Pharmacological Progress of Biased Agonism of the μ Opioid Receptor

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Abstract

Traditional μ opioid receptor agonists have been heavily researched, largely due to the negative side effects observed in opioid drugs such as morphine and oxycodone. The opioid epidemic continues to plague the United States and without a solution, progress will be unable to proceed. Recently, biased agonism has come to the forefront of research as an alternative method of opioid development to optimize pain relief and minimize addictive properties with other negative side effects. This review evaluates recent evidence of the development of opioid pharmaceuticals demonstrating biased agonism. These include herkinorin, mitragynine, PZM21, and TRV130 or oliceridine. Biased agonism is a promising approach for drug development; however, it is still unclear if it will truly improve the therapeutic index of the analgesic effects while minimizing adverse effects in vivo.

Introduction

Opioid medications have been available for centuries to treat a variety of maladies; however, they remain in clinical practice due to their unmatched effects of pain relief (1–2). Over time, the adverse effects of this medication class became apparent through abuse, dependency, and addiction arising in patients seeking to ease acute or chronic pain. In the United States, this has led to a nationwide epidemic of opioid substance abuse. According to the 2015 National Survey on Drug Use and Health, an estimated 37.8% of the United States population self-reported using prescription opioids that year, 4.7% of the population self-reported misusing prescription opioids, and 0.8% of the population reported an opioid misuse disorder (2). As of 2019, these rates have been rising exponentially because it has not yet been possible to achieve the same level of analgesia opioids provide without adverse effects (1). The prevalence of opioid use and misuse in addition to opioid-related harm and death have generated great concern throughout the country. This has led to various interventions by the justice system, social services, public health officials, and novel developments in neuropharmacological research. Opioid pharmaceuticals already in clinical practice and new drugs in development are being analyzed to enhance understanding and potentially optimize their physiological action on a molecular level.

The International Union of Basic and Clinical Pharmacology (IUPHAR) defines the receptors that interact with endogenous and exogenous opioids as opioid peptide receptors (OP) (4). The first of these receptors to be discovered was defined as the μ opioid peptide receptor, abbreviated MOP or MOR, and named for its affinity for morphine (5–6). MOR is distributed throughout the central nervous system, most notably in the periaqueductal gray, raphe magnus nuclei, thalamus (brain areas associated with the sensation and processing of painful stimuli – locus coeruleus) and in the superficial laminae of the dorsal horn of the spinal cord (3, 7–8). Opioid consumption triggers dopaminergic neurons in the nucleus accumbens, which activates feelings of reward and motivation, creating conditions susceptible to opioid abuse, withdrawal, dependency, and addiction (9). Over time, more evidence is being discovered to no longer classify opioid receptor agonist

