Potential of Methocinnamox to Treat Opioid Misuse

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Abstract: The opioid epidemic is an ongoing public health crisis, and the United States health system is overwhelmed with increasing numbers of opioid-related overdoses. Methocinnamox (MCAM) is a novel mu-opioid receptor antagonist with an extended duration of action and potential to reduce the burden of the opioid epidemic through overdose rescue and could treat opioid use disorder (OUD) long-term. We compared the efficacy and effects of MCAM to the current treatments available to treat OUD including naloxone, naltrexone, methadone, and buprenorphine which have their own limitations including short duration of action, patient non-compliance, and diversion. A literature review was conducted using PubMed and Google Scholar databases covering the history of the opioid epidemic, pain receptors, current OUD treatments and the novel drug MCAM. MCAM could potentially be used as both a rescue and long-term treatment for opioid misuse. This is due to its pseudo-irreversible antagonism of the mu opioid receptor, abnormally long duration of action of nearly two weeks, and the possibility of using kappa or delta opioid receptor agonists for pain management during OUD treatment. MCAM's novel pharmacokinetic and pharmacodynamic properties open a new avenue for treating the opioid crisis.

Keywords: methocinnamox; opioid; naloxone; naltrexone; methadone; buprenorphine; overdose; treatment; receptors; addiction

1. Introduction

Over one-million Americans have died from overdoses during the opioid epidemic.[1] Opioid addiction and misuse remains a prevalent issue in the United States (US) leading to millions of deaths.[2] Opioids were originally discovered from poppy plants and were used to reduce pain sensation ranging from acute to severe, but they have become more accessible for recreational use outside of pain relief therapy.[3,4] The intended use of opioids was for the reduction of pain sensation by agonizing the opioid receptors located in the central nervous system (CNS).[5] There are three major opioid receptor types, mu (μ), delta (δ), and kappa (κ), but the mu-receptor is the main target of exogenous opioids[5,6]. In the past, many people turned to opioids to relieve daily suffering from chronic pain, and the drugs easily became addictive and created dependence.[2] The ubiquitous use of opioids and the addiction to these drugs in the US have exacerbated the strain on resources in hospitals, emergency rooms, and on first responders as they try to save lives with the limited resources currently available.[2] Naloxone is the only drug available to treat opioid overdose to be approved by the US Food and Drug Administration (FDA) in the last 50 years, and the opioid users are younger and experimenting with synthetic opioids beyond pain relief.[7,8] Naloxone is a competitive mu opioid antagonist with a high affinity for the mu-receptor used to reverse respiratory and CNS depression in those enduring an opioid overdose.[9,10] Naloxone does not help decrease future use of opioids, and the use of

synthetic opioids will require higher doses of naloxone which could increase adverse effects such as tachycardia and hypertension.[11,12] Naloxone is also currently misused at "Narcan parties," where attendees intentionally overdose knowing they will be rescued by naloxone.[13] Naltrexone has extended-release formulas intended to reduce relapse and promote compliance, yet patient noncompliance and retention continue to be limiting factors.[14] Methadone is commonly used to treat opioid addiction as a replacement for illicit opiates but is itself an addictive substance that can lead to withdrawal if dosage is not closely monitored by a licensed professional.[15] Buprenorphine is currently used to treat OUD and while it reduces illicit drug use, it is equal to or even less effective than methadone in patient retention in treatment.[15] Additionally, buprenorphine is sold on the black-market for those attempting to treat opioid dependency on their own and was involved in more drug arrests than methadone.[16,17] Methadone and buprenorphine are substitution treatments with substantial reduction of opioid deaths during treatment but immediately following release from treatment mortality risk notably returns to increased levels.[18] For these reasons,[1,2] there is a dire need for a new opioid misuse intervention.[19]

Methocinnamox (MCAM) is a novel drug candidate that is a pseudo-irreversible antagonist for the mu opioid receptor (MOR), thereby preventing other opioid agonists from binding for a two-week period[19–21]. Due to the long-lasting effect of MCAM, it can be a safer and more effective alternative medication for the misuse of opioids.[22,23] MCAM has the potential to change the course of opioid misuse and help prevent relapse after administration.[24,25] This brief review will explore how MCAM's unique function could be useful in reducing the burden of the opioid crisis.

