Current and Prospective Opioid Analgesics: Assessing their value for ongoing research & promise for therapeutic/clinical use

*Name & Affiliation not given due to Blind Review guidelines

Abstract

Opioid analgesics, though among the most potent tools for pain relief at our disposal, sit at the epicenter of a growing clinical and societal crisis. Currently, most opioid analgesic drugs like fentaNYL function at the μ-OR, which has notably been linked to respiratory depression, constipation, and high abuse potential. In fact, the abuse of fentaNYL alone has led to over 80,000 deaths in the United States just in the last year. As demand for safer analgesics has surged, the field has responded with a range of innovative approaches, many involving the strategic use of other opioid receptors such as the δ-OR, κ-OR, and NOP. Each of these receptors plays a role in analgesia, yet also creates a unique set of complications to accompany it. To combat this issue, dozens of opioid agonists and antagonists are being developed. We have seen new concepts such as biased and bitopic agonism emerge, presenting an updated outlook on how these drugs function. Thus far, no single method has yielded a drug to outcompete fentaNYL in the global market. This review not only brings to light the new classes of opioid drugs, but also discusses their relevance to the field. Moreover, many prevalent examples of opioids and their mechanisms are discussed throughout the paper, giving clinically-backed insight into the drugs' varying levels of efficacy.

Introduction

Since first being recorded by the Sumerian Empire for their hypnotic properties in 3400 B.C., opioids have been employed by a myriad of civilizations, including the Egyptians, Indians, Chinese, and Greeks. There is even evidence showing two of the oldest medical systems using opium derived from poppy seeds to include analgesia. In Ayurveda (An ancient medical practice from India) "Ahiphena" or poppy seeds were used for sedation, pain relief, and gastrointestinal relief. Similarly, in Chinese Traditional Medicine, the same plant, though here called "Ying Su Ke", was used for pain and cough suppression. Through the years, opioid use has been refined through medical, religious, and recreational contexts,

ultimately culminating in the isolation of morphine in the early 19th century and synthesis of fentaNYL in the 20th century.

Morphine, the first true opioid analgesic, has been one of the most prominent drugs in medical and pharmaceutical history (Krishnamurti & Rao, 2016). Isolated by Friedrich Sertürner in Germany in 1804, this opium poppy derivative broke ground in the research of analgesics. Morphine functions by binding to the μ-opioid receptors in the brain and spinal cord to block the perception of pain (Zhuang et al., 2022). Its introduction into the clinical and therapeutic settings revolutionized pain management, saving countless lives. In fact, during the American Civil War, Morphine was widely employed as an analgesic via hypodermic injection or laudanum (Reilly, 2016). Beyond that, however, it helped the scientific community understand addiction, receptor theory, and tolerance. These ramifications have made morphine both a medical breakthrough and cautionary tale, sparking the development of newer, safer, and more potent opioid analgesics.

This undertaking eventually gave rise to a new breed of opioid analgesics optimized for the clinical field: synthetic opioids. The most notable of which is fentaNYL, an opioid-based drug first synthesized in Belgium by Dr. Paul Janssen in 1959. This drug is widely accepted as the greatest discovery in the field since the introduction of morphine, of which it is 50–100 times more potent (Zhuang et al., 2022). Originally developed for surgical anesthesia and severe pain management, fentaNYL's high lipid solubility and rapid onset coupled with its relatively low cost have made it one of the most universal analgesics of the modern world. However, its high potency and rapid onset make even 2 mg of this substance lethal, underscoring the need for precaution and safety when in use (Bird et al., 2023). Nevertheless, as of now, fentaNYL is still favored in most developed nations for analgesia.

In America, the for-profit healthcare & pharmacological system artificially inflate the price of life-saving medicines, making them inaccessible to the majority of Americans living under the poverty line. Thus, many Americans are forced to resort to unlicensed distributors to attain their prescriptions at a reasonable price. Unfortunately, however, this results in thousands of preventable deaths every year. The issue is exacerbated by the recreational use of opioids and high mental health crisis rates (usually resulting in substance abuse) among American youths. Moreover, many medical professionals are encouraged to use opioids to treat pain

therapeutically, creating high addiction rates in many chronic pain patients. Together, these issues—among many others—have plunged Americans into an opioid crisis.

This problem, however, is not uniform throughout the world. Nations like Switzerland, Rwanda, Saudi Arabia, New Zealand, China, Japan, South Korea, and Singapore have been able to keep drug abuse rates low through strict pharmaceutical monitoring and low prescription medication costs. In stark contrast, regions like Latin America, Eastern Europe, Central & South Asia, and Africa are globally lambasted for being illicit drug hotspots & trafficking routes. Overall, this disparity can be attributed to an array of factors from cultural taboos to geopolitical connections to government regulations.

Opioids, unlike other substances like marajuana or nicotine products, can be immediately fatal. While most addicting substances create long-term issues sometimes leading to cancer, opioid drugs create respiratory depression in overdose, thus making them fatal in minutes if not counteracted with an antagonist drug. To combat this, many disparate approaches are being taken by researchers and corporations alike. One prevalent avenue involves exploring the different opioid receptors.

Opioid receptors are a specific type of GPCR (G-Protein-Coupled-Receptor) located throughout the brain, spinal cord, and peripheral nervous system. Currently, we know of four main types of these receptors: μ-OR (mu-opioid-receptor), κ-OR (kappa-opioid-receptor), δ-OR (delta-opioid-receptor), and NOP (Nociceptin/Orphanin Receptor) (Wang et al., 2023). Each plays a distinct role in analgesia, pain management, and the effects of both endogenous and synthetic opioids. The μ-OR has historically been used for the majority of analgesic drugs, including morphine, heroin, oxycodone, and fentaNYL. It governs euphoria and analgesia, but its use also often leads to respiratory depression and addiction (Zhuang et al., 2022). The κ-OR also deals in the domain of analgesia, but comes with the complications of dysphoria and hallucinations. Whilst it has historically been overshadowed by the μ-OR, and disregarded due to its hallucinogenic properties, it has had renewed interest in recent years for non-addictive therapies (Beck et al., 2019). On the other hand, the δ-OR continues to dispel researchers due to its low selectivity and efficacy. For while it may be another route to drug discovery, it lacks promise, and thus intrigue in the receptor is scarce. More

recently, an opioid-like receptor has taken the international stage. The Nociceptin/Orphanin Receptor, being the newest of the four, has been shown to play a part in stress, mood regulation, and pain. As it has shown reduced side effects in comparison to its counterparts, it represents a promising target for next-generation pain killers (Lu et al., 2021; Cipriano et al., 2024).

In addition to exploring the use of different receptors, two major pathways to mitigating side effects have emerged in the field: bitopic and biased ligands. Bitopic ligands work by interacting with both allosteric and orthosteric sites, offering enhanced signaling control (Gado et al., 2022). Biased ligands present a way to activate only certain signaling pathways preferentially. They aim to retain the therapeutic effects while minimizing the complications (Stahl et al., 2021). Until now, opioid drug design focused primarily on orthosteric sites, but recent efforts with biased and bitopic signaling have yielded some positive results, making them a popular topic for continued research.

These discoveries have sparked a surge of interest in the field. Soon after they arose, we saw innumerable researchers begin leveraging these concepts to address the opioid crisis. When hundreds of ligands entered the screening pipeline at once, they quickly overwhelmed existing infrastructure and techniques, underscoring the need for faster, more scalable approaches. With aid from new technologies like high-throughput screening (HTS), scientists are now able to test thousands of compounds simultaneously at a fraction of the cost, significantly accelerating drug discovery.

Alas, with such a vast repertoire of recent innovation in the field, pinpointing promising candidates has become a highly time-intensive task for researchers new to the field. Fortunately, this review aims to sift through the growing body of opioid ligand candidates and identify those with the most consistent reproducible therapeutic and clinical promise.

Methodology:

To report the trends in the field of opioid analgesic drugs, this review utilized primarily qualitative data drawn from open-access sources through PubMed. As the focus of this paper covers next-generation opioid agonists and antagonists, and

sources of quantitative data varied greatly between labs for many of these drugs, it would have been counterproductive and scientifically irresponsible to include data collected through such heterogenous methods. The most accurate method of discussing the various opioid agonists and antagonists was by reviewing clinical studies and reporting trends and inconsistencies in the current data. By using this methodology, this article is able to accurately display the current landscape of the field of opioid agonists and antagonists while mitigating bias through reference of a wide breadth of sources and studies yet still maintaining accuracy.

Discussion:

Body Section 1: Analysis & Overview of μ-OR, κ-OR, δ-OR, and NOP

The main opioid receptors—μ-OR, κ-OR, δ-OR, and NOP—are part of the Class A G protein-coupled receptor (GPCR) family. GPCRs are a large group of cell-surface receptors that transmit signals into the cell via the activation of intracellular G proteins (Wang et al., 2023). When discussing opioid receptors and their agonists/antagonists, a cascade of intricate processes must occur to create the desired, and undesired, effects that we're familiar with.

As per our current understanding of said processes, we focus on three main proteins within the body: $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. While their respective roles in the system are not yet fully understood, recent findings have linked G protein subunits ($G_{\alpha i/o}$ and $G_{\beta\gamma}$) to primarily positive effects (i.e. analgesia and sedation) and β-arrestin to mainly negative effects (i.e. respiratory depression, constipation, and tolerance development) (Bateman & Levitt, 2021; Faouzi et al., 2020; Mores et al., 2019). Opioids usually activate $G\alpha_{i/o}$ and $G_{\beta\gamma}$, subsequently phosphorylating the receptor, causing β-arrestin to bind to it. Thus, we receive nearly every effect, every time. To that end, many researchers believe that creating ligands biased to G proteins—or even just one subunit of G protein—over β-arrestins could be the foundation for many next generation opioid drugs, hopefully aiding the opioid addiction crisis by mitigating tolerance issues.

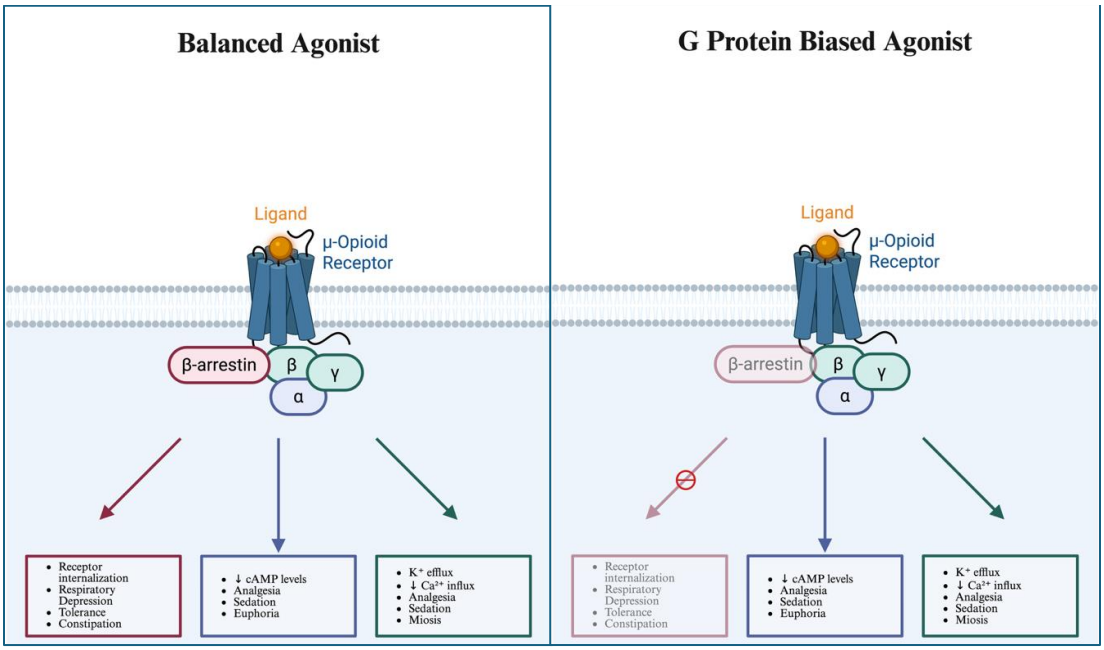

Figure 1.
Both figures show the proteins activated by agonists at the μ-OR. These are the $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. Additionally, a set of common effects associated with each protein type is shown in the boxes below. The balanced agonists (shown left) activate both G protein signaling and β-arrestin pathways to a similar extent. In contrast, G protein biased agonists (shown right) preferentially activate G protein signaling while minimizing β-arrestin recruitment.

Biased agonists have become increasingly prominent in our ongoing pharmacological search for a drug with the aforementioned qualities. They function primarily through the controlled phosphorylation of the opioid receptor. By preventing phosphorylation, they reduce the recruitment of β-arrestins, becoming a G protein biased agonist. Inversely, by increasing the recruitment of β-arrestins, they become β-arrestins biased agonists. Each is hypothesized to take on solely the properties of their protein, thus giving researchers greater governance over the opioid functions (Jayakody et al., 2025). Generally, scientists favor the G protein activity due to its more desirable analgesic effect, however, both routes have some exploration as the concept is a very recent development.

While the information and processes mentioned can be generalized to all the opioid receptors, there also lie distinct pharmacological profiles, therapeutic & clinical potentials, and sets of complications among the μ-OR, κ-OR, δ-OR, and NOP. Understanding and exploiting these factors is vital for the development of

more effective opioid agonists and antagonists. For any researcher looking to do so, it is crucial to acknowledge these disparities.

The μ-OR, encoded by the OPRM1 gene, is primarily involved in the analgesic and euphoric effects of opioids. It's predominantly expressed in the periaqueductal gray, thalamus, dorsal horn of the spinal cord, nucleus accumbens, and brainstem respiratory centers, allowing it a great degree of control over pain management. This receptor has strong supraspinal and spinal analgesia, making it effective for acute pain. Thus far, it has been considered the gold standard for analgesia due to our longstanding knowledge of its nature and its effectiveness. However, especially in recent years, it has become infamous due to its high risk of respiratory depression, constipation, tolerance, dependence, and euphoria-driven abuse (Pellissier et al., 2018; Madariaga-Mazón et al., 2017; Ehrlich et al., 2019; Mann et al., 2015).

The κ-OR is encoded by the OPRK1 gene, and while perhaps overshadowed by the μ-OR, has consistently shown promise in analgesia. It produces potent spinal analgesia, antipruritic effects, and minimal respiratory depression. Dense in hypothalamus, amygdala, periaqueductal gray, spinal cord dorsal horn, and pituitary, this receptor has become increasingly valuable as we search for a replacement to traditional μ-OR drugs like fentaNYL. Alas, it is also known to cause dysphoria, hallucinations, sedation, and aversion in many patients. For this reason, it has historically been avoided for opioid use. Recently, however, significant promise with the receptor has been shown. In Japan, a κ-OR drug, nalfurafine, has even been conditionally approved for certain therapeutic prescriptions, showing net positive effects in many patients so far (Liu-Chen & Huang, 2022; Hampsey et al., 2024; Escudero-Lara et al., 2021; Han et al., 2023).

On the other hand, the δ-OR, encoded by the OPRD1 gene, is predominantly expressed in the cortex, olfactory bulb, dorsal root ganglia, hippocampus, and limbic regions. In general consensus, it has shown little promise compared to its counterparts. While it does show some mild analgesic, antidepressant, and anxiolytic effects, its risk of seizure is high and potency for pain relief is low. To that end, it has been largely passed over by researchers in the field (Gavériaux-Ruff & Kieffer, 2011; Saigusa et al., 2017).

More recently, the atypical NOP has come into play. Encoded by the OPRL1 gene, this receptor is widespread at the cerebral cortex, amygdala, spinal cord,

locus coeruleus, and dorsal root ganglia. It has shown great promise in the production of spinal and peripheral analgesia without the creation of respiratory depression, euphoria, or extreme tolerance issues. However, due to its often dual analgesic/anti-analgesic behavior, many feel it to be counterintuitive. Regardless, it has shown significant promise in the field, especially in combination with other receptors (Post et al., 2016; Raffaeli et al., 2006; Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017).

Body Section 2: The Rise of New Classes of Opioid Agonists: Biased and Dual Agonism

Until the late 1990s medical professionals and researchers alike were wary of opioid drugs, using them only when absolutely necessary (i.e. late-stage cancer) and in small quantities, but in 1996 the company Purdue Pharma produced OxyContin®, a drug that would change the opioid landscape for decades to come. OxyContin®, a brand name for an extended-release formulation of oxycodone, was introduced by Purdue Pharma to treat moderate–severe pain over long periods of time. As opioids had long-since been considered addictive and having many complications, most care providers were averse to their use. Recklessly, Purdue Pharma cited a now infamous 1-paragraph letter from the renowned *New England Journal of Medicine* (Porter & Jick, 1980). This report—using a small test group of hospitalized patients—was taken wildly out of context, cited as definite proof that opioids were safe and non-addicting for long-term outpatient use. When coupled with more influential clinical papers; aggressive, misleading, and FDA-backed promotional marketing; and pressure from the "Pain as the 5th vital sign marketing", doctors' fears were assuaged, and the mass prescription of opioids began (Rosenman et al., 2025). In 2020, Purdue Pharma pleaded guilty to their false advertising, taking OxyContin's extended-release form off the market. Unfortunately, by then, the damage was done, leaving us with an opioid crisis we don't have a solution to. Even today, while under closer security and restriction, opioids are being prescribed to those with chronic pain-causing afflictions, as they are currently thought to be the best method of pain-mitigation. However, even when medical professionals stop the opioid prescription, there is a high likelihood of addiction, tempting patients to continue their use through non-controlled substances like diacetylmorphine (heroin), illicit morphine, or fentaNYL-laced drugs.

Currently, for outpatient therapeutic use, we have a variety of opioids at our disposal. For this purpose, we tend to use longer-acting drugs such as morphine (Zhuang et al., 2022; Krishnamurti & Rao, 2016; Reilly, 2016), oxycodone, hydromorphone, methadone, and fentaNYL transdermal patches (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019). We do this for several reasons including duration of action, potency, overdose risk, abuse risk, cost, and government regulation. Conversely, for inpatient clinical care, shorter-acting drugs with faster onset and offset, like fentaNYL and remifentanil, are often utilized (Brown et al., 2020; Sutcliffe et al., 2022). This can also be attributed to the aforementioned reasons but their inverse.

Perhaps some of the most acute examples of this idea are the uses of morphine and fentaNYL. Morphine (a large, hydrophilic substance) has a much longer onset and offset when compared to fentaNYL (a smaller, lipophilic substance) (Brown et al., 2020; Sutcliffe et al., 2022). Thus, morphine is mostly used for chronic and cancerous conditions, whilst fentaNYL is reserved for general surgery under the watch of an anesthesiologist. Each has their benefits and drawbacks, making them ideal for different scenarios. Morphine lasts longer than fentaNYL, increasing the risk of complications like nausea and constipation, but decreasing the risk of overdose in long-term situations, as it will be administered less often. FentaNYL is ~50–100 times more potent than morphine, making it cheaper when diluted and given properly, but deadly if overdosed. FentaNYL is generally considered at higher risk for addiction than morphine, but if taken for prolonged periods of time, as morphine usually is, both can become extremely addictive due to euphoric effects and unregulated dopamine levels. To synthesize, morphine and fentaNYL are two very different drugs, targeting the same issue but in unique ways, making them best suited for different tasks. While often discussed, these are not the only two opioid drugs that follow these principles. As mentioned earlier, medical professionals have dozens of drugs—approved, obsolete, and in development—to treat patients with. However, especially with more recently developed opioids, most of the medical community is wary of change, with good reason, considering the recent affair with OxyContin®. Thus, it is important to recognize the disparate effects (both short and long term) and tailor opioid use to the task it is performing. We can do this through clinical trials, where a near-definite assessment is reached, but even before that we are able to form a rough hypothesis based on the structure and intended route of function. Here, we will be comparing the structure, receptor, and other known factors of next generation

agonists to their clinically and therapeutically established counterparts, reporting trends and inconsistencies between these factors and the drugs' effects.

