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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Recent Advances in the Treatment of Opioid Use Disorder

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Abstract

Purpose of Review Opioid use disorder (OUD) remains a national epidemic with an immense consequence to the United States' healthcare system. Current therapeutic options are limited by adverse effects and limited efficacy.

Recent Findings Recent advances in therapeutic options for OUD have shown promise in the fight against this ongoing health crisis. Modifications to approved medication-assisted treatment (MAT) include office-based methadone maintenance, implantable and monthly injectable buprenorphine, and an extended-release injectable naltrexone. Therapies under investigation include various strategies such as heroin vaccines, gene-targeted therapy, and biased agonism at the G protein-coupled receptor (GPCR), but several pharmacologic, clinical, and practical barriers limit these treatments' market viability.

Summary This manuscript provides a comprehensive review of the current literature regarding recent innovations in OUD treatment.

Keywords Opioids · Substance abuse · Opioid epidemic · Opioid use disorder

Introduction

Opioids are an essential component of the management of perioperative pain and cancer-related pain. They are the oldest and most efficacious group of drugs for managing severe pain. Opioids act on opioid receptors that are located along the nociceptive pathway, found on multiple presynaptic and postsynaptic nerve terminals [1]. However, the misuse of these medications in the treatment of chronic pain has contributed greatly to the opioid crisis [2]. The opioid epidemic has developed into a major public health crisis related to the abuse of prescription opioids, rise in heroin use, and increased availability of high-potency synthetic opioids. In 2019, drug overdose deaths increased 4.6% to 70,980 with over 70% involving opioids [3]. Opioid agonist therapy (OAT) with methadone or buprenorphine remains the gold standard for the treatment of opioid use disorder (OUD) [4]. Although effective, OAT has undesirable effects including abuse liability, respiratory depression, cardiac arrhythmias, immunosuppression, and hyperalgesia. Additionally, it requires patient participation in a maintenance program with no universal agreement on the length of therapy, with approximately 40–60% of

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patients relapsing while on maintenance therapy [2]. The current limitations and subpar outcomes of OUD treatment have led to the study and research of new targeted therapies. This review, therefore, focuses on recent advancements in novel pharmacological treatment in OUD.

Opioid Use Disorder

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), defines opioid use disorder as a problematic pattern of opioid use leading to clinically significant impairment or distress [5]. The full diagnostic criteria for OUD are outlined in Table 1 per DSM-5. OUD is a chronic disease that affects over 16 million people worldwide and over 2.1 million in the USA [6]. A hallmark of OUD is the "intense cravings" that lead to compulsive drug seeking and use despite harmful consequences [7]. Opioid addiction has become a substantial economic burden on the United States economy, with an estimated economic cost of more than $500 billion per year [8]. OUD is a complex medical disease with multifaceted individual, social, and economic factors.

It is imperative to understand the neurobiology behind opioid tolerance, dependence, and withdrawal, which culminates clinically as opioid addiction or OUD. Repeated exposure to opioids first results in tolerance, which is the need to take higher amounts of a drug in order to achieve a similar euphoric effect [9, 10]. Opioid tolerance occurs as opioid receptors in the brain become less responsive to opioid stimulation, requiring more drugs to produce the same pleasurable effect [10]. Dependence manifests as an individual becomes susceptible to withdrawal symptoms in the setting of acute cessation of opioid use [7, 10]. Opioid withdrawal occurs in the locus coeruleus of the brain, as opioid receptor activation suppresses noradrenergic neurons and repeated opioid exposure leads to increased activity of these neurons [10, 11]. Opioid withdrawal symptoms include abdominal pain, nausea, vomiting, diarrhea, lacrimation, rhinorrhea, piloerection, yawning, sneezing, elevated blood pressure, and elevated heart rate [12]. These symptoms can be agonizing, sometimes even life-threatening, and perpetuate drug-seeking behavior. This vicious cycle of dependence and withdrawal has prompted the investigation into long-acting active opioids for the treatment of OUD.