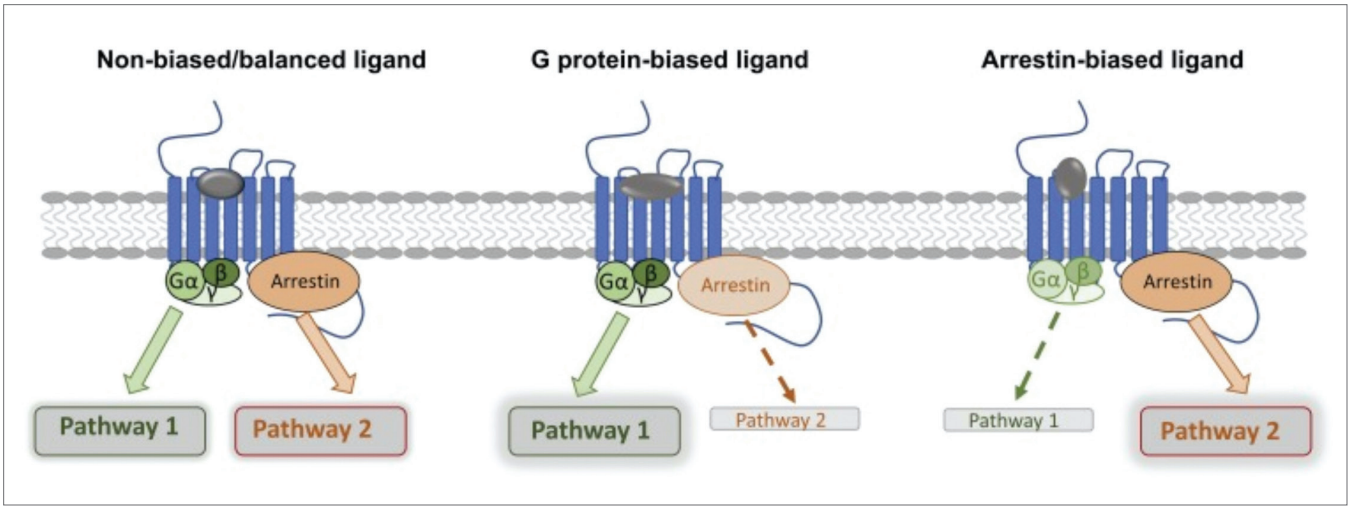

Figure 1. This diagram shows an example of biased agonism signaling activating either G protein- or arrestin-dependent signaling (50).

pharmaceuticals by their "strength," but by the different molecular pathways that are activated when the drug binds to the receptor. A concept being investigated recently with the goal of producing analgesia while reducing opioid-related side effects like respiratory depression is biased agonism.

Even though it has been known by many different names since its application to opioid receptors in 2007 (10), biased agonism has shown potential to be a novel pharmacological treatment to aid in the opioid epidemic. Biased agonism describes when a ligand preferentially binds and activates one of multiple signaling pathways over another (11). An example of biased agonism involves the activation of the G-protein MOP and its altered recruitment of β-arrestin (Figure 1). Initially, the rationale for biased agonism stemmed from experiments that used β-arrestin knockout mice in which MOP activation produced analgesia, but lacked some of the negative associated effects of opioid administration (12). Studies show a range in bias of G-protein and β-arrestin recruitment, from partial to full agonism of MOP, with a strong correlation of a large therapeutic window for G-protein biased ligands (13). It is difficult to produce a specific calculation of bias; however, an approach that generates an array of biases in a single scaffold is useful for translation of studies from *in vitro* to *in vivo* (12). Ultimately, biased agonism is a promising approach for analgesic drug discovery, but more evidence needs to be gathered that analyzes the pharmacokinetics, antinociception, and side effects before any biased agonists can be incorporated into the treatment of pain.

Like all medications, opioids have a wide array of adverse reactions. The major side effects in question are the severe gastrointestinal distress and respiratory depression; however, many individuals experience other mild adverse side effects. Another side effect to note is hyperalgesia, which was initially discovered when studying morphine in 1987 (14). The β-arrestin signaling, downstream of the μ opioid receptor is linked to both respiratory depression and constipation but is not related to the addictive properties of opioids (15).

The dopamine reward pathway is modulated via the recruitment of β-arrestin, therefore it should be thought to decrease addictive properties. *In vitro* studies support β-arrestin's involvement with dopamine receptors one and two; however, studies *in vivo* have given a more complex picture (16). In knock-out mice, lack of β-arrestin results in reduced or minimal behavioral responses to certain drugs that affect the dopamine reward system, meaning that it is potentially involved in other cellular processes (16). Despite completion of studies to evaluate the involvement of the dopaminergic pathway, more refined models are needed to further investigate the involvement of dopaminergic pathway and MOP signaling in addition to biased agonism (17).

Research provides substantial data that displays a correlation between biased agonism of MOP and decreased opioid-related adverse effects. Recent developments in MOR biased agonists have produced four potential candidates to enter into pharmaceuticals. Herkinorin, mitragynine, PZM21, and TRV130 (oliceridine) provide promising research in animal models, but more research will need to be completed in clinical trials for each before they are considered for integration into medical practice.

Methods

A literature review was conducted using Google Scholar and PubMed using combinations of the following terms: biased agonism, bias factor, mu opioid receptor, herkinorin, mitragynine, TRV130, oliceridine, PZM21, beta-arrestin, kratom (the plant from which mitragynine is derived). These therapies were included based on their actions as biased agonists and their significant exclusivity or notable selectivity for the μ opioid peptide receptor. If potential therapies did not meet these criteria or did not have sufficient evidence available, they were not included in this review.

Discussion

Herkinorin

Salvia divinorum is a plant that originates from the sage family and has been used in spiritual practice by the Mazteca Indians of Oaxaca, Mexico, due to its hallucinogenic experiences (18). In 2005, when analyzing the main component of *S. divinorum*, Salvinorin A, its analog herkinorin was discovered (18). Herkinorin is a neoclerodane diterpene that is the result of de-acetylation of salvinorin A.