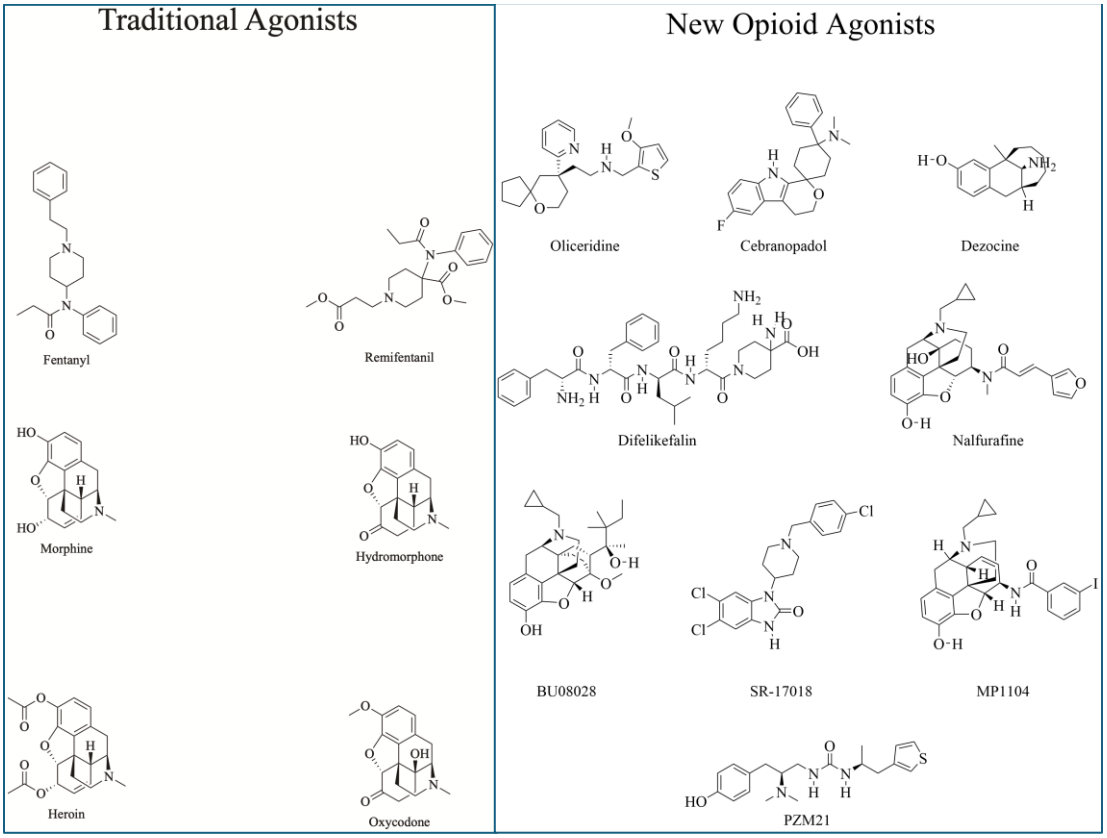

Figure 2.
Chemical structures of traditional and in-development (new) agonists. Each structure is labeled with its name underneath.

Name	Common Brand Name(s)	Target	Positive Effects	Negative Effects	Stage of Development / Use
Oliceridine	Olinvyk	MOR – G protein–partial bias (moderate efficacy)	Strong IV analgesia, slightly reduced GI and respiratory issues compared to morphine	Nausea, dizziness, respiratory depression still possible, limited duration	Approved (US) for acute pain (IV)
PZM21	–	MOR – low β-arrestin recruitment, low intrinsic efficacy	Analgesia in preclinical and early human studies	Respiratory depression in later animal studies, low analgesic effects	Preclinical/early clinical
SR-17018	–	MOR – G protein biased	Potent, long-acting analgesia in animals, reduced tolerance issues in mice	No human data; bias claims debated, possible side effects typical of MOR agonists	Preclinical
Dezocine	Dalgan	MOR partial agonist+ KOR partial anatgonist+ SERT/NET inhibitor	Analgesia, possible mood elevation, lower abuse liability reports	Typical opioid adverse events, mild sedation	Approved (China); formerly marketed in US
Nalfurafine	Remitch	KOR full + MOR partial (atypical signaling)	Antipruritic with reduced dysphoria compared to classical KOR agonists	Low analgesia, Sedation, possible mild dysphoria	Approved (Japan) for uremic pruritus

Difelikefalin	Korsuva	KOR (peripheral peptide)	Pruritus relief, minimal CNS sedation/respiratory depression	Low analgesia, mild nausea, diarrhea	Approved (US) for CKD-associated pruritus; IV in dialysis
MP1104	–	KOR full + DOR full, mixed arrestin/G-protein signaling	Analgesia in rodents, reduced classic KOR aversion	Unknown human safety; possible KOR side effects	Preclinical
BU08028	–	MOR partial + NOP partial	Strong analgesia in NHPs, minimal respiratory depression or abuse liability	Unclear long-term safety, typical opioid effects possible	Preclinical
Cebranopadol	–	MOR full + NOP agonist	Very long-lasting analgesia, fewer classic MOR adverse events	Some sedation, opioid-like side effects	FDA Fast Track Designation for chronic low back pain
Morphine	Zomorph, Sevredol, MS Contin, and Oramorph	MOR full (balanced signaling)	Strong analgesia, sedation	Respiratory depression, constipation, histamine release, tolerance	Approved, widely used
Hydromorphone	Dilaudid	MOR full (balanced)	Potent analgesia, less histamine release than morphine	Respiratory depression, constipation, sedation	Approved, widely used
Diacetylmorphine	Heroin	MOR full (via 6-MAM/morphine)	Very rapid and strong analgesia/euphoria	High abuse liability, respiratory depression, rapid dependence, low regulation	Approved in some countries for opioid dependence; illicit in most
Oxycodone	OxyContin	MOR full/partial + minor KOR activity	Effective oral analgesic	Abuse liability, respiratory depression, constipation	Approved, widely used
Fentanyl	Sublimaze (Intravenous), Duragesic (Transdermal patches), Actiq (Oral transmucosal lozenges), Fentora (Effervescent buccal tablets), Abstral (Sublingual tablets), Subsys (Sublingual sprays), and Lazanda (Nasal sprays)	MOR full (high efficacy)	Very rapid, potent analgesia and sedation	Respiratory depression, tolerance issues, addiction potential	Approved, widely used (anesthesia, severe pain)
Remifentanil	Ultiva	MOR full (high efficacy; ester “soft drug”)	Rapid onset, rapid offset, precise titration	Respiratory depression during infusion, little residual analgesia after stop	Approved, widely used in anesthesia

Figure 3.
Table showing the name, common brand name target, effects (both positive and negative), and stage of development of different established and upcoming agonists.

Based on the factors analyzed, several predictions can be drawn. It is important to note, however, that these are solely predictions, and the true effects of drugs are shown through human clinical studies and continued therapeutic use. With that said, this preemptive style of analysis can be extremely useful for researchers looking to explore very recently developed avenues of creating opioid drugs and assess which growing ideas have had the most success thus far.

Firstly, it is crucial to understand which areas of research have had the least success and least exploration with regard to opioid analgesics. To this end, we can cite the limited results of full and partial δ-OR agonists. Most drugs developed for the δ-OR either show low efficacy with analgesia, inordinate complications, or a combination of both issues. Thus, the data for the receptor is limited, and the

results are not quite promising. Moreover, certain agonists, namely PZM21, were initially thought to be biased agonists, due to their lessened side effects, but it was later discovered that the effects could be attributed to low intrinsic efficacies (Hillhouse & Negus, 2016). Furthermore, the κ-OR, once considered among the most promising candidates for analgesic drug development, has shown mixed results. In many κ-OR agonists in use, low analgesic effects in ratio to dysphoric issues have been noted. However, the antipruritic (anti-itch) benefits of κ-OR agonists such as nalfurafine and difelikefalin haven't gone unnoticed. This receptor—while perhaps not as indicative of heralding future of less issue-prone analgesic drugs—presents a unique pathway for antipruritic drugs, with a plethora of reassuring, trial-based evidence to support it (Beck et al., 2019; Liu-Chen & Huang, 2022).

More optimistically, we have a number of agonists employing a variety of strategic approaches to drug design. Not only is it important to understand which drugs are successful and unsuccessful, but the underlying mechanisms of said drugs are just as important to the field. To that end, we have seen many drugs with success, but it is important to define and categorize that success, as different issues necessitate different criteria. The main uses for analgesic drugs are therapeutic and clinical. In outpatient therapy, the patient will be exposed to the drug for longer durations and generally at lower doses. Conversely, in clinical procedures, higher doses are given, but far less frequently and in tightly controlled settings. Some drugs, like fentaNYL are even used for both cases via different routes like the fast-acting intravenous formula for surgical procedures and the slower-release transdermal patches for chronic pains (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019).

For acute clinical use, we have seen agonists at the μ-OR work the quickest and safest, but still retain some drawbacks of constipation, nausea, respiratory depression, and continually increasing tolerance. However, when biased to the G proteins Gαi/o and Gβγ, several agonists showed reduced complications, especially with tolerance, as the β-arrestin was no longer causing the internalization and degradation of the receptor. For example, oliceridine (an agonist that preferentially activates G protein signaling over β-arrestin recruitment) is already shown to have a lower risk of several side effects. Oliceridine has rapid analgesia like fentaNYL and morphine, but lower respiratory depression and gastrointestinal complications at equianalgesic doses of those same traditional opioids. This drug has shown us that G protein bias can be successful, but it is still not perfect: side effects can still

occur, especially at higher doses (Faouzi et al., 2020; Stahl et al., 2021; Bateman & Levitt, 2021). Additionally, oliceridine has not been widely tested for surgical use, mostly used to counteract moderate–severe acute pain in-clinic. Due to this, the community is still searching for an even better opioid analgesic to compete with fentaNYL, and many feel G protein bias is the way to get there.

In chronic therapeutic development, on the other hand, many of the most promising agonists also utilize the concept of dual agonism/antagonism where agonists target multiple receptors. For example, BU08028 and Cebranopadol are both mixed agonist drugs. BU08028 primarily targets the μ-OR and NOP, reaping analgesia via a classical opioid pathway, and also modulating pain whilst reducing side effects like addiction risk through the NOP. If hypotheses are confirmed by human trials, this drug could provide potent, long-lasting analgesia without as many complications for chronic and acute pain. Cebranopadol is a first-in-class mixed opioid receptor. The drug targets the μ-OR and NOP as a full agonist and δ-OR and κ-OR as a partial agonist. By providing strong analgesia through the μ-OR, modulating pain through the NOP, and utilizing δ-OR & κ-OR for some neuropathic pain, this drug shows use for both acute and long-term pain management (Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017). Taking a different approach, dezocine, a drug widely used in China for chronic pain, but taken off the American market (for economic, not safety concerns), is a μ-OR agonist, κ-OR antagonist, and a serotonin-norepinephrine reuptake inhibitor. By partially agonizing the μ-OR, the drug creates potent analgesia, but with a ceiling effect, lowering the risk of respiratory depression. Being a κ-OR antagonist, this opioid analgesic also reduces dysphoria and sedation risk.

Body Section 3: Opioid Antagonists: Uses, drawbacks, and new technologies

As the opioid drug crisis remains to be solved, more and more people are overdosing on opioid drugs and experiencing respiratory depression, and thus, opioid antagonists are needed increasingly more. In the United States, many school districts located in high-drug-trafficking areas keep a narcotic reversal agent on hand, usually naloxone (Narcan®). However, just as fentaNYL has drawbacks and welcomes alternative agonists, naloxone has sparked a new wave of innovation for better opioid antagonists.

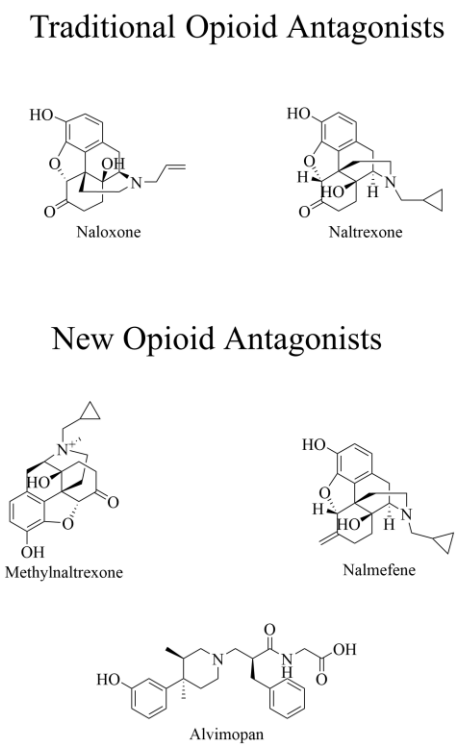

Figure 4.

Chemical structures of traditional and in-development (new) antagonists. Each structure is labeled with its name underneath.

Name / Brand(s)	Delivery Methods	Target	Positive Effects	Negative Effects	Stage of Development / Use
Naloxone (Narcan, Kloxxado, Evzio)	Intravenous (IV), Intramuscular (IM), Subcutaneous (SC), Intranasal spray	Full antagonist at μ-OR; Partial antagonist at κ-OR and δ-OR	Rapid reversal of opioid overdose, restores respiration	Short half-life (risk of re-narcotization), may cause severe withdrawal symptoms in opioid-dependent patients	Approved; gold standard emergency overdose treatment
Naltrexone (ReVia, Vivitrol, Depade)	Oral tablet, Extended-release intramuscular injection	Full antagonist at μ-OR, weak κ-OR antagonism	Prevents relapse in opioid/alcohol use disorder, longer duration than naloxone	Hepatotoxicity risk at high doses, poor adherence in oral form, precipitates withdrawal	Approved for opioid and alcohol dependence treatment
Methylnaltrexone (Relistor)	Subcutaneous injection, Oral tablet	Peripherally acting μ-opioid receptor antagonist (PAMORA); does not cross BBB	Reverses opioid-induced constipation without affecting analgesia	Abdominal pain, won't reverse overdose	Approved for opioid-induced constipation in palliative care or chronic pain
Alvimopan (Entereg)	Oral capsule	PAMORA; selective peripheral μ-opioid receptor antagonist	Reverses opioid-induced constipation without affecting analgesia	Cardiovascular risk with long-term use (restricted to short-term access)	Approved for short-term hospital use post-surgery (REMS program)
Nalmefene (Selincro, Revex)	Intravenous, Intramuscular, Subcutaneous, Oral tablet (Europe)	Full antagonist at μ-OR, partial agonist at κ-OR and δ-OR	Reversal of opioid overdose (longer duration than naloxone), reduces alcohol consumption	Nausea, dysphoria, precipitates withdrawal	Approved in some regions for alcohol dependence; approved in U.S. (IV) for overdose reversal

Figure 5.

Table showing the name, common brand name target, effects (both positive and negative), and stage of development of different established and upcoming antagonists.

Just as with agonists, antagonist drugs are present in a variety of structures, delivery routes, and mechanisms of action. Naloxone is still the gold standard emergency overdose treatment: it works with few complications and is usually life-saving. The largest issue is its short half-life, as it only works for ~30-90 minutes, whereas some opioid agonists function for hours. This can cause re-narcotization, where overdose symptoms return after naloxone wears off, requiring repeat dosing or IV infusion. Some other issues involve rapid withdrawal symptoms in opioid dependent individuals (due to naloxone's rapid onset) and limited efficacy with ultra-potent opioids like carfentanil. Additionally, the intravenous version of naloxone requires training to administer, but trained staff may not be available at the time of overdose (Bird et al., 2023; Beck et al., 2019; Lu et al., 2021; Cipriano et al., 2024).

To that end, researchers and scientists are working to develop and test several new reversal agents to hopefully solve some of naloxone's issues without sacrificing its efficacy. So far, drugs like naltrexone and nalmefene have been created and FDA approved for certain cases. They tend to last much longer than naloxone, but have been associated with immediate acute withdrawal symptoms, so newer opioid antagonist drugs are still in development (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Moreover, we now have several oral sprays, nasal sprays, and oral capsules to make untrained administration easier. While some critics have argued that the widespread availability of reversal agents could embolden opioid users and agitate the issue, widespread consensus agrees that the lives saved overshadow this issue. Additionally, a new class of antagonist drugs known as PAMORAs (peripherally acting μ-opioid receptor antagonists) has emerged. These drugs, like alvimopan and methylnaltrexone, are actually not used to treat opioid overdose. Rather, they are utilized mainly for opioid-induced constipation. PAMORAs, unlike most antagonists, do not reduce analgesic effects, making them a great resource for patients in chronic pain or for post-operative care (Pellissier et al., 2018; Madariaga-Mazón et al., 2017).

Another issue is that while traditional antagonist drugs create a rapid reversal effect, they cannot be given preemptively, as they have a short half-life. However, a unique class of drugs known as monoclonal antibody–based opioid binders present a new way to combat the issue: the idea of opioid "vaccines". Unlike traditional antagonists, monoclonal antibodies could prevent opioid agonists from crossing the blood-brain barrier (BBB). This would effectively reduce the effects of opioids over a long period, thus "vaccinating" patients against them. Nevertheless, many concerns and debates exist over this topic. For instance, the design of these drugs is very specific, usually only targeting one or a few agonists. So, if a person suffering from opioid addiction were to get treated against heroin, thus nulling its effects, they may resort to other drugs such as fentaNYL for the same euphoria. Moreover, if a patient is vaccinated against too many opioids and needs a surgical procedure, the anesthesiologist may have a difficult time finding an opioid drug to administer analgesia. This applies even more so for an emergency room (ER) case in which the patient's medical record may not be on hand. So, even though traditional antagonists and monoclonal antibody–based drugs strive to aid the same issue—the ongoing opioid crisis—both take very different routes and expect very different outcomes (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Thus, they are not in competition with each other, as neither can replace the other, but expanding our research in both areas would benefit the same problem.

Conclusion:

In synthesis, opioid pharmacology represents a path to improving both therapeutic tools and clinical medicine. Our growing understanding of opioid receptor function has revealed opportunities to separate beneficial analgesic effects from unwanted side effects, but the path toward safer and more effective drugs remains largely open. Nevertheless, historical missteps remind us that scientific innovation must not come at the cost of foregoing rigorous testing, regulation, and responsible clinical use. Looking forward, several avenues of continued research appear particularly promising. These include areas such as the development of biased agonists that preferentially activate pathways linked to analgesia or the exploration of dual-acting compounds that target multiple receptors simultaneously. Ultimately, addressing the opioid crisis will not come from a single breakthrough, but rather an integrated approach. Continued research in all of these areas offers the best chance of balancing the essential role of opioids in pain relief with the urgent need to minimize their risks.

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Works Cited

Addiction Rare in Patients Treated with Narcotics. (1980). *New England Journal of Medicine*, *302*(2), 123–123. https://doi.org/10.1056/NEJM198001103020221

Baehr, C., Kelcher, A. H., Khaimraj, A., Reed, D. E., Pandit, S. G., AuCoin, D., Averick, S., & Pravetoni, M. (2020). Monoclonal Antibodies Counteract Opioid-Induced Behavioral and Toxic Effects in Mice and Rats. *The Journal of Pharmacology and Experimental Therapeutics*, *375*(3), 469–477. https://doi.org/10.1124/jpet.120.000124

Balon, T. M., Xia, Y., McKeown, J., Wang, J., Abbott, J. J., Palettas, M., Uribe, A., Echeverria Villalobos, M., Coffman, J. C., & Hu, L.-Q. (2024). Pocket warming of bupivacaine with fentanyl to shorten onset of labor epidural analgesia: A double-blind randomized controlled clinical trial. *PLOS ONE*, *19*(9), e0309515. https://doi.org/10.1371/journal.pone.0309515

Bateman, J. T., & Levitt, E. S. (2021). Evaluation of G protein bias and β-arrestin 2 signaling in opioid-induced respiratory depression. *American Journal of Physiology-Cell Physiology*, *321*(4), C681–C683. https://doi.org/10.1152/ajpcell.00259.2021

Beck, T. C., Reichel, C. M., Helke, K. L., Bhadsavle, S. S., & Dix, T. A. (2019). Non-addictive orally-active kappa opioid agonists for the treatment of peripheral pain in rats. *European Journal of Pharmacology*, *856*, 172396. https://doi.org/10.1016/j.ejphar.2019.05.025

Bird, H. E., Huhn, A. S., & Dunn, K. E. (2023). Fentanyl Absorption, Distribution, Metabolism, and Excretion: Narrative Review and Clinical Significance Related to Illicitly Manufactured Fentanyl. *Journal of Addiction Medicine*, *17*(5), 503–508. https://doi.org/10.1097/ADM.0000000000001185

Brown, J. A., Faley, S. L., Shi, Y., Hillgren, K. M., Sawada, G. A., Baker, T. K., Wikswo, J. P., & Lippmann, E. S. (2020). Advances in blood–brain barrier modeling in microphysiological systems highlight critical differences in opioid transport due to cortisol exposure. *Fluids and Barriers of the CNS*, *17*(1), 38. https://doi.org/10.1186/s12987-020-00200-9

Che, T., & Roth, B. L. (2023). Molecular basis of opioid receptor signaling. *Cell*, *186*(24), 5203–5219. https://doi.org/10.1016/j.cell.2023.10.029

Christoph, A., Eerdekens, M.-H., Kok, M., Volkers, G., & Freynhagen, R. (2017). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience

in patients with chronic low back pain in a randomized clinical trial. *Pain*, 158(9), 1813–1824. https://doi.org/10.1097/j.pain.0000000000000986

Cipriano, A., Kapil, R. P., Zhou, M., Shet, M. S., Whiteside, G. T., Willsie, S. K., & Harris, S. C. (2024). Safety, Tolerability, and Pharmacokinetics of Single- and Multiple-Ascending Doses of Sunobinop in Healthy Participants. *Clinical Pharmacology in Drug Development*, 13(7), 790–800. https://doi.org/10.1002/cpdd.1394

Cook, M. E., Knoph, C. S., Fjelsted, C. A., Frøkjær, J. B., Bilgrau, A. E., Novovic, S., Jørgensen, M. T., Mortensen, M. B., Nielsen, L. B. J., Hadi, A., Berner-Hansen, M., Rutkowski, W., Vujasinovic, M., Löhr, M., Drewes, A. M., & Olesen, S. S. (2023). Effects of a peripherally acting μ-opioid receptor antagonist for the prevention of recurrent acute pancreatitis: Study protocol for an investigator-initiated, randomized, placebo-controlled, double-blind clinical trial (PAMORA-RAP trial). *Trials*, 24(1), 301. https://doi.org/10.1186/s13063-023-07287-z