Table 1 DSM-5 criteria for OUD

DSM-5 criteria for opioid use disorder
Definition: OUD is a problematic pattern of opioid use leading to problems or distress, with at least two of the following occurring within a 12-month period:
1. Taking larger amounts or taking drugs over a longer period than intended.
2. Persistent desire or unsuccessful efforts to cut down or control opioid use.
3. Spending a great deal of time obtaining or using the opioid or recovering from its effects.
4. Craving or a strong desire or urge to use opioids.
5. Problems fulfilling obligations at work, school, or home.
6. Continued opioid use despite having recurring social or interpersonal problems.
7. Giving up or reducing activities because of opioid use.
8. Using opioids in physically hazardous situations.
9. Continued opioid use despite ongoing physical or psychological problem likely to have been caused or worsened by opioids.
10. Tolerance (i.e., need for increased amounts or diminished effect with continued use of the same amount).
11. Experiencing withdrawal (opioid withdrawal syndrome) or taking opioids (or a closely related substance) to relieve or avoid withdrawal symptoms.

Modified from the American Psychiatric Association's DSM-5, 2013 [5]

Current Treatment Options

The Center for Disease Control and Prevent (CDC) states that medication-assisted treatment (MAT) remains the best treatment option for OUD [13]. Strong evidence supports long-term opioid therapy as superior to abstinence-based treatment or withdrawal management alone, claiming these methods are associated with increased rates of relapse, morbidity, and death, and are therefore not recommended [14, 15]. There are currently three classes of medications historically used for treatment: full-opioid agonists, partial opioid agonists, and opioid antagonists. The present FDA-approved medications for maintenance treatment of OUD in the USA are methadone, buprenorphine, and naltrexone, as further detailed in Table 2 [16•]. These maintenance programs are typically paired with counseling and behavioral therapy such as cognitive-behavioral therapy (CBT) [17].

Methadone

Methadone was introduced to the USA in 1947 as an opioid analgesic, with methadone maintenance treatment (MMT) subsequently beginning in 1965 in response to the New York City heroin epidemic [18]. Methadone is an oral pure MOR agonist, with some agonistic effects on KOR and DOR, a slow onset and offset of action, and the ability to curtail the withdrawal effects and cravings from opioids. A licensed physician at a specialty treatment center that is certified by the Substance Abuse and Mental Health Services Administration and registered with the Drug Enforcement Administration (DEA) can prescribe methadone for addiction [19]. MMT generally has three phases: induction, stabilization, and maintenance. The induction phase starts at 15 to 30 mg daily, reaching 50 to 80 mg by week two, and finally increased to the optimal effective dose of 80 to 100 mg [20]. The maintenance phase begins at week six with treatment lasting a minimum of one year to indefinite use based on an individual's

Table 2 FDA-approved medications for OUD and future treatment options

FDA-approved medications for OUD	Future treatment options
Methadone (PO)	*Heroin vaccine*
• 80–150 mg/day	• Heroin-tetanus toxoid (TT) conjugated with adjuvants alum and CpG ODN
• Maintenance dosing is determined during the early weeks of treatment following upward titration	• Reduced heroin potency by greater than 15-fold in animal studies
• FDA approved in 1972	• Beneficial for those with difficulty adhering to maintenance therapy
Buprenorphine-naloxone (SL or BUC)	*CRISPR*
• Suboxone®	• Gene-editing method with therapeutic potential
• 8–24 mg/day buprenorphine	• GWAS superior to candidate gene studies as it prevents inherent bias and can analyze a greater number of polymorphisms
• 1–6 mg/day naltrexone	*Biased agonism agents*
• 4:1 ratio of buprenorphine-naloxone	• Mitragynine: natural product derived from a plant
• FDA approved in 2002	• Oliceridine (TRV130): previously in clinical trials, reapplied for continued trials this year
Buprenorphine transdermal patch	• PZM21: morphine-equivalent analgesia but concerns for respiratory depression
• Butrans™	• NAN: partial agonist that may mitigate opioid-induced adverse effects
• 5 to 20 mcg/h doses	*Ion channel targets*
• Approved for chronic pain requiring around-the-clock opioid therapy	• Nav1.7, Nav1.8 inhibitors: tetrodotoxin, saxitoxin, synthetic acyl sulfonamides
Buprenorphine implant	• Cav2.2 inhibitors: ziconotide, CNCB-2, physalin F
• Probuphine	• TRPV-1 agonists: capsaicin, resiniferatoxin
• Delivers steady state of medication over a 6-month period	*KOR agonists*
• FDA approved in 2016	• Butorphanol: partial MOR with 20-fold higher affinity to KOR
Buprenorphine extended-release formulation (SQ)	*OREX-19*
• Sublocade®	• Animal studies demonstrate mechanism similar to buprenorphine/naltrexone
• 80–300 mg/monthly injection	*Medical cannabinoid*
• Two formulations available FDA approved in 2016 and 2017	• Animal and clinical studies reduce opioid reward effect and decrease cravings
Naltrexone tablets (PO)/extended-release formulation (IM)	• Dronabinol and nabilone: synthetic partial agonist cannabinoids under investigation for analgesic effects
• Vivitrol®: 380 mg/monthly IM injection FDA approved in 2010	*Cholinesterase Inhibitors*
• 50 or 100 mg/day orally	• May reduce opioid adverse effects without affecting analgesia
• Requires a patient to be opioid free for 7–10 days before administration	*Lorcaserin*
	• 5-HT agonist with animal studies demonstrating reduced oxycodone cravings