Herkinorin has been the target of numerous studies during the last decade to analyze its analgesic effects. A 2012 experiment used the formalin test in rats in order to assess acute and inflammatory pain (19). Herkinorin was found to possess antinociceptive properties that are reversible with the antagonist naloxone, and activity is relatively localized to injection sites (19). Additionally, tolerance testing has been performed in rats to analyze if herkinorin would produce similar tolerance that is seen in traditional opioids like fentanyl or morphine. Traditional opioids resist tolerance after repeated paw injections due to chronic inflammation, so in order to adequately assess the tolerance potential of herkinorin, a secondary approach was taken using a systemic pump (20). Following systemic treatment, morphine tolerance was induced in the animals whereas herkinorin maintained antinociceptive properties and effectively reduced formalin-induced flinch responses (20). The formalin test functions as a measure of tonic inflammatory pain, with an increased flinch response displaying that the animal has developed tolerance to a previously effective dose of the drug in question (21). Primarily, herkinorin causes antinociception ipsilaterally, making it unclear whether there is selective activity in the periphery, or if it is unable to cross the blood-brain barrier, meaning that more studies involving its pharmacokinetics are necessary (20).

Herkinorin does not cause recruitment of β-arrestin-2 to the μ opioid receptor and does not result in internalization, leading to the question of its antinociceptive effects *in vivo*. More recently, a 2019 literature review from Frontiers in Psychiatry has noted the significance of herkinorin's ability to promote the phosphorylation of ERK1/2 without recruitment and signaling of β-arrestin-2 (21). This article notes that the lack of internalization of the μ opioid receptor could potentially improve the adverse drug effects that are seen in traditional opioids like morphine, making it a potential analgesic (21). While other Salvinorin A derivatives are more selective for the μ opioid receptor than herkinorin, it is important to note that

herkinorin has the highest analgesic potential for application (21). It should also be recognized that while herkinorin is in fact a biased agonist at the μ opioid receptor, it is a full agonist at the κ opioid receptor (15).

In the future, more work needs to be done in the studies of herkinorin to ensure that it does not induce physical dependence. In 2018, the FDA publicized the potential of herkinorin as a potential analgesic, but it has not yet gone through clinical trials (22). In order to further understand the potential for pharmacological use, herkinorin will need to undergo various clinical trials that analyze the potential for abuse and dependence in humans. So far, herkinorin is a promising alternative for opioid therapy in the future.

Mitragynine

Mitragynine has been used for over 100 years in traditional medicine as it originates from the evergreen tree *Mitragyna speciosa* in the jungles of Southeast Asia (23). Mitragynine is a terpenoid indole alkaloid that has primarily been used in the illicit market; however, recent studies prove hopeful for its abilities to become a recognized pharmacological drug.

While the exact metabolic mechanism is unknown, there are multiple possibilities to explain its metabolism. Through oxidation, [bis(trifluoroacetoxy)iodo]benzene acts on mitragynine to produce 7-OH (23). It is also hypothesized that CYP3A is able to function in this conversion as well, and the varying degrees of conversion explain some of the variance in the literature. After it was discovered that CYP3A was the primary metabolic pathway for conversion in enzyme preparations, mitragynine was incubated in human liver microsomes (HLM) alone and in the presence of ketoconazole, a CYP3A inhibitor (23). The presence of the ketoconazole inhibited the degradation of mitragynine to 7-OH in both the human and mouse liver microsomes. Additionally, it was found that while there was significant conversion of mitragynine to 7-OH in the HLM, mitragynine had low stability in the HLM (23). This contradicts a 2014 analysis that found mitragynine to be metabolically stable in HLM and S9 fractions. It was found to be unstable in simulated gastric fluid, but stable in simulated intestinal fluid in this study (23). The researchers concluded that the data could indicate the possibility of drug interactions if administered with drugs that are P-glycoprotein substrates (24). The conversion of mitragynine to 7-OH has also been examined in-vivo in mice (23, Figure 2). It was found that both mitragynine and 7-OH were found in plasma and the brain, but 7-OH was only a minor metabolite (23). More evidence needs to be collected to determine the pharmacokinetics of mitragynine, especially to determine the role of 7-OH as a potent analgesic in humans.