Coombes, L., Burke, K., & Anderson, A.-K. (2017). The use of rapid onset fentanyl in children and young people for breakthrough cancer pain. *Scandinavian Journal of Pain*, 17(1), 256–259. https://doi.org/10.1016/j.sjpain.2017.07.010

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., Bernstein, S. L., & Fiellin, D. A. (2015). Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. *JAMA*, 313(16), 1636. https://doi.org/10.1001/jama.2015.3474

Eggleston, W., Calleo, V., Kim, M., & Wojcik, S. (2020). Naloxone Administration by Untrained Community Members. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 40(1), 84–88. https://doi.org/10.1002/phar.2352

Ehrlich, A. T., Kieffer, B. L., & Darcq, E. (2019). Current strategies toward safer mu opioid receptor drugs for pain management. *Expert Opinion on Therapeutic Targets*, 23(4), 315–326. https://doi.org/10.1080/14728222.2019.1586882

Escudero-Lara, A., Cabañero, D., & Maldonado, R. (2021). Kappa opioid receptor modulation of endometriosis pain in mice. *Neuropharmacology*, 195, 108677. https://doi.org/10.1016/j.neuropharm.2021.108677

Faouzi, A., Varga, B. R., & Majumdar, S. (2020). Biased Opioid Ligands. *Molecules*, 25(18), 4257. https://doi.org/10.3390/molecules25184257

Gado, F., Ferrisi, R., Polini, B., Mohamed, K. A., Ricardi, C., Lucarini, E., Carpi, S., Domenichini, F., Stevenson, L. A., Rapposelli, S., Saccomanni, G., Nieri, P.,

Ortore, G., Pertwee, R. G., Ghelardini, C., Di Cesare Mannelli, L., Chiellini, G., Laprairie, R. B., & Manera, C. (2022). Design, Synthesis, and Biological Activity of New CB2 Receptor Ligands: From Orthosteric and Allosteric Modulators to Dualsteric/Bitopic Ligands. *Journal of Medicinal Chemistry*, 65(14), 9918–9938. https://doi.org/10.1021/acs.jmedchem.2c00582

Gavériaux-Ruff, C., & Kieffer, B. L. (2011). Delta opioid receptor analgesia: Recent contributions from pharmacology and molecular approaches. *Behavioural Pharmacology*, 22(5 and 6), 405–414. https://doi.org/10.1097/FBP.0b013e32834a1f2c

Glenn, J. K., & Goldman, J. (1976). Task delegation to physician extenders—Some comparisons. *American Journal of Public Health*, 66(1), 64–66. https://doi.org/10.2105/ajph.66.1.64

Göhler, K., Sokolowska, M., Schoedel, K. A., Nemeth, R., Kleideiter, E., Szeto, I., & Eerdekens, M.-H. (2019). Assessment of the Abuse Potential of Cebranopadol in Nondependent Recreational Opioid Users: A Phase 1 Randomized Controlled Study. *Journal of Clinical Psychopharmacology*, 39(1), 46–56. https://doi.org/10.1097/JCP.0000000000000995

Guo, S.-B., Meng, Y., Lin, L., Zhou, Z.-Z., Li, H.-L., Tian, X.-P., & Huang, W.-J. (2024). Artificial intelligence alphafold model for molecular biology and drug discovery: A machine-learning-driven informatics investigation. *Molecular Cancer*, 23(1), 223. https://doi.org/10.1186/s12943-024-02140-6

Hampsey, E., Jelen, L., & Young, A. H. (2024). Aticaprant: (A κ-opioid receptor antagonist) for major depressive disorder. *Expert Opinion on Emerging Drugs*, 29(3), 193–204. https://doi.org/10.1080/14728214.2024.2345645

Han, J., Zhang, J., Nazarova, A. L., Bernhard, S. M., Krumm, B. E., Zhao, L., Lam, J. H., Rangari, V. A., Majumdar, S., Nichols, D. E., Katritch, V., Yuan, P., Fay, J. F., & Che, T. (2023). Ligand and G-protein selectivity in the κ-opioid receptor. *Nature*, 617(7960), 417–425. https://doi.org/10.1038/s41586-023-06030-7

Hovah, M. E., & Holzgrabe, U. (2024). Bivalent and bitopic ligands of the opioid receptors: The prospects of a dual approach. *Medicinal Research Reviews*, 44(6), 2545–2599. https://doi.org/10.1002/med.22050

Jang, J. S., Hwang, S. M., Kwon, Y., Tark, H., Kim, Y. J., Ryu, B. Y., & Lee, J. J. (2018). Is the transdermal fentanyl patch an efficient way to achieve acute postoperative pain control?: A randomized controlled trial. *Medicine*, 97(51), e13768. https://doi.org/10.1097/MD.0000000000013768

Jayakody, T., Budagoda, D. K., Mendis, K., Dilshan, W. D., Bethmage, D., Dissasekara, R., & Dawe, G. S. (2025). Biased agonism in peptide-GPCRs: A structural perspective. *Pharmacology & Therapeutics*, *269*, 108806. https://doi.org/10.1016/j.pharmthera.2025.108806

Kelly, E., Conibear, A., & Henderson, G. (2023). Biased Agonism: Lessons from Studies of Opioid Receptor Agonists. *Annual Review of Pharmacology and Toxicology*, *63*, 491–515. https://doi.org/10.1146/annurev-pharmtox-052120-091058

Kieffer, B. L. (1999). Opioids: First lessons from knockout mice. *Trends in Pharmacological Sciences*, *20*(1), 19–26. https://doi.org/10.1016/S0165-6147(98)01279-6

Kliewer, A., Gillis, A., Hill, R., Schmiedel, F., Bailey, C., Kelly, E., Henderson, G., Christie, M. J., & Schulz, S. (2020). Morphine-induced respiratory depression is independent of β-arrestin2 signalling. *British Journal of Pharmacology*, *177*(13), 2923–2931. https://doi.org/10.1111/bph.15004

Koch, E. D., Kapanadze, S., Eerdekens, M.-H., Kralidis, G., Létal, J., Sabatschus, I., & Ahmedzai, S. H. (2019). Cebranopadol, a Novel First-in-Class Analgesic Drug Candidate: First Experience With Cancer-Related Pain for up to 26 Weeks. *Journal of Pain and Symptom Management*, *58*(3), 390–399. https://doi.org/10.1016/j.jpainsymman.2019.05.012

Krishnamurti, C., & Rao, S. C. (2016). The isolation of morphine by Serturner. *Indian Journal of Anaesthesia*, *60*(11), 861–862. https://doi.org/10.4103/0019-5049.193696

Lee, J. D., Nunes, E. V., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C. C., King, J., Lindblad, R., Liu, D., Matthews, A. G., May, J., Peavy, K. M., Ross, S., Salazar, D., Schkolnik, P., … Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. *The Lancet*, *391*(10118), 309–318. https://doi.org/10.1016/S0140-6736(17)32812-X

Liu-Chen, L.-Y., & Huang, P. (2022). Signaling underlying kappa opioid receptor-mediated behaviors in rodents. *Frontiers in Neuroscience*, *16*, 964724. https://doi.org/10.3389/fnins.2022.964724

Lorch, U., Pierscionek, T., Freier, A., Spencer, C. S., & Täubel, J. (2021). Safety, Tolerability, and Dose Proportionality of a Novel Transdermal Fentanyl Matrix Patch and Bioequivalence With a Matrix Fentanyl Patch: Two Phase 1 Single-

Center Open-Label, Randomized Crossover Studies in Healthy Japanese Volunteers. *Clinical Pharmacology in Drug Development*, 10(3), 260–271. https://doi.org/10.1002/cpdd.846

Lu, J. J., Polgar, W. E., Mann, A., Dasgupta, P., Schulz, S., & Zaveri, N. T. (2021). Differential In Vitro Pharmacological Profiles of Structurally Diverse Nociceptin Receptor Agonists in Activating G Protein and Beta-Arrestin Signaling at the Human Nociceptin Opioid Receptor. *Molecular Pharmacology*, 100(1), 7–18. https://doi.org/10.1124/molpharm.120.000076

Madariaga-Mazón, A., Marmolejo-Valencia, A. F., Li, Y., Toll, L., Houghten, R. A., & Martinez-Mayorga, K. (2017). Mu-Opioid receptor biased ligands: A safer and painless discovery of analgesics? *Drug Discovery Today*, 22(11), 1719–1729. https://doi.org/10.1016/j.drudis.2017.07.002

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. *Nature*, 485(7398), 321–326. https://doi.org/10.1038/nature10954

Mann, A., Illing, S., Miess, E., & Schulz, S. (2015). Different mechanisms of homologous and heterologous μ-opioid receptor phosphorylation. *British Journal of Pharmacology*, 172(2), 311–316. https://doi.org/10.1111/bph.12627

Martinez, S., Harris, H., Chao, T., Luba, R., Pravetoni, M., Comer, S. D., & Jones, J. D. (2023). The potential role of opioid vaccines and monoclonal antibodies in the opioid overdose crisis. *Expert Opinion on Investigational Drugs*, 32(3), 181–185. https://doi.org/10.1080/13543784.2023.2187286

Mathur, V. S., Kumar, J., Crawford, P. W., Hait, H., Sciascia, T., & for the TR02 Study Investigators. (2017). A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Nalbuphine ER Tablets for Uremic Pruritus. *American Journal of Nephrology*, 46(6), 450–458. https://doi.org/10.1159/000484573

Merivirta, R., Äärimaa, V., Aantaa, R., Koivisto, M., Leino, K., Liukas, A., & Kuusniemi, K. (2013). Postoperative Fentanyl Patch Versus Subacromial Bupivacaine Infusion in Arthroscopic Shoulder Surgery. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, 29(7), 1129–1134. https://doi.org/10.1016/j.arthro.2013.04.018

Mitchell, S. G., Monico, L. B., Gryczynski, J., Fishman, M. J., O'Grady, K. E., & Schwartz, R. P. (2021). Extended-release naltrexone for youth with opioid use disorder. *Journal of Substance Abuse Treatment*, 130, 108407. https://doi.org/10.1016/j.jsat.2021.108407

Morales, P., Scharf, M. M., Bermudez, M., Egyed, A., Franco, R., Hansen, O. K., Jagerovic, N., Jakubík, J., Keserű, G. M., Kiss, D. J., Kozielewicz, P., Larsen, O., Majellaro, M., Mallo-Abreu, A., Navarro, G., Prieto-Díaz, R., Rosenkilde, M. M., Sotelo, E., Stark, H., … Wingler, L. M. (2025). Progress on the development of Class A GPCR-biased ligands. *British Journal of Pharmacology*, 182(14), 3249–3300. https://doi.org/10.1111/bph.17301

Mores, K. L., Cassell, R. J., & Van Rijn, R. M. (2019). Arrestin recruitment and signaling by G protein-coupled receptor heteromers. *Neuropharmacology*, 152, 15–21. https://doi.org/10.1016/j.neuropharm.2018.11.010

Moss, L., Hijma, H., Demitrack, M., Kim, J., Groeneveld, G. J., Van Velzen, M., Niesters, M., Olofsen, E., & Dahan, A. (2023). Neurocognitive Effect of Biased μ-Opioid Receptor Agonist Oliceridine, a Utility Function Analysis and Comparison with Morphine. *Anesthesiology*, 139(6), 746–756. https://doi.org/10.1097/ALN.0000000000004758

Ni, Y., Huang, R., Yang, S., Yang, X. Y., Zeng, S., Yao, A., Huang, J., & Yang, G. (2024). Pharmacokinetics and Safety of Oliceridine Fumarate Injection in Chinese Patients with Chronic Non-Cancer Pain: A Phase I, Single-Ascending-Dose, Open-Label Clinical Trial. *Drug Design, Development and Therapy*, *Volume* 18, 2729–2743. https://doi.org/10.2147/DDDT.S461416

Nihadha, P. M., Chugh, A., Kaur, A., Kumar, S., Naveen, K. H., Bhatia, P. K., Kumar, P., & Chaudhry, K. (2022). Transdermal fentanyl patch versus standard analgesia in postoperative oral submucous fibrosis patients: A triple blinded, randomised control trial. *British Journal of Oral and Maxillofacial Surgery*, 60(9), 1246–1253. https://doi.org/10.1016/j.bjoms.2022.07.002

Nunes, E. V., Bisaga, A., Krupitsky, E., Nangia, N., Silverman, B. L., Akerman, S. C., & Sullivan, M. A. (2020). Opioid use and dropout from extended-release naltrexone in a controlled trial: Implications for mechanism. *Addiction*, 115(2), 239–246. https://doi.org/10.1111/add.14735

Pellissier, L. P., Gandía, J., Laboute, T., Becker, J. A. J., & Le Merrer, J. (2018). μ opioid receptor, social behaviour and autism spectrum disorder: Reward matters. *British Journal of Pharmacology*, 175(14), 2750–2769. https://doi.org/10.1111/bph.13808

Post, A., Smart, T. S., Krikke-Workel, J., Dawson, G. R., Harmer, C. J., Browning, M., Jackson, K., Kakar, R., Mohs, R., Statnick, M., Wafford, K., McCarthy, A., Barth, V., & Witkin, J. M. (2016). A Selective Nociceptin Receptor Antagonist to Treat Depression: Evidence from Preclinical and Clinical Studies.

Neuropsychopharmacology, 41(7), 1803–1812. https://doi.org/10.1038/npp.2015.348

Raffaeli, W., Samolsky Dekel, B. G., Landuzzi, D., Caminiti, A., Righetti, D., Balestri, M., Montanari, F., Romualdi, P., & Candeletti, S. (2006). Nociceptin Levels in the Cerebrospinal Fluid of Chronic Pain Patients With or Without Intrathecal Administration of Morphine. *Journal of Pain and Symptom Management*, 32(4), 372–377. https://doi.org/10.1016/j.jpainsymman.2006.05.013

Reilly, R. F. (2016). Medical and surgical care during the American Civil War, 1861-1865. *Proceedings (Baylor University. Medical Center)*, 29(2), 138–142. https://doi.org/10.1080/08998280.2016.11929390

Rosenman, E., Buck, R. K., Anjum, N., Thompson, L., Rist, J., Banuna, L., Dolgoff, E., Hartmann, S., Lelei, S., Feng, Z., & Holmes, L. M. (2025). From dealer to doctor: A case study examining how Purdue Pharma sought to leverage racial health disparities to attenuate flagging OxyContin sales. *Social Science & Medicine*, 382, 118132. https://doi.org/10.1016/j.socscimed.2025.118132

Rudolph, K. E., Díaz, I., Luo, S. X., Rotrosen, J., & Nunes, E. V. (2021). Optimizing opioid use disorder treatment with naltrexone or buprenorphine. *Drug and Alcohol Dependence*, 228, 109031. https://doi.org/10.1016/j.drugalcdep.2021.109031

Saigusa, T., Aono, Y., & Waddington, J. L. (2017). Mechanisms underlying δ- and μ-opioid receptor agonist-induced increases in extracellular dopamine level in the nucleus accumbens of freely moving rats. *Journal of Oral Science*, 59(2), 195–200. https://doi.org/10.2334/josnusd.16-0874

Singla, N. K., Skobieranda, F., Soergel, D. G., Salamea, M., Burt, D. A., Demitrack, M. A., & Viscusi, E. R. (2019). APOLLO-2: A Randomized, Placebo and Active-Controlled Phase III Study Investigating Oliceridine (TRV 130), a G Protein–Biased Ligand at the μ-Opioid Receptor, for Management of Moderate to Severe Acute Pain Following Abdominoplasty. *Pain Practice*, 19(7), 715–731. https://doi.org/10.1111/papr.12801

Smith, L. C., Bremer, P. T., Hwang, C. S., Zhou, B., Ellis, B., Hixon, M. S., & Janda, K. D. (2019). Monoclonal Antibodies for Combating Synthetic Opioid Intoxication. *Journal of the American Chemical Society*, 141(26), 10489–10503. https://doi.org/10.1021/jacs.9b04872

Stahl, E. L., Schmid, C. L., Acevedo-Canabal, A., Read, C., Grim, T. W., Kennedy, N. M., Bannister, T. D., & Bohn, L. M. (2021). G protein signaling–biased mu opioid receptor agonists that produce sustained G protein activation are

noncompetitive agonists. *Proceedings of the National Academy of Sciences*, 118(48), e2102178118. https://doi.org/10.1073/pnas.2102178118

Stevens, R. C., Cherezov, V., Katritch, V., Abagyan, R., Kuhn, P., Rosen, H., & Wüthrich, K. (2013). The GPCR Network: A large-scale collaboration to determine human GPCR structure and function. *Nature Reviews Drug Discovery*, 12(1), 25–34. https://doi.org/10.1038/nrd3859

Sutcliffe, K. J., Corey, R. A., Alhosan, N., Cavallo, D., Groom, S., Santiago, M., Bailey, C., Charlton, S. J., Sessions, R. B., Henderson, G., & Kelly, E. (2022). Interaction With the Lipid Membrane Influences Fentanyl Pharmacology. *Advances in Drug and Alcohol Research*, 2, 10280. https://doi.org/10.3389/adar.2022.10280

Szumiec, L., Bugno, R., Szumiec, L., & Przewlocki, R. (2023). The differential influence of PZM21, a nonrewarding μ-opioid receptor agonist with G protein bias, on behavioural despair and fear response in mice. *Behavioural Brain Research*, 449, 114466. https://doi.org/10.1016/j.bbr.2023.114466

Varga, B. R., Streicher, J. M., & Majumdar, S. (2023). Strategies towards safer opioid analgesics—A review of old and upcoming targets. *British Journal of Pharmacology*, 180(7), 975–993. https://doi.org/10.1111/bph.15760

Verbeek, J., & Brinkman, D. J. (2025). A Comprehensive Narrative Review of Protonitazene: Pharmacological Characteristics, Detection Techniques, and Toxicology. *Basic & Clinical Pharmacology & Toxicology*, 137(2), e70078. https://doi.org/10.1111/bcpt.70078

Wang, Y. & et al. (2023). Structures of the entire human opioid receptor family. *Cell*, 186(2), 413-427.e17. https://doi.org/10.1016/j.cell.2022.12.026

Wikstro[Combining Diaeresis]m, B. D., Gellert, R., Ladefoged, S. D., Danda, Y., Akai, M., Ide, K., Ogasawara, M., Kawashima, Y., Ueno, K., Mori, A., & Ueno, Y. (2005). κ-Opioid System in Uremic Pruritus: Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Studies. *Journal of the American Society of Nephrology*, 16(12), 3742–3747. https://doi.org/10.1681/ASN.2005020152

Yamaguchi, S., Uchida, E., Terahara, T., Okawa, K., Hashimoto, F., & Tanaka, Y. (2020). Efficacy and Safety of Fentanyl Citrate Patch, Including a Low-Dose 0.5 mg Formulation, in Opioid-Naïve Patients with Cancer Pain. *Clinical Drug Investigation*, 40(11), 1041–1052. https://doi.org/10.1007/s40261-020-00965-9

Zhuang, Y., Wang, Y., He, B., He, X., Zhou, X. E., Guo, S., Rao, Q., Yang, J., Liu, J., Zhou, Q., Wang, X., Liu, M., Liu, W., Jiang, X., Yang, D., Jiang, H., Shen, J., Melcher, K., Chen, H., … Xu, H. E. (2022). Molecular recognition of morphine

and fentanyl by the human μ-opioid receptor. *Cell*, 185(23), 4361-4375.e19. https://doi.org/10.1016/j.cell.2022.09.041

EDITOR COMMENTS AND RECOMMENDATION:

Both reviewers agree that the manuscript has strong potential and is a thorough review of opioid analgesics. Both reviewers also raise concerns, however, about the use of informal/imprecise language, lack of important in-text citations, and also advise better use and description of the included figures in the text. The editor suggests that the author particularly address points #4 and #5 raised by Reviewer 1, as well as the "Overall Feedback" section of Reviewer 2's critique for improving the manuscript. Given this feedback, I recommend a major revision prior to publication.

REVIEWER 1:

The manuscript comprehensively reviews opioid ligands, related therapeutic approaches, and clinical trials. The selection of cited studies is abundant and well-represents the current knowledge and recent advances in this field. Well-developed figures are included. The author did an excellent job walking through the mechanisms and providing their perspectives. I also love the incorporation of tables to show differences and clinical trials, pointing out certain stages of technologies. However, the overall manuscript shows notable weakness in writing style, proper word and sentence structures, and the use of in-text citations. In summary, I think the manuscript cannot be published in Convergence in the present form. A future publication depends on complete explanation/consideration of all major points raised below. A major rewrite is required to address issues in writing, and appropriate citations.