2. Methods

A literature review was conducted using PubMed and Google Scholar databases utilizing the following key terms: methocinnamox, MCAM, naloxone, naltrexone, buprenorphine, buprenorphine-naloxone, methadone, opioid overdose, opioid crisis, opioid abuse, mu-receptor, kappa-receptor, delta-receptor, inverse agonist, and naloxone and placebo. These terms and pharmacotherapies were included due to their relevance to the opioid epidemic, opioid overdose, and MCAM. Chemical structure was constructed with ChemDraw version 19.0.0. No date range or journal exclusion criteria were applied.

3. Discussion

3.1 Opioid Epidemic

In the 1800s, opiates were widely marketed as a safe and effective form of pain alleviation.[26] Consequently, the absence of federal regulation on frequent opioid prescription and use drew widespread concern, which eventually led to the enactment of the 1914 Harrison Narcotic Control Act.[27] While this prompted nationwide stigmatization of opioid use for non-cancer chronic pain management, it was later followed by a drastic shift in 1995 in public attitude that advocated for the recognition of pain as a 'fifth vital sign'.[28] As a result, several entities such as the Institute of Medicine, the Federation of State Medical Boards, and the Drug Enforcement Agency, pushed for fewer regulations over opioid prescriptions, thereby encouraging healthcare providers to provide adequate pain relief for patients. Additionally, the FDA approved an extended-release oxycodone formulation in 1995 as a safer opioid alternative to the fast-release version because of its slow and sustained release of medication.[29] Pressure by pharmaceutical companies, patients, and federal funding requirements further contributed to the

overaggressive prescription of opioid analgesics that ultimately led to the opioid epidemic in the US.[30,31] The Centers for Disease Control reported that in 2016, more than 42,000 Americans died from an opioid overdose, marking a 27% increase from the previous year.[32] In 2017, the rate increased by 45.2%, indicating the increased prevalence of opioid misuse.[33] More than 11.5 million Americans misused opioids and roughly 2.1 million were formally diagnosed with an OUD.[34] Later that year, the US Department of Health and Human Services declared the opioid epidemic a public health emergency. Despite concerted efforts by medical practitioners to reduce opioid prescriptions and increased availability of buprenorphine, methadone, and naloxone,[35–37] opioid overdose continues to rise with one-hundred thousand annually,[38] with the illegal manufacturing of fentanyl and its analogs as the leading cause.[39] This can be attributed to fentanyl's high potency, with a strength that is 30-50 times greater than that of heroin, its rapid onset of action, long duration of desired effect, and low production costs. While the rate of heroin-related overdose deaths has started to stabilize, from 2013-2016 synthetic opioid related deaths, such as those caused by fentanyl and its analogs, increased by 88%.[30,40]

Public health experts agree that tackling the opioid epidemic will require interdisciplinary collaboration between medical providers, social service agencies, federal regulation, and community support.[8,41,42] The lingering effects of the epidemic are rampant in low-income communities, predominantly African American and Hispanic communities, and are currently exacerbated by COVID-19's social and health impacts.[43,44] Potential proposed solutions include increasing harm-reduction programs, educating medical providers on safe opioid prescribing, eliminating stigma around OUDs, as well as finding safer alternatives to pain management.[3,42,45] Current OUD therapeutics include methadone, buprenorphine, naloxone, and extended-release naltrexone, all of which function by reducing opioid withdrawal symptoms and cravings.[5,46] However, drug addiction is generally recognized as a complex biopsychosocial condition. These medications can only successfully resolve the opioid crisis by working in tandem with public health efforts that include both prevention and harm-reduction approaches.[47] MCAM presents potential for a new avenue of OUD treatment.

3.2 Pain Receptors

MCAM is a long lasting, pseudo-irreversible (non-covalent binding), potent, MOR antagonist which reversibly binds kappa opioid receptors (KOR) and delta opioid receptors (DOR) that has no known interaction with other nociceptors. Thus, kappa and delta agonists could be provided concomitantly for pain relief during treatment for OUD.[20,22–24,48,49] This unique pharmacodynamic mechanism of MCAM contributes to its long-lasting effects. The need for new MORs to induce the euphoric and depressive effects of opioid receptor agonists as receptor turnover is what limits the DOA.[19,24] This is crucial because MOR agonists can not only induce the G protein-coupled receptor (GPCR) pathway, but can also induce β-arrestin activation, leading to adverse effects such as respiratory depression.[50,51] The opioid receptors: MOR, KOR, and DOR, belong to the largest membrane receptor family called the trimeric GPCR superfamily, with opioids activating the inhibitory (Gi) signaling pathway to initiate analgesic functions.[52–55] The GPCRs are known for their trimeric subunits consisting of alpha (Gα), beta (Gβ), and gamma (Gγ).[56] After the opioid agonist (endogenous or exogenous) binds, a signal stimulates Gα to migrate and suppress adenylate cyclase activity, thereby reducing cyclic AMP production.[56] The G$\beta\gamma$ acts as a modulator for the signaling pathway, resulting in reduced neurotransmitter release and membrane hyperpolarization.[56]

