehdi.** The final version of this manuscript has been read and approved by the authors.

Abbreviations

OUD: Opioid use disorder
MOR: μ-opioid receptor
Oprm1: Opioid receptormu 1
GPCR: G-protein-coupled receptors
NE: norepinephrine
ORL-1: Opioid receptor-like 1
MCAM: Methocinnamox
CRISPR: Clustered regularly interspaced short palindromic repeats
ADH: Anti-diuretic hormone
ALDH: Aldehyde dehydrogenase
Gabra2: Gamma-aminobutyric acid type A receptor subunit alpha2

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Receptors	Normal Physiological Functions	Adverse Effects	Mechanism of Action	Tissue Distribution	Key Drugs/Ligands	References
μ-opioid receptor (μ1, μ2, μ3)	Modulation of pain (supraspinal analgesia), euphoria, regulation of gastrointestinal (GIT) motility, Urinary retention, Respiratory depression due to brainstem action, Physical dependence and tolerance	High dose: Respiratory depression, Pruritus. Chronic use: Constipation (↓GIT motility), Anorexia, Urinary retention, Physical dependence and withdrawal symptoms.	Inhibits adenylate cyclase via Gi/o protein → decreases cAMP → increases K^+ conductance and reduces Ca^{2+} influx → neuronal hyperpolarization and inhibition of neurotransmitter release	Brain (especially pain pathways), submucosal plexus, mesenteric plexus, spinal cord, peripheral nervous system	Endogenous: Endorphins, enkephalins. Agonists: Methadone, Buprenorphine (partial), Nalmefene (inverse). Antagonist: Naloxone.	Herman TF et al., 2024; Dhaliwal A et a., 2023; Rullo et al., 2024; Paul et al., 2021.
κ-opioid receptor (κ-1, κ-2, κ-3).	Pain modulation (analgesia), Sedation, Stress and mood regulation, Miosis, Respiratory depression (less than μ), Diuresis	High and even at therapeutic doses: Dysphoria, Hallucinations. Dose-dependent: Respiratory depression (milder than μ), Aversion, Dyspnea	Similar Gi/o protein-mediated inhibition of adenylate cyclase → neuronal inhibition → decreased neurotransmitter release (notably dopamine in reward pathways)	Brain, mesenteric plexus, peripheral sensory neurons	Endogenous: Dynorphin. Agonists: Methadone, Nalmefene (partial), Butorphanol, Nalbuphine, and Pentazocine (Clinical), Difelikefalin (peripheral) are under investigation. Antagonists: Buprenorphine, Naloxone.	Dhaliwal A et al., 2023; Wikipedia. κ-opioid receptor; Glaudin Alexis 2021.
δ-opioid receptor (δ-1, δ-2).	Pain relief and analgesia (both spinal and supraspinal), Antidepressant effects, Anxiolytic effects	High dose: Potential seizure risk. Dose-related or mild dose: Possible respiratory	Gi/o-mediated inhibition of adenylate cyclase → enhanced potassium conductance and	Brain, mesenteric plexus, peripheral sensory neurons, spinal cord	Agonist: Methadone. Antagonists: Naloxone, Buprenorphine.	Quirion B et al., 2020; Alexander RP and Bender KJ 2025; Wikiped

		depression (rare)	inhibition of calcium channels, promoting neuronal hyperpolarization and decreased neurotransmitter release			ia. Opioid receptor.
Opioid receptor-like 1 (ORL1/NOR)	Modulation of pain including inflammatory and neuropathic pain, Regulation of mood, Fibromyalgia symptom modulation, Control anxiety, Feeding regulation	Dose-dependent: Complex and sometimes opposing effects on pain and mood (e.g., Hyperalgesia in high doses), Potential dysphoria, cognitive impairment with abuse liability.	Activation of Gi/o protein-coupled receptor → inhibits adenylate cyclase → modulates calcium ion channels → modulates neurotransmitter release especially in pain pathways	Forebrain: cortical areas, olfactory regions, limbic structures, thalamus, amygdala	Agonist: Buprenorphine (partial). Natural ligand: Nociceptin (N/OFQ). Synthetic NOP agonists.	Ding H et al., 2023: Wikipedia. Nociceptin receptor: Toll L et L., 2016.
ζ-opioid (ZOR)/ Opioid Growth Factor Receptor (OGFR)	Evidence suggests involvement in neurotransmission and pain modulation, regulates cell proliferation, precise physiological role under investigation	Not associated with classic opioid side effects, limited data available (potential role in tumorigenesis)	Nuclear envelope receptor (non-GPCR): OGF ([Met^5]-enkephalin) binding ↑CDK inhibitors (p16/p21) → cell-cycle arrest but exact pathways under study.	Ubiquitous (CNS, immune cells, epithelium)	Endogenous ligand: [Met^5]-enkephalin (OGF). Antagonist: Naltrexone (low dose).	Zagon IS et al., 2002: Wikipedia. OGFr receptor.