1. I have never seen fentanyl written as fentaNYL. Fentanyl is the standard spelling.
2. The author abbreviated many words without first writing them full in the Abstract (e.g.: μ-OR, NOP). In the main text, despite stating the abbreviation and full name, the author continued to use the full name (e.g. Nociceptin/Orphanin Receptor, instead of NOP). For any abbreviation that is not used later, there is no point of abbreviating them (e.g. HTS).
3. There are errors in word capitalizations and sentence organizations. For example, the author randomly capitalized a word mid-sentence *In Ayurveda (An ancient medical practice from India), Morphine,* or *Traditional Medicine*. I also recommend adding appropriate punctuation. Random abbreviations and symbols like "&" should be written out. Spelling errors (e.g.: marijuana, anatgonist [sic]) were also spotted throughout. Please proofread the entire manuscript.
4. I recommend listing all sources where the author mentioned a fact. For example, the author talked about the history of opioids but did not list any sources. Many other facts were stated without proper in-text citations.
5. While the author created several scientific figures, they did not mention the figures in their writing. The mention of each figure is required. Also, it is unlikely that the author drew all these figures by themselves. I suggest that they put proper citations, especially if they use Biorender.com.
6. Table needs to be titled as Table 1 and must be referred to in the manuscript.

REVIEWER 2:

Title page and abstract

- **L1–2 / Page 1, Title:** Put the title in Title Case. Replace "&" with "and." Change "therapeutic/clinical" to "therapeutic and clinical."
- **L8–10 / Page 1, Abstract, first paragraph:** Standardize spelling to "fentanyl." Choose one abbreviation convention for receptors (μ-OR or MOR) and apply it consistently.
- **L10–13 / Page 1, Abstract, first paragraph:** "Fentanyl alone has led to over 80,000 deaths last year" is too absolute. Rephrase to note fentanyl as the primary driver of opioid
  overdoses without implying it is the only cause.
- **L15–17 / Page 1, Abstract, second paragraph:** The sentence about δ-OR, κ-OR, and NOP receptors could preview the distinct complications tied to each, helping orient the reader.
- **L18–21 / Page 1, Abstract, second paragraph:** Change "biased and bitopic agonism emerge" to "biased and bitopic agonism have emerged." Tighten the fentanyl comparison: "No approach has yet yielded a drug that surpasses fentanyl's potency and prevalence."
- **L21–24 / Page 1, Abstract, last sentence:** Fix the broken word in "clinically backed." Simplify: "This review surveys new opioid drug classes and evaluates their clinical relevance, with examples that illustrate mechanisms and early efficacy signals."

Introduction and Background

- **L28–36 / Page 2, Paragraph 1:** The phrase "An ancient medical practice" would read better with a lowercase "ancient." Italicize historical terms like *Ahiphena* and *Ying Su Ke*. Add a brief parenthetical gloss (for example, what the term translates to) to help readers unfamiliar with the cultural context.
- **L37–38 / Page 2, Paragraph 1:** Revise "culminating in the isolation of morphine… and synthesis of fentanyl" to "culminating in the 19th-century isolation of morphine and the 20th-century synthesis of fentanyl." This makes the timeline precise.
- **L40–43 / Page 2, Paragraph 2:** Instead of "Morphine, the first true opioid analgesic," write "Morphine, the first purified opioid analgesic." "True" sounds subjective.
- **L46–50 / Page 2, Paragraph 2:** The sentence starting with "Beyond that, however…" is long and heavy. Split it into two. Also, note specifically how the morphine era shaped receptor theory and understanding of tolerance.
- **L53–60 / Page 2, Paragraph 3:** The phrase "even 2 mg… lethal" is misleading. Change to "as little as about 2 mg may be lethal in opioid-naïve individuals," and note variability.
- **L61–66 / Page 2, Paragraph 3:** The claim about "for-profit healthcare artificially inflating prices" comes across as opinionated. Reword neutrally: "High costs of treatment and medication have contributed to limited access." Support with data if retained.
- **L68–73 / Page 2, Paragraph 4:** Instead of "Together, these issues—among many others—have plunged Americans into an opioid crisis," use "These factors have contributed to the ongoing U.S. opioid crisis." More precise and professional. Additionally, the use of em-dash is not required in this instance. Please reword.

- **L74–81 / Page 2, Paragraph 5:** Phrases like “globally lambasted” feel too casual. Replace with “frequently identified as hotspots.” Also ensure there are references to support geographic comparisons.
- **L82 / Page 2, Paragraph 5:** Correct spelling to “marijuana.”
- **L89–97 / Page 3, Paragraph 1:** Spell out GPCR at first use. Then introduce μ-OR, δ-OR, κ-OR, and NOP, and provide a short table of abbreviations for clarity.
- **L102–104 / Page 3, Paragraph 2:** Replace “continues to dispel researchers” with “continues to deter researchers” or “continues to puzzle researchers.” “Dispel” is incorrect in this context.
- **L108–111 / Page 3, Paragraph 2:** Change “next-generation pain killers” to “next-generation painkillers.”
- **L111–118 / Page 3, Paragraph 3:** The explanation of biased vs bitopic agonism is strong. Add a short line explaining why bitopic agonists can provide finer control, such as their ability to interact with both orthosteric and allosteric sites.
- **L119–127 / Page 3, Paragraph 3:** The point about infrastructure strain is good. Add a concrete example (for instance, the scale of compounds screened per year) if available.
- **L129–131 / Page 3, Paragraph 4:** Clarify “consistent and reproducible therapeutic promise.” Do you mean replication across labs, consistency across models, or clinical reproducibility? State explicitly.

Methodology

- **L135–139 / Page 3, Methodology, Paragraph 1:** The reasoning for focusing on qualitative synthesis is fine, but the explanation is vague. Specify inclusion criteria such as date ranges, receptor targets, and whether only peer-reviewed articles were included. Mention which databases were searched besides PubMed, if any.
- **L142–146 / Page 3, Methodology, Paragraph 2:** The phrase “mitigating bias through reference of a wide breadth of sources” is awkward. Suggest: “Bias was mitigated by drawing from a wide range of studies across different labs and experimental designs.” Also, clarify whether you excluded certain study types (for example, animal-only studies, unpublished trials).

Discussion – Section 1: Receptors and Signaling

- **L151–156 / Page 4, Paragraph 1:** Good introduction to GPCR cascades. To improve clarity, you could cross-reference Figure 1 here, so the reader knows where to look for a visual representation.
- **L158–168 / Page 4, Paragraph 2:** You frame G-protein signaling as “positive” and arrestin signaling as “negative.” This is an oversimplification. Suggest softening: “G-protein signaling is often associated with analgesic effects, while arrestin recruitment is frequently linked to adverse effects, though exceptions exist.”
- **Figure 1, Caption / Page 6 (L171–177):** Replace “Both figures show” with “Panels show.” Standardize phrasing to “G-protein–biased” and “β-arrestin–biased.” Consider adding a legend to clarify icons used in the diagram.
- **L179–187 / Page 6, Paragraph below Fig. 1:** Change “β-arrestins biased agonists” to “β-arrestin–biased agonists.” Also rephrase “becoming a G protein biased agonist” to

"producing a G-protein–biased signaling profile."

- **L194–204 / Page 6–7, Paragraph 1 (μ-OR/MOR):** Strong anatomical overview. When you call μ-OR the "gold standard," soften to "has long been considered the clinical standard for analgesia." Standardize spelling to **MOR** throughout to avoid issues with the Greek letter μ.
- **L205–216 / Page 7, Paragraph 2 (κ-OR/KOR):** Good summary of promise and liabilities. Clarify nalfurafine's approval: specify indication (for example, pruritus in dialysis patients in Japan). Preview that its analgesic effects are limited compared with its antipruritic use.
- **L217–223 / Page 7, Paragraph 3 (δ-OR/DOR):** Concise summary. Add one sentence noting seizure risk observed in some DOR-selective agonists and why this complicates drug development.
- **L224–232 / Page 7, Paragraph 4 (NOP):** Balanced overview. The final sentence could hint at later discussion: "NOP's synergy with MOR signaling has spurred interest in dual agonists, which are discussed in a later section."

Discussion – Section 2: Biased and Dual Agonism; Clinical vs Therapeutic Use

- **L235–246 / Page 8, Paragraph 1:** The history of Purdue and OxyContin is important, but the tone is too strong. Replace "recklessly" with "aggressively" or "widely." Make clear that the NEJM letter was misinterpreted rather than malicious.
- **L247–254 / Page 8, Paragraph 1–2:** "FDA-backed promotional marketing" needs rewording. Unless there is evidence, say "marketing campaigns were allowed despite limited evidence of safety in long-term outpatient use."
- **L255–258 / Page 8, Paragraph 2:** Replace "fentanyl-laced drugs" with "illicitly manufactured fentanyl." This is the accepted terminology in recent literature.
- **L259–268 / Page 9, Paragraph 1:** Strong distinction between outpatient and inpatient prescribing. Consider presenting this information in a comparative table that includes onset, duration, potency, and major risks.
- **L270–281 / Page 9, Paragraph 2:** Be careful with the statement "fentanyl is generally considered at higher risk for addiction than morphine." A more accurate phrasing: "Fentanyl may have greater reinforcement potential due to rapid onset and high potency."
- **L285–293 / Page 10, Paragraph 1:** "The recent affair with OxyContin" sounds informal. Replace "affair" with "experience" or "history." Remove the trademark symbol — scientific writing does not usually use ® or ™.
- **Figure 2, Caption / Page 10, L299–303:** Revise caption to "Panels show traditional agonists (left) and new opioid agonists (right)." Ensure drawings have consistent stereochemistry and resolution.

- **Table under Fig. 2 / Page 11, L303–319:**
  - Correct spelling of "anatgonist" to "antagonist."
  - Format multi-target entries consistently (for example, "SERT/NET inhibitor" instead of mixed styles).
  - Add a "Key references" column or footnotes.
  - Clarify what "Stage of development" means (preclinical, phase I, approved, etc.).

Discussion – Section 3: Advances, Limitations, and Outlook

- **L320–332 / Page 12, Paragraph 1:** Good coverage of new opioid scaffolds. Add examples of compounds in early clinical trials to make this more concrete.
- **L333–340 / Page 12, Paragraph 2:** When discussing biased agonists, acknowledge that not all studies replicate the same arrestin vs G-protein outcomes. This avoids overstating the certainty.
- **L341–350 / Page 12–13, Paragraph 2–3:** When you describe preclinical successes, indicate whether these are in rodent models, non-human primates, or early human studies. This distinction is important for readers.
- **L351–364 / Page 13, Paragraph 3:** The discussion of limitations is solid. You could strengthen by naming specific barriers: cost of large-scale synthesis, difficulty with receptor selectivity, or poor blood–brain barrier penetration.
- **L365–373 / Page 13, Paragraph 4:** The statement about the infrastructure of clinical trials being overwhelmed is strong but vague. Add a brief example (for instance, average cost of phase II studies, or dropout rates).

Discussion – Section 4: Future Directions

- **L374–382 / Page 14, Paragraph 1:** The optimism about computational drug design is good. Suggest citing specific advances such as cryo-EM–guided docking or machine-learning–based ligand prediction.
- **L383–390 / Page 14, Paragraph 2:** You mention dual agonists combining MOR and NOP activity. Strengthen this by referencing examples (for instance, cebranopadol, which has advanced to late-stage trials).
- **L391–400 / Page 14–15, Paragraph 3:** The broader conclusion that “no approach has produced a drug to dethrone fentanyl” is fair, but soften the phrasing. Consider: “Despite promising new scaffolds, no candidate has yet matched fentanyl’s potency and ubiquity in illicit markets.”

Figures and Tables (General Comments)

- **Figures 1 and 2:** Ensure resolution is high enough for print and online formats. Consider enlarging receptor schematics and labeling icons clearly. Use consistent styles for arrows and colors.
- **Tables:** Make column headings uniform (capitalize each, or use sentence case consistently). Provide definitions for abbreviations directly under the table.

Conclusion

- **L401–415 / Page 15, Final Paragraph:** This section is strong but could be more structured. Suggest summarizing in three points: (1) progress in biased/bitopic agonism,
  (2) ongoing limitations in translation from preclinical to clinical, and (3) outlook for rational design.

References

- Standardize reference style: journal abbreviations, italicization, and punctuation should follow the target journal's guidelines.
- Check consistency in author initials, year formatting, and DOI inclusion.
- If possible, update with the most recent clinical trial data (past 2–3 years) to strengthen currency.

Overall Feedback.

- **Tone**
  - Avoid casual or opinionated phrases such as "recklessly," "affair with OxyContin," or "globally lambasted."
  - Use neutral, academic wording to maintain credibility.
- **Consistency**
  - Standardize terminology (choose either μ-OR or MOR and apply it consistently).
  - Ensure drug names like fentanyl and morphine are spelled and capitalized the same way throughout.
  - Apply uniform style to abbreviations, figure captions, and table formatting.
- **Precision**
  - Rephrase sweeping generalizations (for example, fentanyl being solely responsible for overdose deaths) into qualified, evidence-based statements.
  - Correct small grammatical issues such as "pain killers" → "painkillers" and "dispels researchers" → "confounds researchers."
- **Structure and Readability**
  - Break up long sentences into shorter, clearer ones for easier reading.
  - Add tables or schematic comparisons when presenting multiple drugs or receptor types side by side.
- **Figures and Tables**
  - Standardize figure resolution, labeling, and style.
  - Use consistent column formatting in tables.
  - Add footnotes for abbreviations and clarify terms such as "Stage of development."
- **Conclusion**
  - Keep the closing balanced: recognize both the promise of new approaches and the reality that none have yet surpassed fentanyl.
  - Avoid dramatic or absolute phrasing; use precise, measured language instead

Current and Prospective Opioid Analgesics: Assessing Their Value for Ongoing Research and Promise for Therapeutic and Clinical Use

*Name & Affiliation not given due to Blind Review guidelines

Abstract

Opioid analgesics, though among the most potent tools for pain relief at our disposal, sit at the epicenter of a growing clinical and societal crisis. Currently, most opioid analgesic drugs like fentanyl function at the Mu Opioid-Receptor (μ-OR), which has notably been linked to respiratory depression, constipation, and high abuse potential. In fact, the abuse of fentanyl been a primary driver of opioid overdose, leading to over 80,000 deaths in the United States just in the last year. As demand for safer analgesics has surged, the field has responded with a range of innovative approaches, many involving the strategic use of other opioid receptors such as the Delta Opioid-Receptor, Kappa Opioid-Receptor, and Nociceptin/Orphanin Receptor (δ-OR, κ-OR, and NOP respectively). Each of these receptors plays a role in analgesia yet also creates a unique set of complications to accompany it. To combat this issue, dozens of opioid agonists and antagonists are being developed. We have seen new concepts such as biased and bitopic agonism emerge, presenting an updated outlook on how these drugs function. Thus far, no single method has yielded a drug to outcompete fentanyl's potency and prevalence in the global market. This review not only brings to light the new classes of opioid drugs, but also discusses their relevance to the field. Moreover, many prevalent examples of opioids and their mechanisms are discussed throughout the paper, giving clinically backed insight into the drugs' varying levels of efficacy.

Introduction

Since first being recorded by the Sumerian Empire for their hypnotic properties in 3400 B.C., opioids have been employed by a myriad of civilizations, including the Egyptians, Indians, Chinese, and Greeks. There is even evidence showing two of the oldest medical systems using opium derived from poppy seeds to induce analgesia. In Ayurveda (an ancient holistic medical practice from India) *Ahiphena*—also known as poppy seeds—were used for sedation, pain relief, and gastrointestinal relief. Similarly, in Chinese Traditional Medicine, the same plant, though here called "*Ying Su Ke*", was used for pain and cough suppression. Through

the years, opioid use has been refined through medical, religious, and recreational contexts, ultimately culminating in the 19th-century isolation of morphine and the 20th-century synthesis of fentanyl (Benet et al., 2017).

Morphine, the first purified opioid analgesic, has been one of the most prominent drugs in medical and pharmaceutical history (Krishnamurti & Rao, 2016). Isolated by Friedrich Sertürner in Germany in 1804, this opium poppy derivative broke ground in the research of analgesics. Morphine functions by binding to the μ-opioid receptors in the brain and spinal cord to block the perception of pain (Zhuang et al., 2022). Its introduction into the clinical and therapeutic settings revolutionized pain management, saving countless lives. During the American Civil War, morphine was widely employed as an analgesic via hypodermic injection or laudanum (Reilly, 2016). Beyond that, however, it helped the scientific community understand addiction, receptor theory, and tolerance. Namely, early patterns of dose-dependent effects and diminishing efficacy with prolonged use provided some of the first evidence for discrete receptor sites and the adaptive changes of tolerance. These ramifications have made morphine both a medical breakthrough and cautionary tale, sparking the development of newer, safer, and more potent opioid analgesics.

This undertaking eventually gave rise to a new breed of opioid analgesics optimized for the clinical field: synthetic opioids. The most notable of which is fentanyl, an opioid-based drug first synthesized in Belgium by Dr. Paul Janssen in 1959. This drug is widely accepted as the greatest discovery in the field since the introduction of morphine, of which it is 50–100 times more potent (Zhuang et al., 2022). Originally developed for surgical anesthesia and severe pain management, fentanyl's high lipid solubility and rapid onset coupled with its relatively low cost have made it one of the most universal analgesics of the modern world. However, its high potency and rapid onset could make even as little as about 2 mg lethal in opioid-naïve individuals, underscoring the need for precaution and safety when in use (Bird et al., 2023). Nevertheless, as of now, fentanyl is still favored in most developed nations for analgesia.

In America, the for-profit healthcare and pharmacological system artificially inflate the price of life-saving medicines, making them inaccessible to most Americans living under the poverty line (Blumenthal & Shapiro, 2025). Thus, many Americans are forced to resort to unlicensed distributors to attain their

prescriptions at a reasonable price. Unfortunately, however, this results in many preventable deaths every year. The issue is exacerbated by the recreational use of opioids and high mental health crisis rates (usually resulting in substance abuse) among American youths. Moreover, many medical professionals are encouraged to use opioids to treat pain therapeutically, creating high addiction rates in many chronic pain patients. Together, these factors—among many others—have contributed to the ongoing U.S. opioid crisis.

This problem, however, is not uniform throughout the world. Nations like Switzerland, Rwanda, Saudi Arabia, New Zealand, China, Japan, South Korea, and Singapore have been able to keep drug abuse rates low through strict pharmaceutical monitoring and low prescription medication costs (Chan et al., 2021). In stark contrast, regions like Latin America, Eastern Europe, Central & South Asia, and Africa are frequently identified as illicit drug hotspots & trafficking routes. Overall, this disparity can be attributed to an array of factors from cultural taboos to geopolitical connections to government regulations.

Opioids, unlike other substances like marijuana or nicotine products, can be immediately fatal. While most addicting substances create long-term issues sometimes leading to cancer, opioid drugs create respiratory depression in overdose, thus making them fatal in minutes if not counteracted with an antagonist drug. To combat this, many disparate approaches are being taken by researchers and corporations alike. One prevalent avenue involves exploring the different opioid receptors.

Standard Terminology	Abbreviation Used
G Protein-Coupled Receptor	GPCR
Mu Opioid-Receptor	μ-OR
Kappa Opioid-Receptor	κ-OR
Delta Opioid-Receptor	δ-OR
Nociceptin/Orphanin Receptor	NOP

Table 1.

This table outlines the abbreviations used in lieu of standard terminology throughout the paper.

Opioid receptors are a specific type of GPCR located throughout the brain, spinal cord, and peripheral nervous system. Currently, we know of four main types

of these receptors: μ-OR, κ-OR, δ-OR, and NOP (Refer to table 1) (Wang et al., 2023). Each plays a distinct role in analgesia, pain management, and the effects of both endogenous and synthetic opioids. The μ-OR has historically been used for the majority of analgesic drugs, including morphine, heroin, oxycodone, and fentanyl. It governs euphoria and analgesia, but its use also often leads to respiratory depression and addiction (Zhuang et al., 2022). The κ-OR also deals in the domain of analgesia, but comes with the complications of dysphoria and hallucinations. Whilst it has historically been overshadowed by the μ-OR, and disregarded due to its hallucinogenic properties, it has had renewed interest in recent years for non-addictive therapies (Beck et al., 2019). On the other hand, the δ-OR continues to deter researchers due to its low selectivity and efficacy. For while it may be another route to drug discovery, it lacks significant promise, and thus intrigue in the receptor is scarce. More recently, an opioid-like receptor has taken the international stage. The NOP, being the newest of the four, has been shown to play a part in stress, mood regulation, and pain. As it has shown reduced side effects in comparison to its counterparts, it represents a promising target for next-generation painkillers (Lu et al., 2021; Cipriano et al., 2024).

In addition to exploring the use of different receptors, two major pathways to mitigating side effects have emerged in the field: bitopic and biased ligands. Bitopic ligands interact with both allosteric and orthosteric sites, offering enhanced control over receptor signaling. By engaging the allosteric site in addition to the orthosteric site, they enable finer modulation of receptor activity. This dual binding confers greater differentiation between receptor subtypes and, consequently, more precise control over receptor activation (Gado et al., 2022). Biased ligands present a way to activate only certain signaling pathways preferentially. They aim to retain therapeutic effects while minimizing complications (Stahl et al., 2021). Until now, opioid drug design focused primarily on orthosteric sites, but recent efforts with biased and bitopic signaling have yielded some positive results, making them a popular topic for continued research.

These discoveries have sparked a surge of interest in the field. Soon after they arose, we saw innumerable researchers begin leveraging these concepts to address the opioid crisis. When hundreds of ligands entered the screening pipeline at once, they quickly overwhelmed existing infrastructure and techniques, underscoring the need for faster, more scalable approaches (Chatterjee et al., 2023). With aid from new technologies like high-throughput screening, scientists are now able to test

thousands of compounds simultaneously at a fraction of the cost, significantly accelerating drug discovery.