FDA-approved medications modified from Kreek et al. 2019 [14]

progress and motivation [20]. MMT has been an effective, well-established treatment option for more than 50 years, decreasing mortality by 50% in those with OUD as well as decreases in relapse, infection, and crime [20]. In comparison to buprenorphine, MMT has higher retention rates and is more effective for injection opioid users [15, 16]. Additionally, methadone has antagonistic properties at N-methyl-D-aspartate (NMDA) receptor, which produces not only analgesic effects but may also mitigate the development of tolerance [21].

Despite its success, methadone is not a benign agent and is associated with several adverse effects, including the potential for abuse. Metabolism occurs through the cytochrome P450 (CYP450), primarily through CYP3A4 and CYP2B6, leading

to variable effects due to enzyme polymorphisms and drug-drug interactions [22]. Another major concern is QT prolongation at effective dosages, also known as methadone toxicity [23]. In this regard, a baseline EKG is recommended for anyone being evaluated to start on methadone treatment. Those at highest risk include the elderly, female gender, heavy alcohol users, cardiopulmonary disease patients, and users of QT-prolonging medications [15]. Additionally, access to a treatment center continues to be an obstacle for patients as some must travel hundreds of miles or into different states for treatment [18, 24]. An alternative strategy to facilitate ease of access may be to allow physician practices to prescribe methadone, which is termed office-based methadone maintenance. This method has been successfully trialed in the USA for patients transferred from traditional methadone clinics [18].

Buprenorphine

Buprenorphine is a partial MOR agonist that was developed in the 1970s for analgesia but was not approved for OUD in the USA until 2002 [25•]. Similar to methadone, it has a long functional half-life that assists with opioid withdrawal symptoms without the euphoric effects. The induction phase usually lasts 1 week with starting doses between 4 and 8 mg with usually no more than 30 mg by the end of the week [20]. The stabilization phase begins at week eight when cravings have reduced until a stable dose has been reached, typically between 16 and 24 mg per day [20]. The maintenance phase begins once a stable dose has been reached and lasts a minimum of one year [20]. Related to its partial agonism, buprenorphine has less potential for the dangerous side effects of opioids but remains capable of mitigating opiate withdrawal symptoms [21, 26]. Any licensed physician under the Drug Addiction Treatment Act of 2000 can prescribe buprenorphine, allowing for office-based treatment of OUD unlike methadone [27].