Table 1: Summary of the classification of opioid receptors: physiological functions, adverse effects, mechanism of action, tissue distribution, and key pharmacological agents.

Features	Naloxone	Nalmefene	Methocinnamox (MCAM)
Receptor Binding	Competitive antagonist (mu, delta, kappa)	Competitive antagonist (mu, delta, kappa)	Pseudo-irreversible antagonist (mu), Competitive antagonist (delta, kappa)
Half-life	1-2 hours	8-11 hours	more than 2 Weeks (preclinical)
Duration of Action	Short	Longer than naloxone	Exceptionally long
Intranasal Bioavailability	Good	Poor (requires enhancers)	Not yet established for humans
Insurmountable Antagonism	No	No	Potential (preclinical)
Clinical Use	Overdose reversal, OUD (nasal spray)	Overdose reversal (injectable)	Investigational (preclinical studies)

Table 2: Comparison of Naloxone, Nalmefene, and Methocinnamox (MCAM).

Study Focus	Animal Model	Key Findings
Reversal of Respiratory Depression	Rats, Non-human Primates	Effective reversal of fentanyl- and heroin-induced respiratory depression; longer duration than naloxone.
Attenuation of Self-Administration	Rodents, Non-human Primates	Reduced self-administration of heroin and fentanyl; selective (no effect on cocaine self-administration).
Safety Profile	Mice, Rats, Non-human Primates	No significant effects on cardiovascular function, body temperature, or cognitive function at effective doses; no tolerance/dependence.

Table 3: Preclinical studies of MCAM.

	Receptors and MOA	Pros	Cons	Current and Prospective areas of use
Naloxone	Non-selective opioid receptor antagonist with binding capacity to μ-, κ-, and δ-opioid receptors	Rapid onset of action, no agonistic action at mu opioid receptor, proven intranasal efficacy in use by lay person	Short duration of action, repeated dosing required for more potent opioids like fentanyl	First choice for emergency care
Buprenorphine	Partial agonism at μ- and antagonist at κ-, δ-opioid receptors. Affinity for ORL-1, but no discernible effect.	Reduces opioid craving by working on kappa receptors, prolonged receptor occupancy, "ceiling effect" allows for usage in pain.	Not useful in acute reversal of opioid overdose, apnea is seen in solo use for drug reversal.	Reducing withdrawals and cravings in opioid de addiction.
Nalmefene	Antagonistic function at mu, delta-opioid receptors with partial agonism at kappa receptors	Longer duration of action, no addiction potential.	Shown to precipitate withdrawals in dependent patients	Acute Opioid Crisis.

Methocinnamox (pre-clinical findings)	Pseudo-irreversible binding to mu-opioid receptors with antagonism, competitive antagonist at delta and kappa receptors	Very long duration of action (up to 2 weeks), reduced self-administration of heroin and fentanyl, minimal physiological side effects.	No effect on cocaine self-administration.	Current effects have only been demonstrated on animal models
Methadone	Full agonism at mu-opioid receptors, antagonism at NMDA receptors	Long-term therapy to reduce withdrawals and cravings.	Must be administered in a registered clinic; it has the danger of abuse, diversion, and overdose.	Patients undergoing maintenance therapy for OUD.
Mitragynine				
	Partial agonist at the μ-opioid receptor (MOR) and competitive antagonist at κ- and δ-opioid receptors	No induction of withdrawal symptoms, no increase in self-administration behaviour	Metabolite 7-hydroxymitragynine has exhibited abuse potential in experimental studies.	The vast receptor profile and effects can be channeled for usage in cancer patients.
Clonidine	Agonist at pre-synaptic alpha-2 receptors	Alleviates symptoms of opioid withdrawal such as yawning, sweating, hypertension and pupil dilation.	No independent opioid blocking effect can be used adjunctively to alleviate withdrawal symptoms.	In conjunction with other agents like naloxone
Lofexidine	Agonist at pre-synaptic alpha-2 receptors	Profile similar to Clonidine with reduced risk of hypotension and sedation due to its higher selectivity for α2 receptors over imidazoline receptors and reduces withdrawal ratings.	No independent opioid blocking effect can be used adjunctively to alleviate withdrawal symptoms.	In conjunction with other agents like naloxone
CNCP=chronic non-cancer pain.		MOUD=medications for opioid use disorder.	OUD=opioid use disorder.	

Table 4: Review of OUD and withdrawal using medications with suitable indications.