Alas, with such a vast repertoire of recent innovation in the field, pinpointing promising candidates has become a highly time-intensive task for researchers new to the field. Fortunately, this review aims to sift through the growing body of opioid ligand candidates to identify those demonstrating the most consistent and reproducible therapeutic and clinical promise across clinical studies.

Methodology:

To report the trends in the field of opioid analgesic drugs, this review utilized primarily qualitative data drawn from open-access sources through PubMed. As the focus of this paper covers next-generation opioid agonists and antagonists, and sources of quantitative data varied greatly between labs for many of these drugs, it would have been counterproductive and scientifically irresponsible to include data collected through such heterogenous methods. The most accurate method of discussing the various opioid agonists and antagonists was by reviewing clinical studies and reporting trends and inconsistencies in the current data. The inclusion criteria consisted of studies published between 2017 and 2025, with some exceptions made for historical data critical to contextualizing newer developments. Moreover, only peer-reviewed articles were included. Study types were selected with a preference for human clinical trials; however, in cases where such studies were unavailable, particularly for newer opioid drugs, animal studies were included to fill in important knowledge gaps. By using this methodology, bias was mitigated by drawing from a wide range of studies across different labs and experimental designs, accurately displaying the current landscape of the field of opioid agonists and antagonists.

Discussion:

Body Section 1: Analysis & Overview of μ-OR, κ-OR, δ-OR, and NOP

The main opioid receptors—μ-OR, κ-OR, δ-OR, and NOP—are part of the Class A G protein-coupled receptor (GPCR) family. GPCRs are a large group of cell-surface receptors that transmit signals into the cell via the activation of intracellular G proteins (Wang et al., 2023). When discussing opioid receptors and their agonists/antagonists, a cascade of intricate processes must occur to create the desired, and undesired, effects that we're familiar with.

As per our current understanding of said processes, we focus on three main proteins within the body: $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. While their respective roles in the system are not yet fully understood, recent findings have linked G protein subunits ($G_{\alpha i/o}$ and $G_{\beta\gamma}$) to primarily positive effects (i.e. analgesia and sedation) and β-arrestin to mainly negative effects (i.e. respiratory depression, constipation, and tolerance development), though exceptions exist (Bateman & Levitt, 2021; Faouzi et al., 2020; Mores et al., 2019). Opioids usually activate $G\alpha_{i/o}$ and $G_{\beta\gamma}$, subsequently phosphorylating the receptor, causing β-arrestin to bind to it. Thus, we receive nearly every effect, every time. To that end, many researchers believe that creating ligands biased to G proteins—or even just one subunit of G protein—over β-arrestins could be the foundation for many next generation opioid drugs, hopefully aiding the opioid addiction crisis by mitigating tolerance issues (Figure 1).

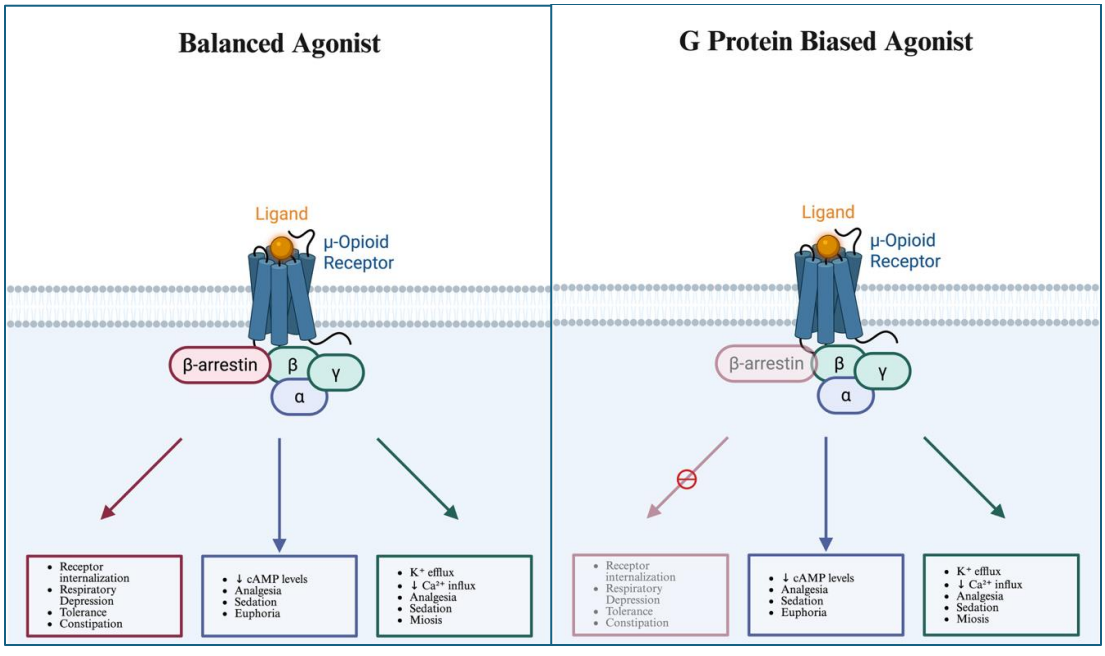

Figure 1.

Both panels show the proteins activated by agonists at the μ-OR. These are the

$G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. Additionally, a set of common effects associated with each protein type is shown in the boxes below. The balanced agonists (shown left) activate both G protein signaling and β-arrestin pathways to a similar extent. In contrast, G protein-biased agonists (shown right) preferentially activate G protein signaling while minimizing β-arrestin recruitment. The figure was created using BioRender (Roy, A. 2025).

Biased agonists have become increasingly prominent in our ongoing pharmacological search for a drug with the aforementioned qualities. They function primarily through the controlled phosphorylation of the opioid receptor. By preventing phosphorylation, they reduce the recruitment of β-arrestins, producing a G protein-biased agonist (Figure 1 shown right). Inversely, by increasing the recruitment of β-arrestins, they become β-arrestin-biased agonists. Each is hypothesized to take on solely the properties of their protein, thus giving researchers greater governance over the opioid functions (Jayakody et al., 2025). Generally, scientists favor the G protein activity due to its more desirable analgesic effect, however, both routes have some exploration as the concept is a very recent development.

While the information and processes mentioned can be generalized to all the opioid receptors, there also lie distinct pharmacological profiles, therapeutic and clinical potentials, and sets of complications among the μ-OR, κ-OR, δ-OR, and NOP. Understanding and exploiting these factors is vital for the development of more effective opioid agonists and antagonists. For any researcher looking to do so, it is crucial to acknowledge these disparities.

The μ-OR, encoded by the OPRM1 gene, is primarily involved in the analgesic and euphoric effects of opioids. It's predominantly expressed in the periaqueductal gray, thalamus, dorsal horn of the spinal cord, nucleus accumbens, and brainstem respiratory centers, allowing it a great degree of control over pain management. This receptor has strong supraspinal and spinal analgesia, making it effective for acute pain. Thus far, it has long been considered the clinical standard for analgesia due to our longstanding knowledge of its nature and its effectiveness. However, especially in recent years, it has become infamous due to its high risk of respiratory depression, constipation, tolerance, dependence, and euphoria-driven abuse (Pellissier et al., 2018; Madariaga-Mazón et al., 2017; Ehrlich et al., 2019; Mann et al., 2015).

The κ-OR is encoded by the OPRK1 gene, and while perhaps overshadowed by the μ-OR, has consistently shown promise in analgesia. It produces potent spinal analgesia, antipruritic effects, and minimal respiratory depression. Dense in hypothalamus, amygdala, periaqueductal gray, spinal cord dorsal horn, and pituitary, this receptor has become increasingly valuable as we search for a replacement to traditional μ-OR drugs like fentanyl. Alas, it is also known to cause dysphoria, hallucinations, sedation, and aversion in many patients. For this reason, it has historically been avoided for opioid use. Recently, however, significant promise with the receptor has been shown. In Japan, a κ-OR drug, nalfurafine, has even been conditionally approved for certain therapeutic prescriptions like pruritus in dialysis patients (Table 3), showing net positive effects in many patients thus far (Liu-Chen & Huang, 2022; Hampsey et al., 2024; Escudero-Lara et al., 2021; Han et al., 2023).

On the other hand, the δ-OR, encoded by the OPRD1 gene, is predominantly expressed in the cortex, olfactory bulb, dorsal root ganglia, hippocampus, and limbic regions. In general consensus, it has shown little promise compared to its counterparts. While it does show some mild analgesic, antidepressant, and anxiolytic effects, its risk of seizure is high and potency for pain relief is low. Generally, the risk of seizures alongside analgesia is not a tradeoff viewed favorably in drug development. To that end, DOR-selective agonists have been largely passed over by researchers in the field (Gavériaux-Ruff & Kieffer, 2011; Saigusa et al., 2017).

More recently, the atypical NOP has come into play. Encoded by the OPRL1 gene, this receptor is widespread at the cerebral cortex, amygdala, spinal cord, locus coeruleus, and dorsal root ganglia. It has shown great promise in the production of spinal and peripheral analgesia without the creation of respiratory depression, euphoria, or extreme tolerance issues. However, due to its often dual analgesic/anti-analgesic behavior, many feel it to be counterintuitive. Regardless, it has shown significant promise in the field, especially in combination with other receptors. Notably, NOP's synergy with μ-OR signaling has spurred interest in dual agonists, which will be discussed in a later section (examples can be seen in Table 3) (Post et al., 2016; Raffaeli et al., 2006; Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017).

Body Section 2: The Rise of New Classes of Opioid Agonists: Biased and Dual Agonism

Until the late 1990s medical professionals and researchers alike were wary of opioid drugs, using them only when absolutely necessary (i.e. late-stage cancer) and in small quantities, but in 1996 the company Purdue Pharma produced OxyContin, a drug that would change the opioid landscape for decades to come. OxyContin, a brand name for an extended-release formulation of oxycodone, was introduced by Purdue Pharma to treat moderate–severe pain over long periods of time. As opioids had long-since been considered addictive and having many complications, most care providers were averse to their use. Nevertheless, Purdue Pharma confidently cited a 1-paragraph letter from the renowned *New England Journal of Medicine* (Porter & Jick, 1980). This report—using a small test group of hospitalized patients—was taken out of context by Purdue Pharma, cited as definite proof that opioids were safe and non-addicting for long-term outpatient use. When coupled with more influential clinical papers; aggressive, misleading, and FDA-backed promotional marketing (Van Zee, 2009); and pressure from the "Pain as the 5th vital sign marketing", doctors' fears were assuaged, and the mass prescription of opioids began (Rosenman et al., 2025). In 2020, Purdue Pharma pleaded guilty to their false advertising, taking OxyContin's extended-release form off the market. Unfortunately, by then, the damage was done, leaving us with an opioid crisis we don't have a solution to. Even today, while under closer security and restriction, opioids are being prescribed to those with chronic pain-causing afflictions, as they are currently thought to be the best method of pain-mitigation. However, even when medical professionals stop the opioid prescription, there is a high likelihood of addiction, tempting patients to continue their use through non-controlled substances like diacetylmorphine (heroin), illicit morphine, or illicitly manufactured fentanyl (Refer to Figure 2 for structures).

	Duration	Risk of Addiction	Level of Supervision
Therapeutic (Outpatient) Use	~2 Months – Indefinite	Usually **higher risk** than clinical	Initially prescribed by medical professional, generally with occasional updates
Clinical (Inpatient) Use	~2 Hours – 24 Hours	Usually **lower risk** than therapeutic	Near-constant monitoring and adjusting by medical professional

Table 2.

Table detailing common characteristics of therapeutic and clinical opioid usage.

Currently, for outpatient therapeutic use (Table 2), we have a variety of opioids at our disposal. For this purpose, we tend to use longer-acting drugs such as morphine (Zhuang et al., 2022; Krishnamurti & Rao, 2016; Reilly, 2016), oxycodone, hydromorphone, methadone, and fentanyl transdermal patches (Figure 2 and Table 3) (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019). We do this for several reasons including duration of action, potency, overdose risk, abuse risk, cost, and government regulation. Conversely, for inpatient clinical care (Table 2), shorter-acting drugs with faster onset and offset, like fentanyl and remifentanil, are often utilized (Figure 2 and Table 3) (Brown et al., 2020; Sutcliffe et al., 2022). This can also be attributed to the aforementioned reasons but their inverse.

Perhaps some of the most acute examples of this idea are the uses of morphine and fentanyl. Morphine (a large, hydrophilic substance) has a much longer onset and offset when compared to fentanyl (a smaller, lipophilic substance) (refer to Figure 2 for structures) (Brown et al., 2020; Sutcliffe et al., 2022). Thus, morphine is mostly used for chronic and cancerous conditions, whilst fentanyl is reserved for general surgery under the watch of an anesthesiologist. Each has its benefits and drawbacks, making them ideal for different scenarios. Morphine lasts longer than fentanyl, increasing the risk of complications like nausea and constipation, but decreasing the risk of overdose in long-term situations, as it will be administered less often (Table 2). Fentanyl is ~50–100 times more potent than morphine, making it cheaper when diluted and given properly, but deadly if overdosed. Fentanyl may have greater reinforcement potential due to rapid onset and high potency, but if taken for prolonged periods of time, as morphine usually is, both can become extremely addictive due to euphoric effects and unregulated dopamine levels. To synthesize, morphine and fentanyl are two very different drugs, targeting the same issue but in unique ways, making them best suited for different tasks. While often discussed, these are not the only two opioid drugs that follow these principles. As mentioned earlier, medical professionals have dozens of drugs—approved, obsolete, and in development—to treat patients with (Table 3). However, especially with more recently developed opioids, most of the medical community is wary of change, with good reason, considering the recent history with OxyContin. Thus, it is important to recognize the disparate effects (both short and long term) and tailor opioid use to the task it is performing. We can do this through clinical

trials, where a near-definite assessment is reached, but even before that we are able to form a rough hypothesis based on the structure (Figure 2) and intended route of function (Table 3). Here, we will be comparing the structure, receptor, and other known factors of next generation agonists to their clinically and therapeutically established counterparts, reporting trends and inconsistencies between these factors and the drugs' effects.

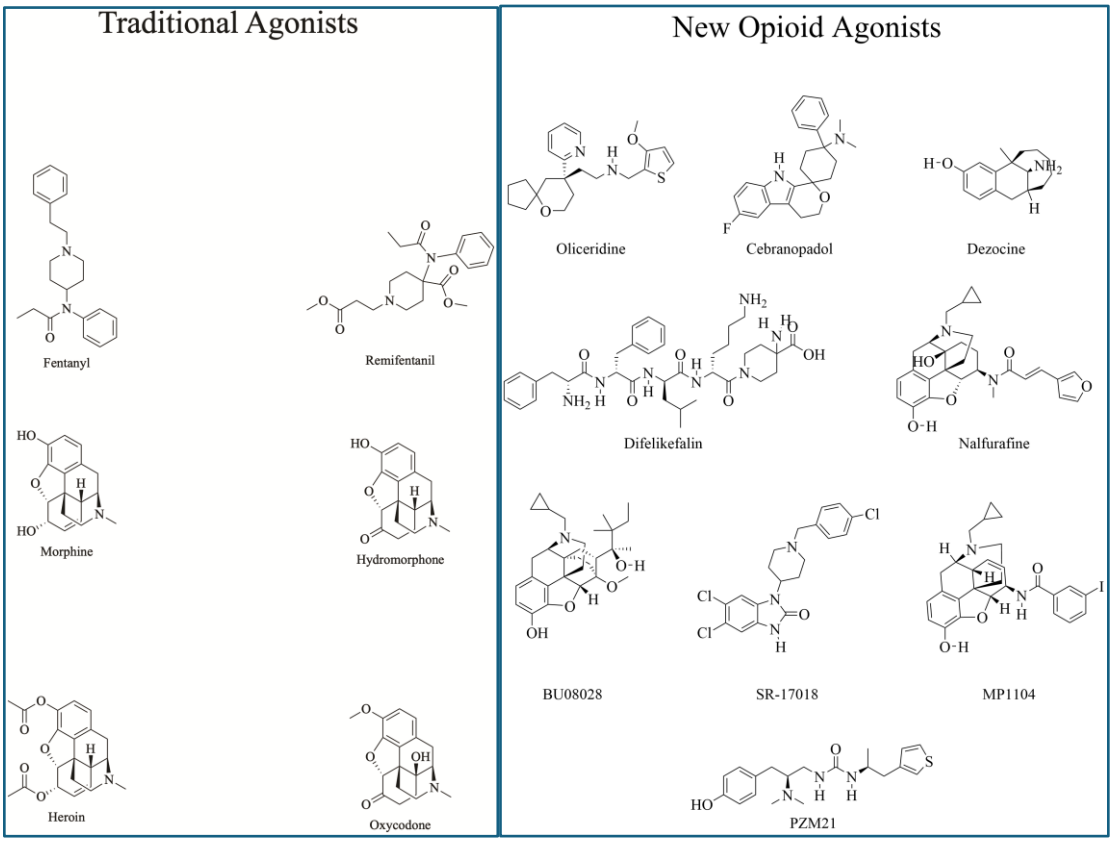

Figure 2.

Panels show structures of traditional agonists (left) and new opioid agonists (right).

Name	Common Brand Name(s)	Target	Positive Effects	Negative Effects	Stage of Development / Use
Oliceridine	Olinvyk	μ-OR – G protein–partial bias	Strong IV analgesia, slightly reduced GI and respiratory issues compared to morphine	Nausea, dizziness, respiratory depression still possible, limited duration	Approved (US) for acute pain (IV)
PZM21	–	μ-OR – low β-arrestin recruitment	Analgesia in preclinical and early human studies	Respiratory depression in later animal studies, low analgesic effects	Preclinical/early clinical
SR-17018	–	μ-OR – G protein biased	Potent, long-acting analgesia in animals, reduced tolerance issues in mice	No human data; bias claims debated, possible side effects typical of μ-OR agonists	Preclinical
Dezocine	Dalgan	μ-OR partial agonist + κ-OR partial antagonist + SERT/NET inhibitor	Analgesia, possible mood elevation, lower abuse liability reports	Typical opioid adverse events, mild sedation	Approved (China); formerly marketed in US

Nalfurafine	Remitch	κ-OR full agonist + μ-OR partial agonist	Antipruritic with reduced dysphoria compared to classical κ-OR agonists	Low analgesia, Sedation, possible mild dysphoria	Approved (Japan) for uremic pruritus
Difelikefalin	Korsuva	κ-OR peripheral agonist	Pruritus relief, minimal CNS sedation/respiratory depression	Low analgesia, mild nausea, diarrhea	Approved (US) for CKD-associated pruritus; IV in dialysis
MP1104	–	κ-OR full agonist + δ-OR full agonist	Analgesia in rodents, reduced classic κ-OR aversion	Unknown human safety; possible κ-OR side effects	Preclinical
BU08028	–	μ-OR partial agonist + NOP partial agonist	Strong analgesia in NHPs, minimal respiratory depression or abuse liability	Unclear long-term safety, typical opioid effects possible	Preclinical
Cebranopadol	–	μ-OR full agonist + NOP agonist	Very long-lasting analgesia, fewer classic μ-OR adverse events	Some sedation, opioid-like side effects	FDA Fast Track Designation for chronic low back pain
Morphine	Zomorph, Sevredol, MS Contin, and Oramorph	μ-OR full agonist (balanced signaling)	Strong analgesia, sedation	Respiratory depression, constipation, histamine release, tolerance	Approved, widely used
Hydromorphone	Dilaudid	μ-OR full agonist (balanced signaling)	Potent analgesia, less histamine release than morphine	Respiratory depression, constipation, sedation	Approved, widely used
Diacetylmorphine	Heroin	μ-OR full agonist	Very rapid and strong analgesia/euphoria	High abuse liability, respiratory depression, rapid dependence, low regulation	Approved in some countries for opioid dependence; illicit in most
Oxycodone	OxyContin	μ-OR full agonist + minor κ-OR agonist	Effective oral analgesic	Abuse liability, respiratory depression, constipation	Approved, widely used
Fentanyl	Sublimaze (Intravenous), Duragesic (Transdermal patches), Actiq (Oral transmucosal lozenges), Fentora (Effervescent buccal tablets), Abstral (Sublingual tablets), Subsys (Sublingual sprays), and Lazanda (Nasal sprays)	μ-OR full agonist	Very rapid, potent analgesia and sedation	Respiratory depression, tolerance issues, addiction potential	Approved, widely used (anesthesia, severe pain)
Remifentanil	Ultiva	μ-OR full agonist	Rapid onset, rapid offset, precise titration	Respiratory depression during infusion, little residual analgesia after stop	Approved, widely used in anesthesia

Table 1.

Table showing the name, common brand name target, effects (both positive and negative), and stage of development (indicating how far a drug has advanced through testing and approval)) of different established and upcoming agonists.