Since GPCRs are so widespread, these are the target for 50% of marketed pharmacological

therapeutics, revolving around the common amino-terminal peptide sequence, Tyr-Gly-Gly-Phe, which is referred to as the "opioid motif" as it directly interacts with the opioid receptor[57]. The MOR agonists include oxycodone, fentanyl, heroin, morphine, and methadone. Buprenorphine is a partial MOR agonist and KOR antagonist.[58,59] MOR antagonists include naloxone, naltrexone, and MCAM. It is believed the activation of KORs antagonizes MOR mediated analgesia; activation of the KOR hyperpolarizes neurons that are active indirectly by the MOR.[7] Pain is multidimensional and dependent on subjective thresholds. Chronic pain, which may be concurrent with anxiety, may be associated with neuroplastic changes in the amygdala, which may heighten the emotional and affective consequences of pain.[60,61] Analgesics are highly effective in most cases against acute pain, but the desired effects mediated by the opioid receptor family may lead to craving, addiction, or dependence as a result of neurological changes.[62–65] Repetitive opioid use will thus increase the threshold for analgesic effects secondary to compensatory upregulation of vesicular calcium content while developing opioid tolerance and may decrease one's quality of life.[53,66,67]

3.3 Current OUD Treatments

The current pharmacological treatments for opioid overdose and misuse are administration of methadone, buprenorphine, naloxone, and naltrexone.[9,10,12,68–70] Methadone and buprenorphine are opioid agonists which may prevent withdrawal symptoms in those recovering from OUD, but pose risk for opioid overdose particularly when combined with other substances.[68,71,72] However, naltrexone and naloxone are opioid antagonists, the latter being the only emergency rescue for opioid overdose and opioid induced respiratory symptoms.[10,73] Naltrexone is used to treat OUD and opioid dependency, usually post-opioid cessation, whereas naloxone can be used concomitantly with prescribed opioids such as buprenorphine.[68–70,74] Other pharmacological uses have been identified for

naloxone and naltrexone such as treatment for alcohol dependence, and possible treatments for internet sex addiction, and Hailey–Hailey disease, but studies show these medications are not effective for smoking cessation.[75–78]

Administration of methadone or buprenorphine significantly reduced opioid-related deaths caused by nonfatal opioid overdose over a 12-month follow-up period by 59% and 38%, respectively.[79] The abrupt discontinuation of opioids does not show great success rates and may result in relapse.[8,68] Use of these drugs in conjunction with psychosocial therapy are the best for treatment success in those with OUD.[8,68,70] While both methadone and buprenorphine are synthetic derivatives of opiates and used in medication assisted treatment (MAT) of OUD, they possess different mechanisms of action and adverse drug reactions (ADRs). Methadone is a long-acting full agonist that binds the MOR, preventing withdrawal symptoms such as nausea and vomiting for at least 24 hours, while conferring analgesia and reducing opioid cravings.[80,81] Dextromethadone is an NMDA glutamate receptor antagonist. Conversely, buprenorphine is a partial agonist at the MOR, making it less potent than methadone with decreased ADRs.[81,82] Buprenorphine and its metabolite norbuprenorphine also bind to KOR as an antagonist and DOR as an agonist.[58,82] Methadone has restricted availability in the US and requires daily dosing raising the issue of patient compliance; close monitoring of dosing for detoxification by a practitioner for each individual is an additional healthcare burden.[83] Buprenorphine is less effective for patient retention than methadone, even at high doses.[15] Buprenorphine's purported 'ceiling effect' reduces the risk of misuse or overdose by preventing the increase of opioid effects, or euphoria, beyond a designated threshold.[81] However, buprenorphine may precipitate withdrawal, a condition that occurs without an adequate detoxification period from opioid drugs, due to its high affinity for the MOR.[81,82] The

combination of buprenorphine with benzodiazepines causes respiratory depression.[81,82]