Mitragynine and its analog, 7-hydroxymitragynine (7-OH), are both biased agonists of the μ opioid receptor and potentially have a larger therapeutic window between analgesia and the adverse side effects of traditional opioids (23). It is suspected that the severe respiratory depression that is seen in other opioids would not occur in mitragynine, as the 7-OH metabolite is seen to be a partial G-protein biased agonist at the μ opioid receptor (23). Mitragynine functions as a partial agonist of the human μ opioid receptor, and a competitive antagonist at the κ and δ opioid receptors (25). A lack of β-arrestin recruitment after receptor activation allows for a potentially improved therapeutic profile. This is due to a binding position that differs from classic opioids, creating a safer *in vivo* profile (11). Promising research portrays the potential for pharmacological use of mitragynine; however, controlled clinical trials will still be necessary to determine the safety profile of the drug *in vivo*.

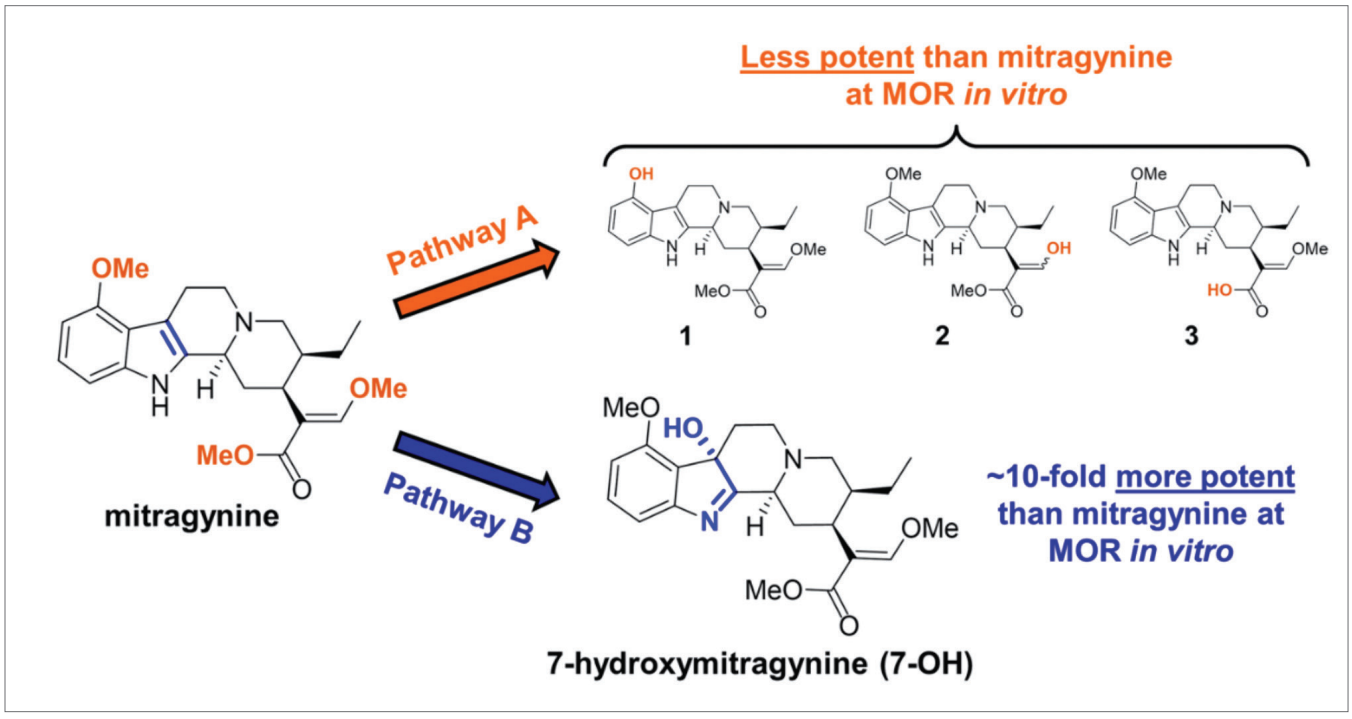

Figure 2. Molecular structures and metabolic transformations of mitragynine (23).