Note. Data for Oliceridine are from Wolf et al. (2024). Data for PZM21 are from Manglik et al. (2016). Data for SR-17018 are from Pradhan et al. (2021). Data for Dezocine are from Zhou et al. (2023). Data for Nalfurafine are from Kozono et al. (2018). Data for Difelikefalin are from Fishbane et al. (2022). Data for MP1104 are from Zádor et al. (2019). Data for BU08028 are from Ding et al. (2016). Data for Cebranopadol are from Schroeder et al. (2021). Data for Morphine are from Gutstein and Akil (2025). Data for Hydromorphone are from Kharasch (2020). Data for Diacetylmorphine are from Darke et al. (2019). Data for Oxycodone are from Gudin and Fudin (2021). Data for Fentanyl are from Volpe (2023). Data for Remifentanil are from Egan (2019).

Based on the factors analyzed, several predictions can be drawn. It is important to note, however, that these are solely predictions, and the true effects of drugs are shown through human clinical studies and continued therapeutic use. With that said, this preemptive style of analysis can be extremely useful for researchers looking to explore very recently developed avenues of creating opioid drugs and assess which growing ideas have had the most success thus far.

Firstly, it is crucial to understand which areas of research have had the least success and least exploration with regard to opioid analgesics. To this end, we can cite the limited results of full and partial δ-OR agonists. Most drugs developed for the δ-OR either show low efficacy with analgesia, inordinate complications, or a combination of both issues (for specific examples, refer to Table 3). Thus, the data for the receptor is limited, and the results are not quite promising. Moreover, certain agonists, namely PZM21, were initially thought to be biased agonists, due to their lessened side effects (Figure 1), but it was later discovered that the effects could be attributed to low intrinsic efficacies (Hillhouse & Negus, 2016). Furthermore, the κ-OR, once considered among the most promising candidates for analgesic drug development, has shown mixed results. In many κ-OR agonists in use, low analgesic effects in ratio to dysphoric issues have been noted (Table 3). However, the antipruritic (anti-itch) benefits of κ-OR agonists such as Nalfurafine and Difelikefalin haven't gone unnoticed (Table 3). This receptor—while perhaps not as indicative of heralding the future of less issue-prone analgesic drugs—presents a unique pathway for antipruritic drugs, with a plethora of reassuring, trial-based evidence to support it (Beck et al., 2019; Liu-Chen & Huang, 2022).

More optimistically, we have a number of agonists employing a variety of strategic approaches to drug design. Not only is it important to understand which drugs are successful and unsuccessful, but the underlying mechanisms of said drugs are just as important to the field. To that end, we have seen many drugs with success, but it is still important to define and categorize that success, as different issues necessitate different criteria. The main uses for analgesic drugs are therapeutic and clinical. In outpatient therapy, the patient will be exposed to the drug for longer durations and generally at lower doses. Conversely, in clinical procedures, higher doses are given, but far less frequently and in tightly controlled settings. Some drugs, like fentanyl (see Table 3) are even used for both cases via different routes like the fast-acting intravenous formula for surgical procedures and the slower-release transdermal patches for chronic pains (Nihadha et al., 2022;

Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019).

For acute clinical use, we have seen agonists at the μ-OR work the quickest and safest, but still retain some drawbacks of constipation, nausea, respiratory depression, and continually increasing tolerance. However, when biased to the G proteins $G_{\alpha i/o}$ and $G_{\beta\gamma}$, several agonists showed reduced complications, especially with tolerance, as the β-arrestin was no longer causing the internalization and degradation of the receptor. For example, Oliceridine—an agonist that preferentially activates G protein signaling over β-arrestin recruitment—is already shown to have a lower risk of several side effects in humans. Oliceridine has rapid analgesia like fentanyl and morphine, but lower respiratory depression and gastrointestinal complications at equianalgesic doses of those same traditional opioids (Table 3). This drug has shown us that G protein bias can be successful, but it is still not perfect: side effects can still occur, especially at higher doses (Faouzi et al., 2020; Stahl et al., 2021; Bateman & Levitt, 2021). Oliceridine has not been widely tested for human surgical use, mostly used to counteract moderate–severe acute pain in-clinic. Moreover, it is important to note that not all studies consistently replicate the same balance of β-arrestin versus G protein outcomes, so results should be interpreted with caution and may depend on the specific ligand and experimental system. Due to this, the community is still searching for an even better opioid analgesic to compete with fentanyl, and many feel G protein bias is the way to get there.

In chronic therapeutic development, on the other hand, many of the most promising agonists also utilize the concept of dual agonism/antagonism where agonists target multiple receptors. For example, BU08028 and Cebranopadol are both mixed agonist drugs (Table 3). BU08028 primarily targets the μ-OR and NOP, reaping analgesia via a classical opioid pathway, and also modulating pain whilst reducing side effects like addiction risk through the NOP. If hypotheses are confirmed by human trials, this drug could provide potent, long-lasting analgesia without as many complications for chronic and acute pain. Cebranopadol is a first-in-class mixed opioid receptor. The drug targets the μ-OR and NOP as a full agonist and δ-OR and κ-OR as a partial agonist. By providing strong analgesia through the μ-OR, modulating pain through the NOP, and utilizing δ-OR & κ-OR for some neuropathic pain, this drug shows use for both acute and long-term pain management (Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et

al., 2017). Taking a different approach, dezocine, a drug widely used in China for chronic pain in humans, but taken off the American market (for economic, not safety concerns), is a μ-OR agonist, κ-OR antagonist, and a serotonin-norepinephrine reuptake inhibitor. By partially agonizing the μ-OR, the drug creates potent analgesia, but with a ceiling effect, lowering the risk of respiratory depression. Being a κ-OR antagonist, this opioid analgesic also reduces dysphoria and sedation risk.

Body Section 3: Opioid Antagonists: Uses, drawbacks, and new technologies

As the opioid drug crisis remains to be solved, more and more people are overdosing on opioid drugs and experiencing respiratory depression, and thus, opioid antagonists are needed increasingly more. In the United States, many school districts located in high-drug-trafficking areas keep a narcotic reversal agent on hand, usually naloxone (Narcan). However, just as fentanyl has drawbacks and welcomes alternative agonists, naloxone has sparked a new wave of innovation for better opioid antagonists.

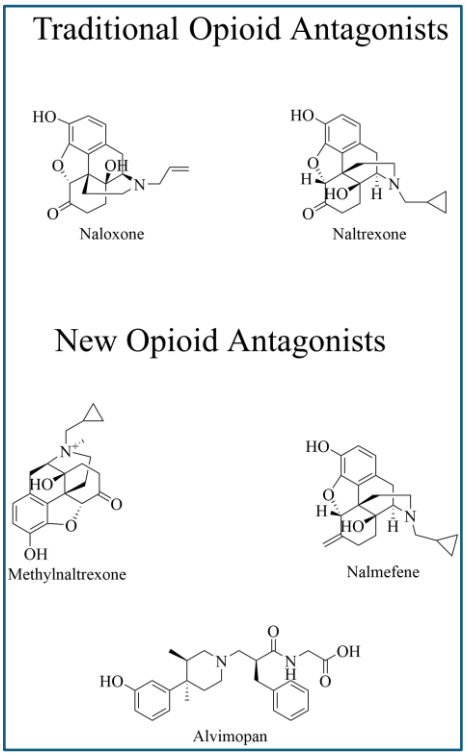

Figure 3.

Chemical structures of traditional and in-development (new) antagonists. Each structure is labeled with its name underneath.

Name / Brand(s)	Delivery Methods	Target	Positive Effects	Negative Effects	Stage of Development / Use
Naloxone (Narcan, Kloxxado, Evzio)	Intravenous (IV), Intramuscular (IM), Subcutaneous (SC), Intranasal spray	Full antagonist at μ-OR; Partial antagonist at κ-OR and δ-OR	Rapid reversal of opioid overdose, restores respiration	Short half-life (risk of re-narcotization), may cause severe withdrawal symptoms in opioid-dependent patients	Approved; gold standard emergency overdose treatment
Naltrexone (ReVia, Vivitrol, Depade)	Oral tablet, Extended-release intramuscular injection	Full antagonist at μ-OR, weak κ-OR antagonism	Prevents relapse in opioid/alcohol use disorder, longer duration than naloxone	Hepatotoxicity risk at high doses, poor adherence in oral form, precipitates withdrawal	Approved for opioid and alcohol dependence treatment
Methylnaltrexone (Relistor)	Subcutaneous injection, Oral tablet	Peripherally acting μ-opioid receptor antagonist (PAMORA); does not cross BBB	Reverses opioid-induced constipation without affecting analgesia	Abdominal pain, won't reverse overdose	Approved for opioid-induced constipation in palliative care or chronic pain
Alvimopan (Entereg)	Oral capsule	PAMORA; selective peripheral μ-opioid receptor antagonist	Reverses opioid-induced constipation without affecting analgesia	Cardiovascular risk with long-term use (restricted to short-term access)	Approved for short-term hospital use post-surgery (REMS program)
Nalmefene (Selincro, Revex)	Intravenous, Intramuscular, Subcutaneous, Oral tablet (Europe)	Full antagonist at μ-OR, partial agonist at κ-OR and δ-OR	Reversal of opioid overdose (longer duration than naloxone), reduces alcohol consumption	Nausea, dysphoria, precipitates withdrawal	Approved in some regions for alcohol dependence; approved in U.S. (IV) for overdose reversal

Table 2.

Table showing the name, common brand name target, effects (both positive and negative), and stage of development of different established and upcoming antagonists.

Note. Naloxone data are from Bailey and Wermeling (2014) and Barton et al. (2005). Naltrexone data are from Comer et al. (2018) and Mark and Jones (2022). Methylnaltrexone data are from Webster et al. (2023) and Deibert (2011). Alvimopan data are from Viscusi and Singla (2019) and Tan et al. (2008). Nalmefene data are from LiverTox (2015) and Smith et al. (2025).

Just as with agonists, antagonist drugs are present in a variety of structures, delivery routes, and mechanisms of action (Figure 3 and Table 4). Naloxone is still the gold standard emergency overdose treatment: it works with few complications and is usually life-saving. The largest issue is its short half-life, as it only works for ~30-90 minutes, whereas some opioid agonists function for hours (Table 3). This can cause re-narcotization, where overdose symptoms return after naloxone wears off, requiring repeat dosing or IV infusion. Some other issues involve rapid withdrawal symptoms in opioid dependent individuals (due to naloxone's rapid onset) and limited efficacy with ultra-potent opioids like Carfentanil. Additionally,

the intravenous version of naloxone requires training to administer, but trained staff may not be available at the time of overdose (Bird et al., 2023; Beck et al., 2019; Lu et al., 2021; Cipriano et al., 2024).

To that end, researchers and scientists are working to develop and test several new reversal agents to hopefully solve some of naloxone's issues without sacrificing its efficacy. So far, drugs like Naltrexone and Nalmefene have been created and FDA approved for certain cases (Table 4 and Figure 3). They tend to last much longer than naloxone, but have been associated with immediate acute withdrawal symptoms, so newer opioid antagonist drugs are still in development (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Moreover, we now have several oral sprays, nasal sprays, and oral capsules to make untrained administration easier (Table 4). While some critics have argued that the widespread availability of reversal agents could embolden opioid users and agitate the issue, widespread consensus agrees that the lives saved overshadow this issue. Additionally, a new class of antagonist drugs known as PAMORAs (peripherally acting μ-opioid receptor antagonists) has emerged (Table 4). These drugs, like alvimopan and methylnaltrexone, are actually not used to treat opioid overdose. Rather, they are utilized mainly for opioid-induced constipation. PAMORAs, unlike most antagonists, do not reduce analgesic effects, making them a great resource for patients in chronic pain or for post-operative care (Pellissier et al., 2018; Madariaga-Mazón et al., 2017).

Another issue is that while traditional antagonist drugs create a rapid reversal effect, they cannot be given preemptively, as they have a short half-life. However, a unique class of drugs known as monoclonal antibody–based opioid binders present a new way to combat the issue: the idea of opioid "vaccines". Unlike traditional antagonists, monoclonal antibodies could prevent opioid agonists from crossing the blood-brain barrier (BBB). This would effectively reduce the effects of opioids over a long period, thus "vaccinating" patients against them. Nevertheless, many concerns and debates exist over this topic. For instance, the design of these drugs is very specific, usually only targeting one or a few agonists. So, if a person suffering from opioid addiction were to get treated against heroin, thus nulling its effects, they may resort to other drugs such as fentanyl for the same euphoria. Moreover, if a patient is vaccinated against too many opioids and needs a surgical procedure, the anesthesiologist may have a difficult time finding an opioid drug to administer analgesia. This applies even more so for an emergency room (ER) case in

which the patient's medical record may not be on hand. So, even though traditional antagonists and monoclonal antibody–based drugs strive to aid the same issue—the ongoing opioid crisis—both take very different routes and expect very different outcomes (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Thus, they are not in competition with each other, as neither can replace the other, but expanding our research in both areas would benefit the same problem.

Conclusion:

In synthesis, opioid pharmacology represents a path to improving both therapeutic tools and clinical medicine. Our growing understanding of opioid receptor function has revealed opportunities to separate beneficial analgesic effects from unwanted side effects, but the path toward safer and more effective drugs remains largely open. Nevertheless, historical missteps remind us that scientific innovation must not come at the cost of foregoing rigorous testing, regulation, and responsible clinical use. This evolving landscape can be summarized in three key areas. First, progress in biased and bitopic agonism has highlighted promising strategies, such as the development of biased agonists that preferentially activate pathways linked to analgesia and the exploration of dual-acting compounds that target multiple receptors simultaneously. Second, persistent limitations remain in translating encouraging preclinical findings into reliable clinical outcomes, underscoring the need for cautious interpretation and stringent validation. Third, the outlook for rational design—integrating receptor structure and pharmacological innovation—offers a forward-looking path toward safer and more effective opioid drugs. It is important to note, however, that in the global market thus far, no opioid agonist has yet surpassed fentanyl and similarly, no opioid antagonist has yet usurped naloxone; both are remarkable innovations that have saved countless lives, regardless of their shortcomings. Ultimately, addressing the opioid crisis will not come from a single breakthrough, but rather an integrated approach. Continued research in all of these areas offers the best chance of balancing the essential role of opioids in pain relief with the urgent need to minimize their risks.

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References

Addiction Rare in Patients Treated with Narcotics. (1980). New England Journal of Medicine, 302(2), 123–123. https://doi.org/10.1056/NEJM198001103020221

Baehr, C., Kelcher, A. H., Khaimraj, A., Reed, D. E., Pandit, S. G., AuCoin, D., Averick, S., & Pravetoni, M. (2020). Monoclonal antibodies counteract opioid-induced behavioral and toxic effects in mice and rats. The Journal of Pharmacology and Experimental Therapeutics, 375(3), 469–477. https://doi.org/10.1124/jpet.120.000124

Bailey, A., & Wermeling, D. (2014). Naloxone for opioid overdose prevention: Pharmacists' role in community-based practice settings. Annals of Pharmacotherapy, 48(5), 601-606. https://doi.org/10.1177/1060028014523730

Balon, T. M., Xia, Y., McKeown, J., Wang, J., Abbott, J. J., Palettas, M., Uribe, A., Echeverria Villalobos, M., Coffman, J. C., & Hu, L.-Q. (2024). Pocket warming of bupivacaine with fentanyl to shorten onset of labor epidural analgesia: A double-blind randomized controlled clinical trial. PLOS ONE, 19(9), e0309515. https://doi.org/10.1371/journal.pone.0309515

Barton, E., Colwell, C., Wolfe, T., Fosnocht, D., Gravitz, C., Bryan, T., et al. (2005). Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. Journal of Emergency Medicine, 29(3), 265-271. https://doi.org/10.1016/j.jemermed.2005.03.007

Bateman, J. T., & Levitt, E. S. (2021). Evaluation of G protein bias and β-arrestin 2 signaling in opioid-induced respiratory depression. American Journal of Physiology-Cell Physiology, 321(4), C681–C683. https://doi.org/10.1152/ajpcell.00259.2021

Beck, T. C., Reichel, C. M., Helke, K. L., Bhadsavle, S. S., & Dix, T. A. (2019). Non-addictive orally-active kappa opioid agonists for the treatment of peripheral pain in rats. European Journal of Pharmacology, 856, 172396. https://doi.org/10.1016/j.ejphar.2019.05.025

Benet, M., Niazi, A., & Scott, J. (2017). Reciprocal evolution of opiate science from medical and cultural perspectives. Frontiers in Pharmacology, 8 (Article 782). https://doi.org/10.3389/fphar.2017.00782

Bird, H. E., Huhn, A. S., & Dunn, K. E. (2023). fentanyl Absorption, Distribution, Metabolism, and Excretion: Narrative Review and Clinical Significance Related to Illicitly Manufactured fentanyl. Journal of Addiction Medicine, 17(5), 503–508. https://doi.org/10.1097/ADM.0000000000001185

Blumenthal, D., & Shapiro, J. (2025). Policy options for the drug pricing conundrum. Proceedings of the National Academy of Sciences, 122(13), e2418540122. https://doi.org/10.1073/pnas.2418540122

Brown, J. A., Faley, S. L., Shi, Y., Hillgren, K. M., Sawada, G. A., Baker, T. K., Wikswo, J. P., & Lippmann, E. S. (2020). Advances in blood–brain barrier modeling in microphysiological systems highlight critical differences in opioid transport due to cortisol exposure. Fluids and Barriers of the CNS, 17(1), 38. https://doi.org/10.1186/s12987-020-00200-9

Chan, E. W. Y., Leung, J. C. Y., Wong, I. C. K., & others. (2021). Prescription medicine misuse in the Asia–Pacific region: An evolving issue? British Journal of Clinical Pharmacology, 87(4), 1810-1818. https://doi.org/10.1111/bcp.14638

Chatterjee, A., et al. (2023). Improving the generalizability of protein–ligand binding predictions with AI-Bind. Nature Communications, 14(1), 2347. https://doi.org/10.1038/s41467-023-37572-z

Christoph, A., Eerdekens, M.-H., Kok, M., Volkers, G., & Freynhagen, R. (2017). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience in patients with chronic low back pain in a randomized clinical trial. Pain, 158(9), 1813–1824. https://doi.org/10.1097/j.pain.0000000000000986

Cipriano, A., Kapil, R. P., Zhou, M., Shet, M. S., Whiteside, G. T., Willsie, S. K., & Harris, S. C. (2024). Safety, tolerability, and pharmacokinetics of single- and multiple-ascending doses of sunobinop in healthy participants. Clinical Pharmacology in Drug Development, 13(7), 790–800. https://doi.org/10.1002/cpdd.1394

Comer, S. D., Sullivan, M. A., Hulse, G. K., & Somoza, E. (2018). Naltrexone: A history and future directions. CNS Drugs, 32(9), 825-836.

Cook, M. E., Knoph, C. S., Fjelsted, C. A., Frøkjær, J. B., Bilgrau, A. E., Novovic, S., Jørgensen, M. T., Mortensen, M. B., Nielsen, L. B. J., Hadi, A., Berner-Hansen, M., Rutkowski, W., Vujasinovic, M., Löhr, M., Drewes, A. M., & Olesen, S. S. (2023). Effects of a peripherally acting μ-opioid receptor antagonist for the prevention of recurrent acute pancreatitis: Study protocol for an investigator-initiated, randomized, placebo-controlled, double-blind clinical trial (PAMORA-RAP trial). Trials, 24(1), 301. https://doi.org/10.1186/s13063-023-07287-z

Coombes, L., Burke, K., & Anderson, A.-K. (2017). The use of rapid onset fentanyl in children and young people for breakthrough cancer pain. Scandinavian Journal of Pain, 17(1), 256–259. https://doi.org/10.1016/j.sjpain.2017.07.010

Curran, M. P., Robins, G. W., Scott, L. J., & Perry, C. M. (2008). Alvimopan. Drugs, 68(14), 2011-2019. https://doi.org/10.2165/00003495-200868140-00006

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., Bernstein, S. L., & Fiellin, D. A. (2015). Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. JAMA, 313(16), 1636. https://doi.org/10.1001/jama.2015.3474

Darke, S., Farrell, M., & Degenhardt, L. (2019). The pharmacology of heroin. Drug and Alcohol Review, 38(1), 108–116. https://doi.org/10.1111/dar.12878

Deibert, P. (2011). Opioid-induced constipation in advanced illness. Journal of Pain and Symptom Management, 41(5), 918-929. https://doi.org/10.1038/ajg.2011.30

Ding, H., Czoty, P. W., & Nader, M. A. (2016). A novel orvinol analog, BU08028, as a safe opioid analgesic without abuse liability in primates. Proceedings of the National Academy of Sciences, 113(22), E6269–E6278. https://doi.org/10.1073/pnas.1615248113

Egan, T. D. (2019). Remifentanil pharmacokinetics and pharmacodynamics: A review and update. Anesthesia & Analgesia, 128(5), 925–937. https://doi.org/10.1213/ANE.0000000000004077

Eggleston, W., Calleo, V., Kim, M., & Wojcik, S. (2020). Naloxone Administration by Untrained Community Members. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 40(1), 84–88. https://doi.org/10.1002/phar.2352

Ehrlich, A. T., Kieffer, B. L., & Darcq, E. (2019). Current strategies toward safer mu opioid receptor drugs for pain management. Expert Opinion on Therapeutic Targets, 23(4), 315–326. https://doi.org/10.1080/14728222.2019.1586882

Escudero-Lara, A., Cabañero, D., & Maldonado, R. (2021). Kappa opioid receptor modulation of endometriosis pain in mice. Neuropharmacology, 195, 108677. https://doi.org/10.1016/j.neuropharm.2021.108677

Faouzi, A., Varga, B. R., & Majumdar, S. (2020). Biased Opioid Ligands. Molecules, 25(18), 4257. https://doi.org/10.3390/molecules25184257

Fishbane, S., Jamal, A., Nanovic, L., & Pergola, P. E. (2022). Safety and effectiveness of difelikefalin in patients with moderate-to-severe chronic kidney disease-

associated pruritus. Kidney International Reports, 7(8), 2040–2051. https://doi.org/10.1016/j.ekir.2022.06.019

Gado, F., Ferrisi, R., Polini, B., Mohamed, K. A., Ricardi, C., Lucarini, E., Carpi, S., Domenichini, F., Stevenson, L. A., Rapposelli, S., Saccomanni, G., Nieri, P., Ortore, G., Pertwee, R. G., Ghelardini, C., Di Cesare Mannelli, L., Chiellini, G., Laprairie, R. B., & Manera, C. (2022). Design, synthesis, and biological activity of new CB2 receptor ligands: From orthosteric and allosteric modulators to dualsteric/bitopic ligands. Journal of Medicinal Chemistry, 65(14), 9918–9938. https://doi.org/10.1021/acs.jmedchem.2c00582

Gavériaux-Ruff, C., & Kieffer, B. L. (2011). Delta opioid receptor analgesia: Recent contributions from pharmacology and molecular approaches. Behavioural Pharmacology, 22(5 and 6), 405–414. https://doi.org/10.1097/FBP.0b013e32834a1f2c

Glenn, J. K., & Goldman, J. (1976). Task delegation to physician extenders—Some comparisons. American Journal of Public Health, 66(1), 64–66. https://doi.org/10.2105/ajph.66.1.64

Göhler, K., Sokolowska, M., Schoedel, K. A., Nemeth, R., Kleideiter, E., Szeto, I., & Eerdekens, M.-H. (2019). Assessment of the abuse potential of cebranopadol in nondependent recreational opioid users: A phase 1 randomized controlled study. Journal of Clinical Psychopharmacology, 39(1), 46–56. https://doi.org/10.1097/JCP.0000000000000995

Gutstein, H. B., & Akil, H. (2025). Opioid analgesics. In L. Bruton, J. S. Lazo, & K. L. Parker (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics (14th ed., pp. 175–221). McGraw-Hill Education.