An additional drug that is also used in MAT programs is naloxone, which is often paired with buprenorphine in an oral tablet form to prevent strong withdrawal symptoms and block the euphoric effects induced by other opioids.[69] The mechanistic action of naloxone is by competitive binding to the MOR as a high affinity antagonist, and some researchers suggest it acts as an inverse agonist.[10,84] Administration of naloxone intravenously, intramuscularly, subcutaneously, intranasally, and even inhalation through endotracheal tube for intubated patients during an opioid overdose, competitively binds the opioid receptors to reverse respiratory and CNS depression.[85] The time to decrease fentanyl occupancy at the receptor after 2 mg intramuscular naloxone administration was three minutes, after 25 ng/ml and ten minutes after 50 ng/ml, but there is an increased dose requirement of naloxone due to larger doses of self-administered opioids.[12] After a 13 µg/kg dose of naloxone, 50% of the receptors in the brain were occupied, but due to the rapid association and successive dissociation of naloxone from the receptors, toxicity reversal may be insufficient and the patient may experience renarcotization requiring subsequent doses.[12,85,86] Although regarded as exceedingly safe, ADRs for naloxone can include tachycardia, hypertension, gastrointestinal upset, hyperthermia, cravings, nausea, vomiting, and rarely severe cardiovascular events.[9,12,85] Naloxone also blocks the descending pain control system, thus diminishing the placebo pathway for pain perception by interfering with the coupling between the rostral anterior cingulate cortex and the periaqueductal gray area structures in the brain.[87,88] Though not the first-line treatment for opioid overdose, as it is not as efficacious as naloxone, naltrexone is used to reduce opioid use in those with OUD.[70,73]

Naltrexone is commonly characterized as an opioid receptor antagonist, although some suggest an inverse agonist function based on its intracellular signaling properties, that is prescribed to reduce opioid use in those attempting to practice abstinence from opioids but suffer from OUD.[70,73] Interventions for opioid misuse involving naltrexone, rather than receptor agonists like buprenorphine, have been successful when paired with behavior intervention and are a promising alternative treatment for opioid misuse in pregnant women.[89,90] For opioid dependent pregnancies, naltrexone had reduced opioid misuse in mothers and significantly decreased neonatal abstinence syndrome in infants when compared to buprenorphine.[89] In contrast to naloxone's associated acute withdrawal symptoms, naltrexone reduces symptoms of withdrawal for patients and even lowers the risk for overdose with the use of buprenorphine as an OUD treatment with no significant ADRs.[74] While also having a considerable safety profile like naloxone, the potential side effects of naltrexone include mild to moderate injection site reaction, nausea, and gastrointestinal upset.[91] See Table 1 for a summary comparison of drug treatments. With the intervention's limitations outlined above, MCAM may prove beneficial as a treatment to combat the opioid crisis.

Table 1. Comparison of opioid use disorder and opioid overdose treatment drugs. Table includes naloxone[104,105], naltrexone[106,107], methadone[108,109], buprenorphine[110,111] and methocinnamox (MCAM)[19,24,96,98,99,101].

Treatment Drug	Method of Administration	Mechanism of Action	Onset and Duration of Action	Strengths	Limitations
naloxone	Intravenous Intramuscular Subcutaneous Intranasal Inhalation	Reversible MOR, KOR, DOR competitive antagonist	Rapid onset or 1-5 minutes 1–2 hours	Rescue from overdose, wide therapeutic window	Short DOA, community misuse, risk of renarcotization, precipitates withdrawal, drug-drug interactions, surmountable
naltrexone	Intravenous Intramuscular Subcutaneous[1] Oral	Reversible MOR, KOR, DOR competitive antagonist	15 - 30 minutes >72 hours	Use during pregnancy, extended-release formula	May precipitate withdrawal, patient noncompliance, drug-drug interactions
methadone	Intravenous Intramuscular Subcutaneous Oral	MOR, DOR agonist, NMDA antagonist	Rapid onset 4–8 hours, single dose; 22-24 hours, continuous dosing	Prevents withdrawal, reduces opioid cravings, pain relief	Patient noncompliance, dependence, misuse and diversion, restricted availability in US, close monitoring of dosage, many drug-drug interactions, ADRs
buprenorphine	Intravenous Intramuscular Subcutaneous Oral Buccal Sublingual Transdermal	Partial MOR agonist, KOR, DOR competitive antagonist	10-30 minutes 2–24 hours	Prevents withdrawal, use during pregnancy, prevents euphoria and overdose symptoms	Less potent than methadone, patient retention inferior to methadone, may precipitate withdrawal, drug-drug interactions, ADRs
MCAM	Intravenous Subcutaneous	Pseudo-irreversible MOR, not competitive antagonist[2], reversible KOR, DOR competitive antagonism	15-45 minutes 5 days to 2 weeks	Long DOA, not surmountable, prevents renarcotization, lacks notable drug-drug interactions, antinociceptive concomitant treatment possible	Precipitates withdrawal, not yet tested in humans