PZM21

Developed in 2016 via structure-based optimization, PZM21 is a compound that exhibits biased agonism at the μ opioid receptor (15). This experiment used structure-based docking to the μ opioid receptor which visualized the bonding between the inactive receptor and compounds under investigation (15). It was found that PZM21 has a double hydrogen bond coordination not seen in previously studied opioid ligands, and was able to activate the receptor with low levels of β-arrestin 2 recruitment (15). PZM21 is selective for MOP after comparison to 316 other GPCRs despite its structural dissimilarities to traditional opioid drugs (15, 26). Based upon ligand bias calculation, PZM21 has undetectable β-arrestin recruitment to the μ opioid receptor (15, 25). The PZM21 compound has undergone various alterations to its chemical structure to determine which components deplete or enhance its activity as a biased MOR agonist. Following its creation, it was determined that the benzodioxolane group within the structure of PZM21 is required to prevent β-arrestin recruitment and μ opioid receptor selectivity (28). However, in a subsequent study (29), it was determined that replacing the hydroxyl group of a phenol with naphthalene in PZM21 would further decrease β-arrestin recruitment while maintaining selective agonist activity at MOP (Figure 3).

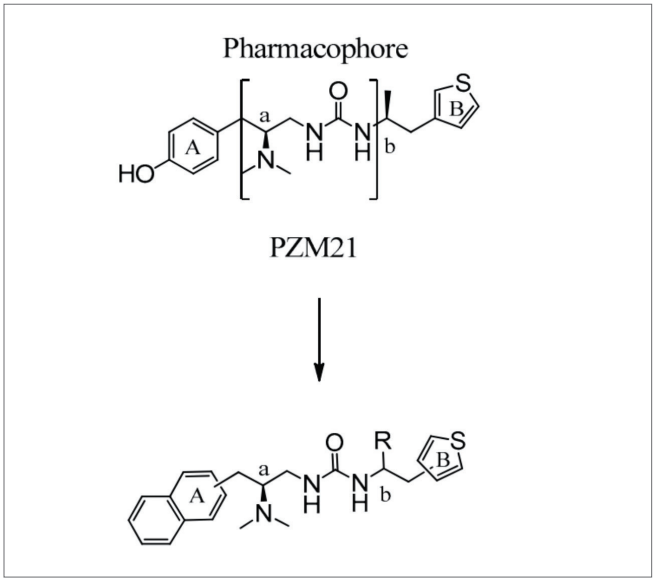

Figure 3. Structure of PZM21 before and after naphthalene replaces the hydroxyl group on ring A (29).

The effects of PZM21 have not been tested in humans; however, several studies have been conducted to determine its functions in rats. PZM21, like other biased μ opioid receptor agonists, was developed with the intention to decrease opioid-related adverse effects including respiratory depression, constipation, hyperalgesia, dependency, and addiction. PZM21 is able to cross the blood-brain barrier and produces analgesia without altering spinal reflexes as determined by a tail-flick assay in rats (15). Upon molecular analysis, PZM21 inhibited serotonin, dopamine, and norepinephrine neurotransmitter transporters in addition to inhibition of the hERG ion channel (15). By inhibiting neurotransmitter transit, the reward pathway is inhibited, thus preventing opioid-induced reinforcement. A conditioned place preference response test was administered to confirm inhibition of reward and reinforcement activation in rat behavior (15, 30). hERG channel inhibition is an increasingly important safety component in development of novel pharmaceuticals (31). hERG activation is associated with potassium channel opening in the heart, causing dangerous arrhythmias that can be visualized as prolonged QT segments on an electrocardiogram (31). No adverse effects of respiratory depression were reported in the rats following PZM21 administration (15). In comparison to morphine, PZM21 was considered to be a more effective analgesic and produced negligible side effects upon initial analysis (15).

Despite promising results from its inception, there is a lack of evidence in initial studies regarding the chronic effects of PZM21 administration. One subsequent analysis (32) associated systematic PZM21 with low doses inducing hyperalgesia and both high and low dosages causing the development of chronic pain over time, called hyperalgesic priming. However, hyperalgesia at doses much lower than therapeutic doses is a common phenomenon associated with opioids, initially discovered by studying morphine in 1987 (14). Based on chemical analysis of PZM21 (28), the future of biased μ opioid receptor agonists is dependent upon compounds which contain benzodioxolane and alkyl benzene groups. These modifications have limited, but promising evidence towards production of maximized analgesic effects and enhanced ligand bias. As of 2020, there are no active clinical trials for PZM21 being completed through the NIH.