Gudin, J. A., & Fudin, J. (2021). Pharmacokinetics and pharmacodynamics of oxycodone: A review of the literature. Pain & Therapy, 10(1), 75–87. https://doi.org/10.1007/s40122-020-00214-3

Guo, S.-B., Meng, Y., Lin, L., Zhou, Z.-Z., Li, H.-L., Tian, X.-P., & Huang, W.-J. (2024). Artificial intelligence alphafold model for molecular biology and drug discovery: A machine-learning-driven informatics investigation. Molecular Cancer, 23(1), 223. https://doi.org/10.1186/s12943-024-02140-6

Hampsey, E., Jelen, L., & Young, A. H. (2024). Aticaprant: (A κ-opioid receptor antagonist) for major depressive disorder. Expert Opinion on Emerging Drugs, 29(3), 193–204. https://doi.org/10.1080/14728214.2024.2345645

Han, J., Zhang, J., Nazarova, A. L., Bernhard, S. M., Krumm, B. E., Zhao, L., Lam, J. H., Rangari, V. A., Majumdar, S., Nichols, D. E., Katritch, V., Yuan, P., Fay, J. F., &

Che, T. (2023). Ligand and G-protein selectivity in the κ-opioid receptor. Nature, 617(7960), 417–425. https://doi.org/10.1038/s41586-023-06030-7

Hovah, M. E., & Holzgrabe, U. (2024). Bivalent and bitopic ligands of the opioid receptors: The prospects of a dual approach. Medicinal Research Reviews, 44(6), 2545–2599. https://doi.org/10.1002/med.22050

Jang, J. S., Hwang, S. M., Kwon, Y., Tark, H., Kim, Y. J., Ryu, B. Y., & Lee, J. J. (2018). Is the transdermal fentanyl patch an efficient way to achieve acute postoperative pain control?: A randomized controlled trial. Medicine, 97(51), e13768. https://doi.org/10.1097/MD.0000000000013768

Jayakody, T., Budagoda, D. K., Mendis, K., Dilshan, W. D., Bethmage, D., Dissasekara, R., & Dawe, G. S. (2025). Biased agonism in peptide-GPCRs: A structural perspective. Pharmacology & Therapeutics, 269, 108806. https://doi.org/10.1016/j.pharmthera.2025.108806

Kelly, E., Conibear, A., & Henderson, G. (2023). Biased Agonism: Lessons from Studies of Opioid Receptor Agonists. Annual Review of Pharmacology and Toxicology, 63, 491–515. https://doi.org/10.1146/annurev-pharmtox-052120-091058

Kharasch, E. D. (2020). Hydromorphone: Clinical pharmacokinetics and pharmacodynamics. Expert Opinion on Drug Metabolism & Toxicology, 16(6), 495–507. https://doi.org/10.1080/17425255.2020.1752200

Kieffer, B. L. (1999). Opioids: First lessons from knockout mice. Trends in Pharmacological Sciences, 20(1), 19–26. https://doi.org/10.1016/S0165-6147(98)01279-6

Kliewer, A., Gillis, A., Hill, R., Schmiedel, F., Bailey, C., Kelly, E., Henderson, G., Christie, M. J., & Schulz, S. (2020). Morphine-induced respiratory depression is independent of β-arrestin2 signalling. British Journal of Pharmacology, 177(13), 2923–2931. https://doi.org/10.1111/bph.15004

Koch, E. D., Kapanadze, S., Eerdekens, M.-H., Kralidis, G., Létal, J., Sabatschus, I., & Ahmedzai, S. H. (2019). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience with cancer-related pain for up to 26 weeks. Journal of Pain and Symptom Management, 58(3), 390–399. https://doi.org/10.1016/j.jpainsymman.2019.05.012

Kozono, H., Yoshimura, M., & Tsukamoto, K. (2018). Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride for the treatment of intractable pruritus in hemodialysis patients. Therapeutics and

Clinical Risk Management, 14, 1579–1587. https://doi.org/10.2147/TCRM.S171803

Krishnamurti, C., & Rao, S. C. (2016). The isolation of morphine by Serturner. Indian Journal of Anaesthesia, 60(11), 861–862. https://doi.org/10.4103/0019-5049.193696

Lee, J. D., Nunes, E. V., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C. C., King, J., Lindblad, R., Liu, D., Matthews, A. G., May, J., Peavy, K. M., Ross, S., Salazar, D., Schkolnik, P., … Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. The Lancet, 391(10118), 309–318. https://doi.org/10.1016/S0140-6736(17)32812-X

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. (2015). Nalmefene. National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Liu-Chen, L.-Y., & Huang, P. (2022). Signaling underlying kappa opioid receptor-mediated behaviors in rodents. Frontiers in Neuroscience, 16, 964724. https://doi.org/10.3389/fnins.2022.964724

Lorch, U., Pierscionek, T., Freier, A., Spencer, C. S., & Täubel, J. (2021). Safety, tolerability, and dose proportionality of a novel transdermal fentanyl matrix patch and bioequivalence with a matrix fentanyl patch: Two phase 1 single-center open-label, randomized crossover studies in healthy Japanese volunteers. Clinical Pharmacology in Drug Development, 10(3), 260–271. https://doi.org/10.1002/cpdd.846

Lu, J. J., Polgar, W. E., Mann, A., Dasgupta, P., Schulz, S., & Zaveri, N. T. (2021). Differential in vitro pharmacological profiles of structurally diverse nociceptin receptor agonists in activating G protein and beta-arrestin signaling at the human nociceptin opioid receptor. Molecular Pharmacology, 100(1), 7–18. https://doi.org/10.1124/molpharm.120.000076

Madariaga-Mazón, A., Marmolejo-Valencia, A. F., Li, Y., Toll, L., Houghten, R. A., & Martinez-Mayorga, K. (2017). Mu-opioid receptor biased ligands: A safer and painless discovery of analgesics? Drug Discovery Today, 22(11), 1719–1729. https://doi.org/10.1016/j.drudis.2017.07.002

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of

the μ-opioid receptor bound to a morphinan antagonist. Nature, 485(7398), 321–326. https://doi.org/10.1038/nature10954

Manglik, A., Lin, H., Aryal, D. K., McCorvy, J. D., Dengler, D., Corder, G., ... & Gmeiner, P. (2016). Structure-based discovery of opioid analgesics with reduced side effects. Nature, 537(7619), 185–190. https://doi.org/10.1038/nature19112

Mark, T. L., & Jones, C. M. (2022). Assessing naltrexone prescribing and barriers to initiation for opioid use disorder. Frontiers in Psychiatry, 13, 856938.

Mann, A., Illing, S., Miess, E., & Schulz, S. (2015). Different mechanisms of homologous and heterologous μ-opioid receptor phosphorylation. British Journal of Pharmacology, 172(2), 311–316. https://doi.org/10.1111/bph.12627

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature, 485(7398), 321-326. https://doi.org/10.1038/nature10954

Martinez, S., Harris, H., Chao, T., Luba, R., Pravetoni, M., Comer, S. D., & Jones, J. D. (2023). The potential role of opioid vaccines and monoclonal antibodies in the opioid overdose crisis. Expert Opinion on Investigational Drugs, 32(3), 181–185. https://doi.org/10.1080/13543784.2023.2187286

Mathur, V. S., Kumar, J., Crawford, P. W., Hait, H., Sciascia, T., & for the TR02 Study Investigators. (2017). A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. American Journal of Nephrology, 46(6), 450–458. https://doi.org/10.1159/000484573

Mark, T. L., & Jones, C. M. (2022). Assessing naltrexone prescribing and barriers to initiation for opioid use disorder. Frontiers in Psychiatry, 13, 856938.

Merivirta, R., Äärimaa, V., Aantaa, R., Koivisto, M., Leino, K., Liukas, A., & Kuusniemi, K. (2013). Postoperative fentanyl Patch versus subacromial bupivacaine infusion in arthroscopic shoulder surgery. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 29(7), 1129–1134. https://doi.org/10.1016/j.arthro.2013.04.018

Mitchell, S. G., Monico, L. B., Gryczynski, J., Fishman, M. J., O'Grady, K. E., & Schwartz, R. P. (2021). Extended-release naltrexone for youth with opioid use disorder. Journal of Substance Abuse Treatment, 130, 108407. https://doi.org/10.1016/j.jsat.2021.108407

Morales, P., Scharf, M. M., Bermudez, M., Egyed, A., Franco, R., Hansen, O. K., Jagerovic, N., Jakubík, J., Keserű, G. M., Kiss, D. J., Kozielewicz, P., Larsen, O., Majellaro, M., Mallo-Abreu, A., Navarro, G., Prieto-Díaz, R., Rosenkilde, M. M.,

Sotelo, E., Stark, H., … Wingler, L. M. (2025). Progress on the development of Class A GPCR-biased ligands. British Journal of Pharmacology, 182(14), 3249–3300. https://doi.org/10.1111/bph.17301

Mores, K. L., Cassell, R. J., & Van Rijn, R. M. (2019). Arrestin recruitment and signaling by G protein-coupled receptor heteromers. Neuropharmacology, 152, 15–21. https://doi.org/10.1016/j.neuropharm.2018.11.010

Moss, L., Hijma, H., Demitrack, M., Kim, J., Groeneveld, G. J., Van Velzen, M., Niesters, M., Olofsen, E., & Dahan, A. (2023). Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine. Anesthesiology, 139(6), 746–756. https://doi.org/10.1097/ALN.0000000000004758

Nanovic, L., Fishbane, S., Jamal, A., & Pergola, P. E. (2022). Safety and effectiveness of difelikefalin in patients with moderate-to-severe chronic kidney disease-associated pruritus. Kidney International Reports, 7(8), 2040–2051.

Ni, Y., Huang, R., Yang, S., Yang, X. Y., Zeng, S., Yao, A., Huang, J., & Yang, G. (2024). Pharmacokinetics and safety of oliceridine fumarate injection in Chinese patients with chronic non-cancer pain: A phase I, single-ascending-dose, open-label clinical trial. Drug Design, Development and Therapy, 18, 2729–2743. https://doi.org/10.2147/DDDT.S461416

Nihadha, P. M., Chugh, A., Kaur, A., Kumar, S., Naveen, K. H., Bhatia, P. K., Kumar, P., & Chaudhry, K. (2022). Transdermal fentanyl patch versus standard analgesia in postoperative oral submucous fibrosis patients: A triple blinded, randomised control trial. British Journal of Oral and Maxillofacial Surgery, 60(9), 1246–1253. https://doi.org/10.1016/j.bjoms.2022.07.002

Nunes, E. V., Bisaga, A., Krupitsky, E., Nangia, N., Silverman, B. L., Akerman, S. C., & Sullivan, M. A. (2020). Opioid use and dropout from extended-release naltrexone in a controlled trial: Implications for mechanism. Addiction, 115(2), 239–246. https://doi.org/10.1111/add.14735

Pellissier, L. P., Gandía, J., Laboute, T., Becker, J. A. J., & Le Merrer, J. (2018). μ opioid receptor, social behaviour and autism spectrum disorder: Reward matters. British Journal of Pharmacology, 175(14), 2750–2769. https://doi.org/10.1111/bph.13808

Post, A., Smart, T. S., Krikke-Workel, J., Dawson, G. R., Harmer, C. J., Browning, M., Jackson, K., Kakar, R., Mohs, R., Statnick, M., Wafford, K., McCarthy, A., Barth, V., & Witkin, J. M. (2016). A selective nociceptin receptor antagonist to treat depression: Evidence from preclinical and clinical studies.

Neuropsychopharmacology, 41(7), 1803–1812. https://doi.org/10.1038/npp.2015.348

Pradhan, A. A., Maguire, D. R., McLaughlin, J. P., & Cahill, C. M. (2021). SR-17018 stimulates atypical μ-opioid receptor phosphorylation and signaling. Frontiers in Pharmacology, 12, 721993. https://doi.org/10.3389/fphar.2021.721993

Raffaeli, W., Samolsky Dekel, B. G., Landuzzi, D., Caminiti, A., Righetti, D., Balestri, M., Montanari, F., Romualdi, P., & Candeletti, S. (2006). Nociceptin levels in the cerebrospinal fluid of chronic pain patients with or without intrathecal administration of morphine. Journal of Pain and Symptom Management, 32(4), 372–377. https://doi.org/10.1016/j.jpainsymman.2006.05.013

Reilly, R. F. (2016). Medical and surgical care during the American Civil War, 1861-1865. Proceedings (Baylor University. Medical Center), 29(2), 138–142. https://doi.org/10.1080/08998280.2016.11929390

Rosenman, E., Buck, R. K., Anjum, N., Thompson, L., Rist, J., Banuna, L., Dolgoff, E., Hartmann, S., Lelei, S., Feng, Z., & Holmes, L. M. (2025). From dealer to doctor: A case study examining how Purdue Pharma sought to leverage racial health disparities to attenuate flagging OxyContin sales. Social Science & Medicine, 382, 118132. https://doi.org/10.1016/j.socscimed.2025.118132

Rudolph, K. E., Díaz, I., Luo, S. X., Rotrosen, J., & Nunes, E. V. (2021). Optimizing opioid use disorder treatment with naltrexone or buprenorphine. Drug and Alcohol Dependence, 228, 109031. https://doi.org/10.1016/j.drugalcdep.2021.109031

Saigusa, T., Aono, Y., & Waddington, J. L. (2017). Mechanisms underlying δ- and μ-opioid receptor agonist-induced increases in extracellular dopamine level in the nucleus accumbens of freely moving rats. Journal of Oral Science, 59(2), 195–200. https://doi.org/10.2334/josnusd.16-0874

Schroeder, B., Lemieux, M., Scherbaum, N., et al. (2021). Assessment of the potential of novel and classical opioids to induce opioid use disorder-like behavior: Cebranopadol and beyond. British Journal of Pharmacology, 178(13), 2632–2648. https://doi.org/10.1111/bph.16199

Singla, N. K., Skobieranda, F., Soergel, D. G., Salamea, M., Burt, D. A., Demitrack, M. A., & Viscusi, E. R. (2019). APOLLO-2: A randomized, placebo and active-controlled phase III study investigating oliceridine (TRV 130), a G protein–biased ligand at the μ-opioid receptor, for management of moderate to

severe acute pain following abdominoplasty. Pain Practice, 19(7), 715–731. https://doi.org/10.1111/papr.12801

Smith, J., et al. (2025). New study examines nalmefene auto-injector and intranasal naloxone for reversal of respiratory depression induced by fentanyl. Purdue Pharma News.

Smith, L. C., Bremer, P. T., Hwang, C. S., Zhou, B., Ellis, B., Hixon, M. S., & Janda, K. D. (2019). Monoclonal antibodies for combating synthetic opioid intoxication. Journal of the American Chemical Society, 141(26), 10489–10503. https://doi.org/10.1021/jacs.9b04872

Stahl, E. L., Schmid, C. L., Acevedo-Canabal, A., Read, C., Grim, T. W., Kennedy, N. M., Bannister, T. D., & Bohn, L. M. (2021). G protein signaling–biased mu opioid receptor agonists that produce sustained G protein activation are noncompetitive agonists. Proceedings of the National Academy of Sciences, 118(48), e2102178118. https://doi.org/10.1073/pnas.2102178118

Stevens, R. C., Cherezov, V., Katritch, V., Abagyan, R., Kuhn, P., Rosen, H., & Wüthrich, K. (2013). The GPCR network: A large-scale collaboration to determine human GPCR structure and function. Nature Reviews Drug Discovery, 12(1), 25–34. https://doi.org/10.1038/nrd3859

Sutcliffe, K. J., Corey, R. A., Alhosan, N., Cavallo, D., Groom, S., Santiago, M., Bailey, C., Charlton, S. J., Sessions, R. B., Henderson, G., & Kelly, E. (2022). Interaction with the lipid membrane influences fentanyl pharmacology. Advances in Drug and Alcohol Research, 2, 10280. https://doi.org/10.3389/adar.2022.10280

Szumiec, L., Bugno, R., Szumiec, L., & Przewlocki, R. (2023). The differential influence of PZM21, a nonrewarding μ-opioid receptor agonist with G protein bias, on behavioural despair and fear response in mice. Behavioural Brain Research, 449, 114466. https://doi.org/10.1016/j.bbr.2023.114466

Tan, Z., et al. (2008). Management of postoperative ileus: Focus on alvimopan. Journal of Pain & Symptom Management, 35(5), 500-501.

Van Zee, A. (2009). The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. American Journal of Public Health, 99(2), 221–227. https://doi.org/10.2105/AJPH.2007.131714

Varga, B. R., Streicher, J. M., & Majumdar, S. (2023). Strategies towards safer opioid analgesics—A review of old and upcoming targets. British Journal of Pharmacology, 180(7), 975–993. https://doi.org/10.1111/bph.15760

Verbeek, J., & Brinkman, D. J. (2025). A comprehensive narrative review of protonitazene: Pharmacological characteristics, detection techniques, and toxicology. Basic & Clinical Pharmacology & Toxicology, 137(2), e70078. https://doi.org/10.1111/bcpt.70078

Viscusi, E. R., & Singla, N. K. (2019). Alvimopan for post-radical cystectomy ileus: What should we know? Therapeutic Advances in Urology, 11, 1756287218822806.