[1] Subcutaneous formula is a pellet implant

[2] MOA incompletely understood

3.3 Methocinnamox

MCAM, shown in Figure 1, was first mentioned in a publication in 2000 by researchers from the University of Michigan Medical School and the University of Bristol, but was initially discarded because it was believed to be useful only for MOR research.[8,92] However, it is currently being studied for its promise in the opioid crisis as a long-term OUD treatment.[93,94] In animal models, a single

subcutaneous dose of MCAM rescues a subject from acute opioid overdose and prevents subsequent overdose for up to two weeks with minimal adverse effects.[21,22,92,95,96] Currently, the only known possible adverse effect for MCAM in non-dependent individuals was hyperventilation upon rescue.[96] Interestingly, one study noted a slightly increased response to food (a non-drug alternative) several days following a single injection.[22] Some studies have shown no statistically significant adverse effects nor potential ADRs with benzodiazepines and alcohol.[19,22,97] MCAM has not been shown to cause a decrease in response to food or alter heart rate, blood pressure, body temperature, or social and physical activity and no indication of developing tolerance nor physical dependence.[19,22] MCAM is currently the most potent and selective MOR antagonist and shows no agonistic effects, even at high concentrations, with the longest duration and highest potency when injected subcutaneously over other methods of administration.[20,96]

Figure 1. Methocinnamox chemical structure. Molecular Formula: C30H32N2O4, PubChem CID: 46877713, IUPAC name: (E)-N-(4R,4aS,7aR,12bR)-3-(cyclopropylmethyl)-9-hydroxy-7-oxo-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro3,2-eisoquinolin-4a-yl-3-(4-methylphenyl)prop-2-enamide (compound/methocinnamox)[112].

Naltrexone and naloxone injections become ineffective in less than a single day with durations of action lasting 1-2 hours.[85,86] A single injection of MCAM has a duration of action of thirteen days, reaching peak concentration 15-45 minutes after injection with a half-life of roughly 70 minutes.[19,24,98] MCAM's exact mechanism of action is currently unknown, but the effectiveness at very low plasma levels suggests the pharmacodynamic properties play a significant role in its long-lasting effects rather than pharmacokinetic factors.[19] The evidence for pseudo-irreversible binding includes its non-reversible, insurmountable, and time-dependent antagonism of mu agonist-inhibition of cAMP production.[99] A recent study using human embryonic kidney (HEK) cells expressing human opioid receptors showed that in addition to pseudo-irreversible orthosteric antagonism of MORs, directly blocking binding, MCAM also utilizes allosteric antagonism at an unknown site at a lower affinity, which alters ligand affinity and/or intrinsic efficacy of MOR agonists.[99] As for MCAM's mechanistic interaction with DORs and KORs, the behavior was consistent in the opioid receptor expressing HEK cells, and in vivo, with simple competitive antagonism.[99]