Buprenorphine is available in multiple FDA-approved formulations for OUD: sublingual buprenorphine, combination sublingual buprenorphine and naloxone, transdermal patch, buprenorphine implant, and monthly injection depot. Buprenorphine is manufactured in a sublingual formulation as a result of its substantial first-pass metabolism and lipid solubility, which results in excellent sublingual bioavailability [21]. Combination buprenorphine and naloxone (Suboxone®) was introduced to discourage intravenous abuse of buprenorphine alone, which can produce a euphoric effect [28]. The low dose of naloxone will only produce withdrawal effects if it is injected intravenously. Transdermal buprenorphine (Butrans™) is available in doses between 5 and 20 mcg/h that is used for chronic pain requiring around-the-clock opioid therapy and may be used for OUD treatment in the future [29]. A long-acting buprenorphine implant called Probuphine was approved by the US Food and Drug Administration in 2016 and delivers a steady state of medication over a 6-month period [30•]. Some initial studies suggested the implant had lower rates of relapse and improved quality of life but may incur more potentially serious side effects from insertion and removal of the implant when compared to sublingual therapy [30•]. The FDA approved the monthly subcutaneous buprenorphine injection depot (Sublocade®) in 2017 with a currently recommended treatment regimen of two 300 mg monthly doses with subsequent 100 mg monthly doses [25•]. Trials are ongoing to assess the formulation's efficacy and the ideal patient population. The monthly injectable produces the highest buprenorphine plasma concentration, and recent studies suggest it may be best for those with greater physical dependence but should be avoided for direct induction due to safety concerns [25•].

Naltrexone

Naltrexone is a semi-synthetic opioid that acts as a competitive antagonist at the MOR and partial agonistic activity at the KOR in the central nervous system [31]. One approved extended-release, injectable formulation of naltrexone exists called Vivitrol® (XR-naltrexone). This formulation was approved by the FDA in 2010 and is available as a 380 mg monthly intramuscular injection [32]. Treatment initiation of XR-naltrexone must occur during a period of abstinence from opioids for 7–10 days in order to prevent acute withdrawal symptoms [33]. A 2018 study comparing XR-naltrexone and sublingual buprenorphine-naloxone shows similar safety and efficacy, although it was more difficult to initiate treatment with XR-naltrexone due to a longer period of opioid abstinence [34]. The difficulty initiating treatment with XR-naltrexone is a well-recognized barrier, and current trials are studying methods outside of opioid abstinence detoxification. A 2017 randomized trial compared rapid induction with a single dose of buprenorphine followed by increasing doses of oral naltrexone (naltrexone-assisted detoxification) until the administration of XR-naltrexone and a 7-day buprenorphine taper followed by a 7-day delay (buprenorphine-assisted detoxification) until the first dose of XR-naltrexone [35]. The study demonstrated improved therapeutic XR-naltrexone initiation among the naltrexone-assisted cohort than the buprenorphine-assisted group, along with improved withdrawal symptoms and treatment dropout rates [35]. Another barrier with naltrexone is screening and monitoring of liver enzymes since it is not recommended in acute liver failure, despite carrying a low risk of hepatoxicity. Although promising, there continues to be obstacles to the successful induction of XR-naltrexone therapy, in addition to treatment continuity concerns that limit its overall clinical utility.

Recent Advances and Future Treatment Options

Although current treatment models have shown efficacy in preventing relapse and maintaining abstinence, approximately 40 to 60% of patients relapse while on MAT [36]. The latest innovations aim to reduce the relapse rate, increase ease of access, and improve upon previous safety profiles. Table 2 provides a summarized list of prospective therapies.

Biologics

An emerging treatment option for OUD is the use of biologics, which entails vaccines or monoclonal antibodies. The model incorporates immunopharmacotherapies, which are defined as the use of specific antibodies, generated from a vaccine response or administered monoclonal antibodies, to target the abused drug in order to prevent action at its targeted receptor [37]. The concept of a vaccine targeting opioids such as heroin, fentanyl, oxycodone, or hydrocodone is unique as a pharmacokinetic approach as it prevents entry of the drug into the central nervous system [38]. This can reduce opioid-related effects such as respiratory depression and bradycardia, yet continue to permit opioid reversal agents such as naloxone and naltrexone to exert their desired effect [39]. A vaccine is beneficial for individuals who have difficulty with adhering to maintenance therapy or is more prone to relapse, as it may prevent the rewarding effects of opioids without requiring stringent dosing (although booster vaccines will likely be required).