TRV130 (Oliceridine)

TRV130 was first introduced by pharmaceutical company Trevena in 2013 to minimize respiratory and gastrointestinal side effects of opioids for the treatment of postoperative pain (33). When compared to morphine, TRV130 had 86% lower β-arrestin recruitment to MOP (33). TRV130 is thought to be MOP selective based on a stabilizing interaction with asparagine at position 2.63 (34). κ and δ opioid receptors contain valine and lysine in the same position respectively and do not produce the same stabilization (34). This provides additional context regarding ligand binding interactions and allosteric modulation of MOP. TRV130 progressed into further clinical trials due to improved opioid-related side effects such as respiratory distress and decreased gastrointestinal motility, compared to the effects of morphine observed in mice and rats (33). An additional experiment was completed using rats to further explore the therapeutic index of analgesia and respiratory suppression, adequate hERG inhibition, and to refine the chemical structure of TRV130 (35). TRV130 was first administered to humans in 2013 for initial determination of dosage, tolerability, pharmacokinetics, and pharmacodynamics (36). CYP2D6 was identified as a cytochrome complex with variability which may affect the clearance of TRV130 from the body (36). In a subsequent analysis involving humans, TRV130 was determined to have quicker, more efficacious analgesic effects as compared to morphine or placebo at doses of 3 milligrams and 4.5 milligrams (37). The decreased engagement and internalization of β-arrestin along with decreased receptor phosphorylation was found to result in reduced

respiratory depression and gastrointestinal dysfunction when initially studied in rodents (37). When analyzing respiration in humans, TRV130 was determined to produce a transient reduction in respiratory drive, but was shorter in duration and lower in intensity as compared to morphine (37). This was a randomized, double-blinded study with 29 participants who completed the course of treatment in 2014 which included a thermal assay called a cold pain test to measure analgesia. It was as early as this publication that participants displayed dependence behaviors measured by a likability scale, demonstrating an abuse potential for TRV130 (38–40).

Throughout the clinical trials, the effects of TRV130 were often compared to the effects of morphine, but not hydrocodone or oxycodone. Oxycodone has a greater potential for abuse and has a greater annual consumption in the United States as opposed to morphine (1, 41). In one analysis, the analgesic action of TRV130 was compared to that of oxycodone in rats exposed to thermal stimuli which showed similar patterns of significantly diminished pain sensation (38). This study also included comparable self-administration behaviors, which presents evidence that TRV130 may have a similar abuse potential to oxycodone (38, 39). Conversely, TRV130 administration in rats did not cause conditioned place preference, indicating a decreased activation of the dopamine-induced reward pathway and reducing opioid-induced reinforcement behavior (21, 30).

It is important to note that the authors of TRV130 clinical trials have disclosed financial conflicts of interest including but not limited to consulting, employment, research funding, and owning stocks in pharmaceutical companies such as Trevena, Inc. and Lotus Clinical Research LLC (33, 35-37, 42-48). In February 2016, the FDA approved TRV130 for breakthrough status as oliceridine for intravenous administration (49). In January 2018, the FDA approved a drug application for oliceridine as a schedule II narcotic for use in a hospital or monitored clinical setting (49). FDA has declined to approve oliceridine due to concerns of its efficacy and safety which did not show improved therapeutic efficacy as compared to morphine (28, 29).

Conclusion

Based upon the available evidence, it is unclear whether biased agonism of the μ opioid peptide receptor is correlated with optimal analgesia and minimal opioid-related adverse effects. The research completed has enhanced understanding of current and newly developed pharmacotherapies in addition to gaining knowledge about the μ opioid peptide receptor. The therapies mentioned are being tested for the treatment of acute pain and are often completed in animal models, if not cellular models. This poses a problem for implementing treatment in humans because MOP is expressed in varying tissue types and even cellular types throughout the body, therefore MOP signaling and β-arrestin involvement will change throughout the body due to varying cellular and tissue contexts.

While the current evidence surrounding biased agonism of β-arrestin recruitment of μ opioid receptor is promising, more evidence regarding the definition and specific action of biased agonists is needed. Degrees of bias for MOP without β-arrestin recruitment for pharmaceuticals ranges from 0.4-fold to 100-fold differences (13, 17). TRV130 provides an example of the risks that this lack of definition can pose to patients, thus future pharmacologic development should proceed with caution. Some suggested approaches for future research in biased agonism include improvements in methods to evaluate bias factor and β-arrestin recruitment *in vivo* and in methods to better predict the ratio of therapeutic benefits to adverse effects (50). The current evidence shows promise for the future of biased agonists of MOP and downregulation of β-arrestin recruitment, however this should be considered to be only a potential contributor to solving the opioid epidemic currently plaguing the United States.

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Disclosures

The authors have no financial conflicts of interest to disclose.

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