Repeated administration of MCAM every twelve days in rodents remained effective for over two-months without altering the duration of opioid withdrawal with no major ADRs and no decrease in effectiveness, suggesting positive potential for long-term OUD treatment.[19,21,96] Naltrexone, naloxone, and MCAM are effective for acute reversal and prevention of respiratory depression and other overdose symptoms due to their effects on opioid receptors, but only MCAM prevents renarcotization in the hours and days following emergency intervention.[19,48,96,98,100] Naltrexone and naloxone bind competitively, meaning higher amounts of an agonist will overcome their intended effects requiring a higher dose of either therapy to reverse initial and subsequent overdoses post-antagonist-injection.[98] MCAM binds non-competitively, making it insurmountable and therefore more
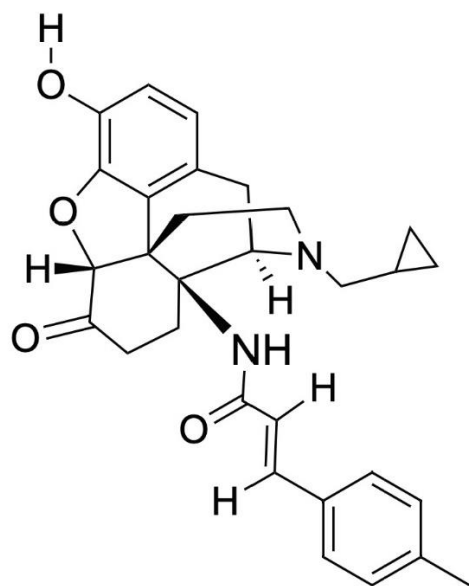
effective at blocking effects of opioids in the short- and long-term.[19,24,99,100] Additionally, MCAM is naloxone-insensitive with no notable drug interactions meaning there is a possibility that the two drugs could be administered concurrently for immediate rescue and prevent subsequent renarcotization.[99] With over-the-counter availability of naloxone, overdose related deaths have decreased but subsequent renarcotization and therefore consequent overdoses leading to death remains an issue.[85,99] If a shorter acting formulation of MCAM was combined with naloxone, renarcotization risk could significantly decrease and potentially further reduce opioid overdose related deaths without inducing withdrawal.

MCAM can act as a preventative therapy for opioid misuse, indicating possible use at discharge from treatment facilities following a detoxification period, as well as use during ongoing therapeutic intervention negating the need for, and misuse of, buprenorphine and methadone.[22,24,48,100] Its prolonged dosing interval is hypothesized to relatively prevent patient noncompliance that is seen with extended-release naltrexone for outpatient treatment, including eliminating the possibility of an individual removing an implant.[22,24] In cases where effects lasting roughly five days or less are needed, such as preventing renarcotization in the hours and few days following an overdose but not for long term treatment of OUD, intravenous administration of MCAM would be preferable.[96,98] There is discussion of creating an oral pill form of MCAM, an extended release form, and faster acting intranasal and intramuscular formulations, but further study of the drug is needed before these will be developed.[19,22,98] MCAM also blocks the physiological and behavioral effects of MOR agonists such as unfavorable impacts of sensitivity to mechanical stimulation, gastrointestinal motility, appetite, and memory and other cognition, suggesting the adverse effect profile is encouraging.[21,22,25,97,101] However, it is important to recognize that no testing has been conducted in humans.[92] It is currently unknown if long-term

blockade of the mu receptor would attenuate endorphin and enkephalin signaling sufficiently to reduce mood. Given the wide-spread impact of opioid overdoses, novel strategies are desperately needed.

4. Conclusion

The increased prevalence of OUD cases and opioid related deaths are an ongoing public health crisis in the US. While opioid antagonists, naltrexone and naloxone, are essential drugs used to treat OUD and reverse the effects of an overdose, respectively, they have risks that pose considerable limitations to their efficacy. These risks include withdrawal, poor patient compliance, short durations of action, lack of concurrent antinociceptive treatment, ability to surmount opioid receptor blockade, and potentially dangerous drug-drug interactions, especially for those with comorbid addictions.[12,19,22,85,91] Opioid agonists methadone and buprenorphine present their own limitations in OUD treatment such as dependence, restricted availability, poor patient retention, patient noncompliance, drug-drug interactions necessary detoxification and potential withdrawal.[15,81–83] Buprenorphine is a Schedule III and methadone is Schedule II substance in the US, so misuse and diversion of these substances is an ongoing challenge.[16,17] The demand for novel therapeutics to decrease the misuse and overuse of opioid drugs and resulting overdoses provides an opportunity for MCAM to make a positive impact. By retaining the safety benefits of naltrexone and naloxone and providing a longer DOA with a novel mechanism, MCAM is a promising pharmacological addition. Using non-MOR agonists such as the KOR agonist spiradoline concomitantly with MCAM also presents a potential intervention method allowing for antinociceptive effects during the withdrawal process and OUD treatment.[48,98,102,103] The preclinical phase of MCAM drug development began in 2005 with testing in mice, rats, and non-human primates.[21,48,95–101] Researchers aim to begin phase I clinical trials by 2022.[92] MCAM has the potential to

transform the future of OUD treatment, thereby reducing the healthcare and societal burden caused by the opioid epidemic,[1,2] and improving the lives of millions.

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