Vaccine design for OUD, specifically for heroin conjugate vaccines, has explored an abundance of combinations including haptens, carrier proteins, and adjuvants. The most successful and potentially clinically viable heroin vaccine is a heroin-tetanus toxoid (TT) conjugated with adjuvants alum and cytosine-guanine oligodeoxynucleotide (CpG ODN), which has been used as a benchmark for new vaccine component combinations [40, 41]. This vaccine was studied on rhesus monkeys and mice, demonstrating reduced heroin potency by greater than 15-fold, generating significant anti-heroin IgG titers, and preventing cross-reactivity with other clinically significant opioids [40]. A 2018 study explored the adjuvants TLR3 agonist, a virus-derived double-stranded RNA (dsRNA), and TLR 9 agonist, which is CpG ODN 1826 [41]. Each agonist alone produced strong anti-heroin antibody titers but a combination of the two agonists failed to improve efficacy [41, 42]. Vaccines directed against other opioids such as fentanyl, oxycodone, and hydrocodone have generated positive results as demonstrated by reduced analgesic potency following administration in a mouse model [38].

Designing a clinically viable vaccine for OUD presents several challenges and barriers. The concept of creating an anti-heroin vaccine that can immediately neutralize molecules within minutes requires a fast-acting, highly potent antibody [38]. The rapid metabolism of heroin to 6-acetylmorphine (6-AM) and morphine requires a creative solution to create a vaccine with antibodies to not only the target but its metabolites. A successful model is a hapten design with greater than a 10-fold higher affinity for 6-AM than heroin with no affinity to morphine since morphine does not readily cross the blood-brain barrier [40, 43]. A common issue among all vaccines is developing one that produces an efficacious antibody response, and a heroin vaccine is no different [40, 41]. Even if these hurdles are overcome, the most significant challenge is to show clinical benefit against currently recommended treatment. A 2019 study comparing the heroin-TT conjugate vaccine and continuous depot naltrexone in animals indicates naltrexone decreased the antinociceptive potency of heroin and its metabolites more effectively than this heroin vaccine formulation [43]. This suggests the limited clinical utility of this vaccine formulation as monotherapy for OUD. Despite these findings, the vaccine is shown to attenuate the antinociceptive potency of naltrexone, suggesting substantial promise as an adjunctive therapy for currently approved maintenance therapies [43].

Gene-Targeted Therapy

There is a significant genetic component to OUD with variants and polymorphisms that are potential targets for therapy. Candidate gene studies have identified variants in specific genes that influence OUD risk. For instance, the OPRM1 gene encodes the MOR and has exhibited specific polymorphisms, such as two variants rs1799972 and rs1799971 that alter the downstream reward pathway in those with OUD, rendering it an attractive option for targeted therapy [44]. The issue with this approach is inherent bias, which can leave other relevant genes unaccounted for since the analyzed genes exhibit a known connection to OUD [44]. Advances in computer processing have led to more extensive analyses over a greater number of polymorphisms across the entire genome with genome-wide association study (GWAS). This method has discovered new associations with variants, such as single-nucleotide polymorphisms (SNPs) in potassium voltage-gated channel subunits KCNC1 and KCNG2 [45]. This challenge has the potential to lead to a clinically relevant biomarker for OUD, a task the Psychiatric Genomics Consortium is currently undertaking in a GWAS with over 100,000 addicted patients [46••]. The individual variability with pharmacotherapy for opioid addiction may have a genetic influence implicit through GWAS to identify SNPs that could alter plasma drug levels [45]. Although GWAS has discovered significant variants, these findings have been inconsistent across different studies, implying that OUD is either overwhelmingly polygenic or that the studies are underpowered [44]. CRISPR, a gene-editing method, is a potential therapeutic option for

OUD if there are specific genetic defects that may be changed for prevention [47•].

Biased Agonism

Opioid receptors belong to the G protein-coupled receptor (GPCR) superfamily, which undergoes conformational changes when ligand bound to activate downstream pathways. Initially, the GPCR was viewed as an "on-off" switch for these cellular mechanisms. However, recent evidence demonstrates a functional selectivity or biased agonism at specific receptor-effector complexes, which can induce a specific conformation of the receptor and activate certain pathways [48••]. This feature can be utilized to provide the analgesic effect without the known opioid adverse effects. MOR activation leads to antinociception via G protein-dependent signaling and cyclic adenosine monophosphate (cAMP) inhibition [49]. Opioid adverse effects, such as respiratory depression, are thought to be due to G protein-independent pathways via beta-arrestin interactions, demonstrated in a study of beta-arrestin 2 knockout mice that displayed enhanced morphine analgesia alongside reduce constipation and respiratory depression [50].

Mitragynine is a natural product derived from the plant kratom that binds the MOR and activates G protein signaling, providing strong analgesia without beta-2 arrestin recruitment [51]. It is used as a medicinal plant in parts of Asia for fatigue and pain but is classified by the drug enforcement agent (DEA) in the USA as a schedule I drug, limiting further investigation of its therapeutic potential [52, 53]. Oliceridine (TRV130) is a biased MOR agonist discovered by Trevena with strong G protein signaling that exhibits analgesic efficacy equivalent to morphine with weak beta-arrestin 2 recruitment [48••]. In rodent studies, it produced less respiratory depression and a reduction of tolerance compared to morphine [54]. Repetitive treatments, however, demonstrated similar gastrointestinal dysfunction [54]. TRV130 is the first G protein-biased MOR agonist to enter clinical trials, undergoing phase III clinical trials in 2017 as a next-generation intravenous opioid analgesic for moderate-to-severe pain in the post-operative period [48••]. The FDA rejected Trevena's drug application for Oliceridine in 2018 citing concerns for abuse and overdose potential similar to other opioids. Trevena reapplied earlier this year to collect data on QT prolongation and confirm levels of an inactive metabolite [55].

PZM21 is another G protein-biased MOR agonist with undetectable beta-arrestin 2 recruitment, discovered by simulating 3 million molecules binding to the computer model MOR crystal structure, unveiling a compound that is chemically different from other opioids [56]. The initial study demonstrated a highly specific and potent analgesic equivalent to morphine with low MOR internalization [56]. However, a 2018 study demonstrated dose-dependent respiratory depression in a similar fashion to morphine, dampening the initial enthusiasm [56, 57]. 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(indole-7-carboxamido)morphinan (NAN) is a G protein-biased partial agonist at the MOR and DOR with low efficacy but high efficacy at the KOR [58•]. In rodent studies, NAN was shown to antagonize agonist-induced MOR internalization and intracellular calcium release, producing less withdrawal symptoms compared to naltrexone at similar doses [58•]. NAN may have therapeutic potential by mitigating opioid-induced adverse effects, a mechanism similar to naltrexone.

Ion Channel Targets

Novel analgesic therapies are targeting afferent pain pathways through specific channel blockades that include voltage-gated sodium channels, voltage-gated potassium channels, and transient receptor potential vanilloid 1 receptors (TRPV-1). These novel analgesic targets are capable of being utilized in OUD treatment. Voltage-gated sodium channels Nav 1.7 and Nav 1.8 isoforms are heavily expressed at the dorsal root ganglion (DRG) and are crucial components in pain transmission by initiating and propagating action potentials [59, 60]. Tetrodotoxin and saxitoxin are natural toxins that act as inhibitors at Nav1.7 and Nav1.8 that have promising antinociceptive effects in preclinical pain models [59]. Additionally, synthetic acyl sulfonamide Nav1.7 inhibitors have shown to be effective analgesics in mouse models [61]. Voltage-gated N-type calcium channel Cav2.2 is concentrated at presynaptic nerve terminals responsible for nociceptive activity [62]. Ziconotide is a synthetic ω-conotoxin developed for severe refractory pain in chronic pain patients that inhibits Cav2.2 by blocking channel pores but is limited in its clinical utility due to required intrathecal administration and a narrow therapeutic window [63]. CNCB-2 and physalin F are currently investigated Cav2.2 channels inhibitors with potentially improved efficacy [64, 65]. TRPV-1 plays a role in inflammatory pain, as these channels are concentrated at DRG neurons activated by various stimuli including capsaicin [66]. Activation by capsaicin can initially lead to hyperalgesia; however, it is hypothesized long-term exposure can deactivate the TPRV-1 channels and disrupt the afferent nociceptive pathways [67]. Resiniferatoxin is a TPRV-1 agonist with greater efficacy than capsaicin that has demonstrated long-lasting analgesic effects with intrathecal administration in animal models and a human subject with severe cancer pain [68]. Although these targets are studied as novel analgesics, they are also prospects for use in OUD treatment.

Alternative Opioid Receptor Agonists

There are three subtypes of opioid receptors: μ (MOR), κ (KOR), and δ (DOR). A majority of opioids are primarily MOR agonists resulting in analgesia with known detrimental

effects; however, there is extensive research utilizing agonistic activity at the KOR and DOR subtypes. The KOR binds to endogenous dynorphins producing an analgesic effect in a similar biochemical nature as MOR with adverse effects such as dysphoria and sedation [69]. Although investigative efforts have focused on creating a new analgesic through this receptor, it also has the potential for OUD treatment by mitigating withdrawal symptoms with less respiratory depression compared to MOR agonists [70]. Additionally, the dysphoric effects, perceived as an adverse effect, are preferred in OUD treatment as it reduces their dependence potential compared to the reinforcing euphoric effects of MOR agonists [71]. Butorphanol is a synthetic opioid acting as a partial MOR agonist with a higher affinity for KOR that has demonstrated greater efficacy and less dependence when compared to morphine [72].

The DOR binds to endogenous enkephalins producing an analgesic response similar to the other opioid subtype receptors [69]. Similar to KOR agonists, DOR agonists are potentially useful for OUD treatment with favorable anti-depressant and anti-anxiolytic effects [73]. Although common opioid side effects such as respiratory depression and constipation are not associated with DOR agonists, rat models demonstrate an increase in convulsive activity [48••]. KOR and DOR agonists are potential targets for OUD treatment due to their quality analgesic effects and desirable side effect profile.

Other Therapies

OREX-1019 is a compound that imitates the mechanism of buprenorphine/naltrexone and produces a dose dependent in MOR agonist effect of remifentanil with the added benefit of low abuse potential [74]. It demonstrates promise for another option in current treatments for OUD, aimed particularly at relapse prevention [74]. The medical cannabinoid is a non-conventional therapy that has regained traction since the legalization of marijuana in several states. Both rodent model and pilot clinical studies indicate exposure to cannabidiol (CBD) reduces the opioid reward effect while also diminishing cravings, with results lasting weeks after CBD exposure [8]. Synthetic cannabinoids dronabinol and nabilone are partial agonists towards cannabinoid receptors that are under investigation for their analgesic effects [75]. Alterations to the cholinergic system have effects on the opioid reward circuit in the central nervous system, representing a potential therapeutic target [76]. Related to the lack of pharmacologic specificity in targeting acetylcholine receptors, this has been challenging to study [76]. However, cholinesterase inhibitors exhibit promising results in clinical studies by reducing opioid adverse effects without reducing analgesia [76]. Lorcaserin is a 5-hydroxytryptamine agonist that has shown a dose-dependent abstinence signal in smokers, with a 2017 rodent study demonstrating suppression of oxycodone self-administration and cue-induced reinstatement [38, 77].

Conclusion

The opioid epidemic continues to inflict devastating consequence on the health of the USA and worldwide. Substantial strides have been made to increase awareness of OUD as a serious healthcare issue and facilitate access to appropriate management options. Significant improvement is required with regard to treatment efficacy, availability, and retention. Enhancements to current treatment options have shown promise, although the medical advancements of biologics, gene-targeted therapy, and biased agonism demonstrate even greater potential. Ultimately, the clinical viability of current research may determine the resolution of the opioid epidemic.

Compliance with Ethical Standards

Conflict of Interest Drs. Kuppalli, Seth, Orhurhu, Urits, Hunter, Alan Kaye, Adam Kaye, and Jones have no conflicts of interest. Dr. Gulati is a medical advisor for AIS, a consultant for Medtronic, Flowonix, SPR Therapeutics, Nalu Medical, Bausch Health. Dr. Adekoya has an active educational grant from Medtronics.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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