Wang, Y., et al. (2023). Structures of the entire human opioid receptor family. Cell, 186(2), 413-427.e17. https://doi.org/10.1016/j.cell.2022.12.026

Webster, L. R., Brenner, D., Israel, R. J., Stambler, N., & Slatkin, N. E. (2023). Reductions in all-cause mortality associated with the use of methylnaltrexone for opioid-induced bowel disorders: A pooled analysis. Pain Medicine, 24(3), 341-350. https://doi.org/10.1093/pm/pnx148

Wikstrom, B. D., Gellert, R., Ladefoged, S. D., Danda, Y., Akai, M., Ide, K., Ogasawara, M., Kawashima, Y., Ueno, K., Mori, A., & Ueno, Y. (2005). κ-Opioid system in uremic pruritus: Multicenter, randomized, double-blind, placebo-controlled clinical studies. Journal of the American Society of Nephrology, 16(12), 3742–3747. https://doi.org/10.1681/ASN.2005020152

Wolf, A., Unterberg, M., Witowski, A., Adamzik, M., & Wolf, A. (2024). Efficacy, safety, and side effects of oliceridine in acute postoperative pain: A protocol for a systematic review and meta-analysis. PLOS ONE, 19(2), e0299320. https://doi.org/10.1371/journal.pone.0299320

Yamaguchi, S., Uchida, E., Terahara, T., Okawa, K., Hashimoto, F., & Tanaka, Y. (2020). Efficacy and safety of fentanyl citrate patch, including a low-dose 0.5 mg formulation, in opioid-naïve patients with cancer pain. Clinical Drug Investigation, 40(11), 1041–1052. https://doi.org/10.1007/s40261-020-00965-9

Zádor, F., Zelena, D., Szegeczki, V., et al. (2019). MP1104, a mixed kappa-delta opioid receptor agonist has anti-hyperalgesic actions without abuse liability in rodents. European Journal of Pharmacology, 857, 172459. https://doi.org/10.1016/j.ejphar.2019.172459

Zhou, X., Wang, W., Fang, B., & Yu, T. (2023). A new formulation of dezocine, Cyc-dezocine, reduces oxycodone consumption in postoperative pain management. Neuroscience Letters, 813, 137486. https://doi.org/10.1016/j.neulet.2023.137486

Zhuang, Y., Wang, Y., He, B., He, X., Zhou, X. E., Guo, S., Rao, Q., Yang, J., Liu, J., Zhou, Q., Wang, X., Liu, M., Liu, W., Jiang, X., Yang, D., Jiang, H., Shen, J., Melcher, K., Chen, H., … Xu, H. E. (2022). Molecular recognition of morphine and fentanyl by the human μ-opioid receptor. Cell, 185(23), 4361-4375.e19. **https://doi.org/10.1016/j.cell.2022.09.041**

Current and Prospective Opioid Analgesics: Assessing Their Value for Ongoing Research and Promise for Therapeutic and Clinical Use

*Name & Affiliation not given due to Blind Review guidelines

Abstract

Opioid analgesics, though among the most potent tools for pain relief at our disposal, sit at the epicenter of a growing clinical and societal crisis. **Currently, most opioid analgesic drugs like fentanyl function at the Mu Opioid-Receptor (μ-OR), which has notably been linked to respiratory depression, constipation, and high abuse potential. In fact, the abuse of fentanyl been a primary driver of opioid overdose, leading to over 80,000 deaths in the United States just in the last year.** As demand for safer analgesics has surged, the field has responded with a range of innovative approaches, many involving the strategic use of other opioid receptors **such as the Delta Opioid-Receptor, Kappa Opioid-Receptor, and Nociceptin/Orphanin Receptor (δ-OR, κ-OR, and NOP respectively). Each of these receptors plays a role in analgesia yet also creates a unique set of complications to accompany it.** To combat this issue, dozens of opioid agonists and antagonists are being developed. We have seen new concepts such as biased and bitopic agonism emerge, presenting an updated outlook on how these drugs function. **Thus far, no single method has yielded a drug to outcompete fentanyl's potency and prevalence in the global market. This review not only brings to light the new classes of opioid drugs, but also discusses their relevance to the field. Moreover, many prevalent examples of opioids and their mechanisms are discussed throughout the paper, giving clinically backed insight into the drugs' varying levels of efficacy.**

Introduction

Since first being recorded by the Sumerian Empire for their hypnotic properties in 3400 B.C., opioids have been employed by a myriad of civilizations, including the Egyptians, Indians, Chinese, and Greeks. **There is even evidence showing two of the oldest medical systems using opium derived from poppy seeds to induce analgesia. In Ayurveda (an ancient holistic medical practice from India) *Ahiphena*—also known as poppy seeds—were used for sedation, pain relief, and gastrointestinal relief.** Similarly, in Chinese Traditional Medicine, the same

plant, though here called "*Ying Su Ke*", was used for pain and cough suppression. Through the years, opioid use has been refined through medical, religious, and recreational contexts, ultimately culminating in the 19th-century isolation of morphine and the 20th-century synthesis of fentanyl **(Benet et al., 2017).**

Morphine, the first purified opioid analgesic, has been one of the most prominent drugs in medical and pharmaceutical history (Krishnamurti & Rao, 2016). Isolated by Friedrich Sertürner in Germany in 1804, this opium poppy derivative broke ground in the research of analgesics. Morphine functions by binding to the μ-opioid receptors in the brain and spinal cord to block the perception of pain (Zhuang et al., 2022). Its introduction into the clinical and therapeutic settings revolutionized pain management, saving countless lives. During the American Civil War, morphine was widely employed as an analgesic via hypodermic injection or laudanum (Reilly, 2016). Beyond that, however, it helped the scientific community understand addiction, receptor theory, and tolerance. Namely, early patterns of dose-dependent effects and diminishing efficacy with prolonged use provided some of the first evidence for discrete receptor sites and the adaptive changes of tolerance. These ramifications have made morphine both a medical breakthrough and cautionary tale, sparking the development of newer, safer, and more potent opioid analgesics.

This undertaking eventually gave rise to a new breed of opioid analgesics optimized for the clinical field: synthetic opioids. The most notable of which is fentanyl, an opioid-based drug first synthesized in Belgium by Dr. Paul Janssen in 1959. This drug is widely accepted as the greatest discovery in the field since the introduction of morphine, of which it is 50–100 times more potent (Zhuang et al., 2022). Originally developed for surgical anesthesia and severe pain management, fentanyl's high lipid solubility and rapid onset coupled with its relatively low cost have made it one of the most universal analgesics of the modern world. **However, its high potency and rapid onset could make even as little as about 2 mg lethal in opioid-naïve individuals, underscoring the need for precaution and safety when in use (Bird et al., 2023).** Nevertheless, as of now, fentanyl is still favored in most developed nations for analgesia.

In America, the for-profit healthcare and pharmacological system artificially inflate the price of life-saving medicines, making them inaccessible to most Americans living under the poverty line **(Blumenthal & Shapiro, 2025)**. Thus, many

Americans are forced to resort to unlicensed distributors to attain their prescriptions at a reasonable price. Unfortunately, however, this results in many preventable deaths every year. The issue is exacerbated by the recreational use of opioids and high mental health crisis rates (usually resulting in substance abuse) among American youths. Moreover, many medical professionals are encouraged to use opioids to treat pain therapeutically, creating high addiction rates in many chronic pain patients. Together, these factors—among many others—have contributed to the ongoing U.S. opioid crisis.

This problem, however, is not uniform throughout the world. Nations like Switzerland, Rwanda, Saudi Arabia, New Zealand, China, Japan, South Korea, and Singapore have been able to keep drug abuse rates low through strict pharmaceutical monitoring and low prescription medication costs **(Chan et al., 2021). In stark contrast, regions like Latin America, Eastern Europe, Central & South Asia, and Africa are frequently identified as illicit drug hotspots & trafficking routes.** Overall, this disparity can be attributed to an array of factors from cultural taboos to geopolitical connections to government regulations.

Opioids, unlike other substances like marijuana or nicotine products, can be immediately fatal. While most addicting substances create long-term issues sometimes leading to cancer, opioid drugs create respiratory depression in overdose, thus making them fatal in minutes if not counteracted with an antagonist drug. To combat this, many disparate approaches are being taken by researchers and corporations alike. One prevalent avenue involves exploring the different opioid receptors.

Standard Terminology	Abbreviation Used
G Protein-Coupled Receptor	GPCR
Mu Opioid-Receptor	μ-OR
Kappa Opioid-Receptor	κ-OR
Delta Opioid-Receptor	δ-OR
Nociceptin/Orphanin Receptor	NOP

Table 1.

This table outlines the abbreviations used in lieu of standard terminology throughout the paper.

Opioid receptors are a specific type of GPCR located throughout the brain, spinal cord, and peripheral nervous system. Currently, we know of four main types of these receptors: μ-OR, κ-OR, δ-OR, and NOP (Refer to table 1) (Wang et al., 2023). Each plays a distinct role in analgesia, pain management, and the effects of both endogenous and synthetic opioids. The μ-OR has historically been used for the majority of analgesic drugs, including morphine, heroin, oxycodone, and fentanyl. It governs euphoria and analgesia, but its use also often leads to respiratory depression and addiction (Zhuang et al., 2022). The κ-OR also deals in the domain of analgesia, but comes with the complications of dysphoria and hallucinations. Whilst it has historically been overshadowed by the μ-OR, and disregarded due to its hallucinogenic properties, it has had renewed interest in recent years for non-addictive therapies (Beck et al., 2019). On the other hand, the δ-OR continues to deter researchers due to its low selectivity and efficacy. For while it may be another route to drug discovery, it lacks significant promise, and thus intrigue in the receptor is scarce. More recently, an opioid-like receptor has taken the international stage. The NOP, being the newest of the four, has been shown to play a part in stress, mood regulation, and pain. As it has shown reduced side effects in comparison to its counterparts, it represents a promising target for next-generation painkillers (Lu et al., 2021; Cipriano et al., 2024).

In addition to exploring the use of different receptors, two major pathways to mitigating side effects have emerged in the field: bitopic and biased ligands. Bitopic ligands interact with both allosteric and orthosteric sites, offering enhanced control over receptor signaling. By engaging the allosteric site in addition to the orthosteric site, they enable finer modulation of receptor activity. This dual binding confers greater differentiation between receptor subtypes and, consequently, more precise control over receptor activation (Gado et al., 2022). Biased ligands present a way to activate only certain signaling pathways preferentially. They aim to retain therapeutic effects while minimizing complications (Stahl et al., 2021). Until now, opioid drug design focused primarily on orthosteric sites, but recent efforts with biased and bitopic signaling have yielded some positive results, making them a popular topic for continued research.

These discoveries have sparked a surge of interest in the field. Soon after they arose, we saw innumerable researchers begin leveraging these concepts to address the opioid crisis. When hundreds of ligands entered the screening pipeline at once, they quickly overwhelmed existing infrastructure and techniques, underscoring the

need for faster, more scalable approaches (Chatterjee et al., 2023). With aid from new technologies like high-throughput screening, scientists are now able to test thousands of compounds simultaneously at a fraction of the cost, significantly accelerating drug discovery.

Alas, with such a vast repertoire of recent innovation in the field, pinpointing promising candidates has become a highly time-intensive task for researchers new to the field. Fortunately, this review aims to sift through the growing body of opioid ligand candidates to identify those demonstrating the most consistent and reproducible therapeutic and clinical promise across clinical studies.

Methodology:

To report the trends in the field of opioid analgesic drugs, this review utilized primarily qualitative data drawn from open-access sources through PubMed. As the focus of this paper covers next-generation opioid agonists and antagonists, and sources of quantitative data varied greatly between labs for many of these drugs, it would have been counterproductive and scientifically irresponsible to include data collected through such heterogenous methods. The most accurate method of discussing the various opioid agonists and antagonists was by reviewing clinical studies and reporting trends and inconsistencies in the current data. The inclusion criteria consisted of studies published between 2017 and 2025, with some exceptions made for historical data critical to contextualizing newer developments. Moreover, only peer-reviewed articles were included. Study types were selected with a preference for human clinical trials; however, in cases where such studies were unavailable, particularly for newer opioid drugs, animal studies were included to fill in important knowledge gaps. By using this methodology, bias was mitigated by drawing from a wide range of studies across different labs and experimental designs, accurately displaying the current landscape of the field of opioid agonists and antagonists.

Discussion:

Body Section 1: Analysis & Overview of μ-OR, κ-OR, δ-OR, and NOP

The main opioid receptors—μ-OR, κ-OR, δ-OR, and NOP—are part of the Class A G protein-coupled receptor (GPCR) family. GPCRs are a large group of cell-surface receptors that transmit signals into the cell via the activation of intracellular G proteins (Wang et al., 2023). When discussing opioid receptors and their agonists/antagonists, a cascade of intricate processes must occur to create the desired, and undesired, effects that we're familiar with.

As per our current understanding of said processes, we focus on three main proteins within the body: $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. While their respective roles in the system are not yet fully understood, recent findings have linked G protein subunits ($G_{\alpha i/o}$ and $G_{\beta\gamma}$) to primarily positive effects (i.e. analgesia and sedation) and β-arrestin to mainly negative effects (i.e. respiratory depression, constipation, and tolerance development), though exceptions exist (Bateman & Levitt, 2021; Faouzi et al., 2020; Mores et al., 2019). Opioids usually activate $G\alpha_{i/o}$ and $G_{\beta\gamma}$, subsequently phosphorylating the receptor, causing β-arrestin to bind to it. Thus, we receive nearly every effect, every time. To that end, many researchers believe that creating ligands biased to G proteins—or even just one subunit of G protein—over β-arrestins could be the foundation for many next generation opioid drugs, hopefully aiding the opioid addiction crisis by mitigating tolerance issues (Figure 1).

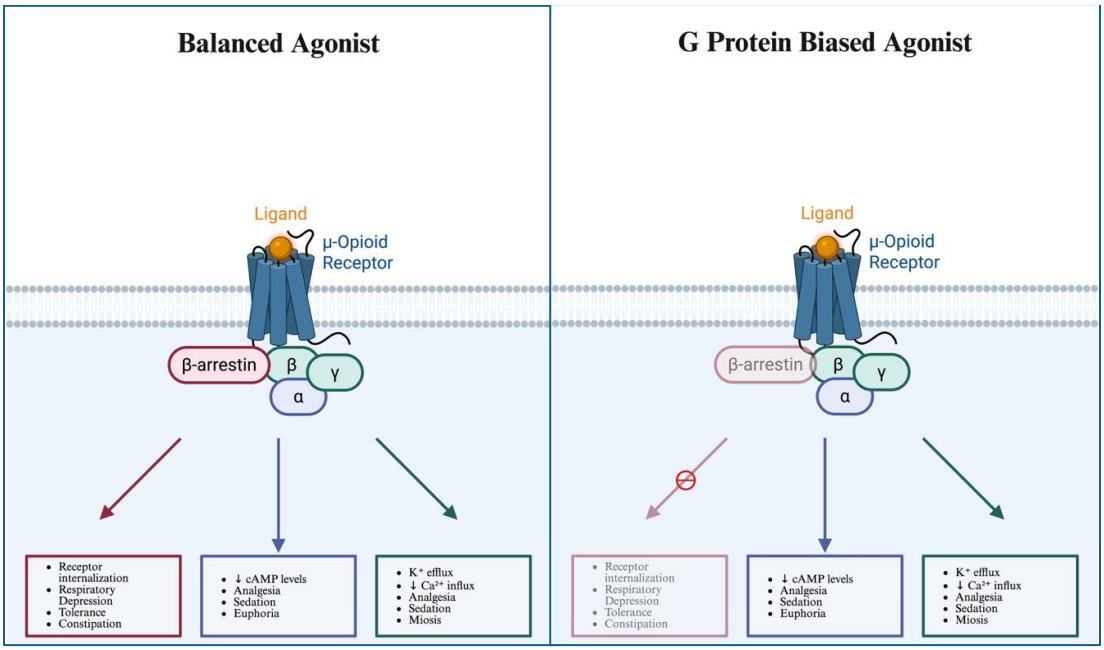

Figure 1.
Both panels show the proteins activated by agonists at the μ-OR. These are the $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. Additionally, a set of common effects associated with each protein type is shown in the boxes below. The balanced agonists (shown left) activate both G protein signaling and β-arrestin pathways to a similar extent. In contrast, G protein-biased agonists (shown right) preferentially activate G protein signaling while minimizing β-arrestin recruitment. The figure was created using BioRender (Roy, A. 2025).

Biased agonists have become increasingly prominent in our ongoing pharmacological search for a drug with the aforementioned qualities. They function primarily through the controlled phosphorylation of the opioid receptor. By preventing phosphorylation, they reduce the recruitment of β-arrestins, producing a G protein-biased agonist (Figure 1 shown right). Inversely, by increasing the recruitment of β-arrestins, they become β-arrestin-biased agonists. Each is hypothesized to take on solely the properties of their protein, thus giving researchers greater governance over the opioid functions (Jayakody et al., 2025). Generally, scientists favor the G protein activity due to its more desirable analgesic effect, however, both routes have some exploration as the concept is a very recent development.

While the information and processes mentioned can be generalized to all the opioid receptors, there also lie distinct pharmacological profiles, therapeutic and clinical potentials, and sets of complications among the μ-OR, κ-OR, δ-OR, and NOP. Understanding and exploiting these factors is vital for the development of more effective opioid agonists and antagonists. For any researcher looking to do so, it is crucial to acknowledge these disparities.

The μ-OR, encoded by the OPRM1 gene, is primarily involved in the analgesic and euphoric effects of opioids. It's predominantly expressed in the periaqueductal gray, thalamus, dorsal horn of the spinal cord, nucleus accumbens, and brainstem respiratory centers, allowing it a great degree of control over pain management. This receptor has strong supraspinal and spinal analgesia, making it effective for acute pain. Thus far, it has long been considered the clinical standard for analgesia due to our longstanding knowledge of its nature and its effectiveness. However, especially in recent years, it has become infamous due to its high risk of respiratory depression, constipation, tolerance, dependence, and euphoria-driven abuse

(Pellissier et al., 2018; Madariaga-Mazón et al., 2017; Ehrlich et al., 2019; Mann et al., 2015).

The κ-OR is encoded by the OPRK1 gene, and while perhaps overshadowed by the μ-OR, has consistently shown promise in analgesia. It produces potent spinal analgesia, antipruritic effects, and minimal respiratory depression. Dense in hypothalamus, amygdala, periaqueductal gray, spinal cord dorsal horn, and pituitary, this receptor has become increasingly valuable as we search for a replacement to traditional μ-OR drugs like fentanyl. Alas, it is also known to cause dysphoria, hallucinations, sedation, and aversion in many patients. For this reason, it has historically been avoided for opioid use. Recently, however, significant promise with the receptor has been shown. In Japan, a κ-OR drug, nalfurafine, has even been conditionally approved for certain therapeutic prescriptions like pruritus in dialysis patients (Table 3), showing net positive effects in many patients thus far (Liu-Chen & Huang, 2022; Hampsey et al., 2024; Escudero-Lara et al., 2021; Han et al., 2023).

On the other hand, the δ-OR, encoded by the OPRD1 gene, is predominantly expressed in the cortex, olfactory bulb, dorsal root ganglia, hippocampus, and limbic regions. In general consensus, it has shown little promise compared to its counterparts. While it does show some mild analgesic, antidepressant, and anxiolytic effects, its risk of seizure is high and potency for pain relief is low. Generally, the risk of seizures alongside analgesia is not a tradeoff viewed favorably in drug development. To that end, DOR-selective agonists have been largely passed over by researchers in the field (Gavériaux-Ruff & Kieffer, 2011; Saigusa et al., 2017).

More recently, the atypical NOP has come into play. Encoded by the OPRL1 gene, this receptor is widespread at the cerebral cortex, amygdala, spinal cord, locus coeruleus, and dorsal root ganglia. It has shown great promise in the production of spinal and peripheral analgesia without the creation of respiratory depression, euphoria, or extreme tolerance issues. However, due to its often dual analgesic/anti-analgesic behavior, many feel it to be counterintuitive. Regardless, it has shown significant promise in the field, especially in combination with other receptors. Notably, NOP's synergy with μ-OR signaling has spurred interest in dual agonists, which will be discussed in a later section (examples can be seen in Table 3) (Post et al., 2016; Raffaeli et al., 2006; Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017).

Body Section 2: The Rise of New Classes of Opioid Agonists: Biased and Dual Agonism

Until the late 1990s medical professionals and researchers alike were wary of opioid drugs, using them only when absolutely necessary (i.e. late-stage cancer) and in small quantities, but in 1996 the company Purdue Pharma produced OxyContin, a drug that would change the opioid landscape for decades to come. OxyContin, a brand name for an extended-release formulation of oxycodone, was introduced by Purdue Pharma to treat moderate–severe pain over long periods of time. As opioids had long-since been considered addictive and having many complications, most care providers were averse to their use. **Nevertheless, Purdue Pharma confidently cited a 1-paragraph letter from the renowned *New England Journal of Medicine* (Porter & Jick, 1980).** This report—using a small test group of hospitalized patients—was taken out of context by Purdue Pharma, cited as definite proof that opioids were safe and non-addicting for long-term outpatient use. When coupled with more influential clinical papers; aggressive, misleading, and FDA-backed promotional marketing (Van Zee, 2009); and pressure from the "Pain as the 5th vital sign marketing", doctors' fears were assuaged, and the mass prescription of opioids began (Rosenman et al., 2025). In 2020, Purdue Pharma pleaded guilty to their false advertising, taking OxyContin's extended-release form off the market. Unfortunately, by then, the damage was done, leaving us with an opioid crisis we don't have a solution to. Even today, while under closer security and restriction, opioids are being prescribed to those with chronic pain-causing afflictions, as they are currently thought to be the best method of pain-mitigation. However, even when medical professionals stop the opioid prescription, there is a high likelihood of addiction, tempting patients to continue their use through non-controlled substances like diacetylmorphine (heroin), illicit morphine, or illicitly manufactured fentanyl (Refer to Figure 2 for structures).

	Duration	Risk of Addiction	Level of Supervision
Therapeutic (Outpatient) Use	**~2 Months – Indefinite**	**Usually higher risk than clinical**	**Initially prescribed by medical professional, generally with occasional updates**
Clinical (Inpatient) Use	**~2 Hours – 24 Hours**	**Usually lower risk than therapeutic**	**Near-constant monitoring and adjusting by medical professional**

Table 2.

Table detailing common characteristics of therapeutic and clinical opioid usage.

Currently, for outpatient therapeutic use (Table 2), we have a variety of opioids at our disposal. For this purpose, we tend to use longer-acting drugs such as morphine (Zhuang et al., 2022; Krishnamurti & Rao, 2016; Reilly, 2016), oxycodone, hydromorphone, methadone, and fentanyl transdermal patches (Figure 2 and Table 3) (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019). We do this for several reasons including duration of action, potency, overdose risk, abuse risk, cost, and government regulation. Conversely, for inpatient clinical care (Table 2), shorter-acting drugs with faster onset and offset, like fentanyl and remifentanil, are often utilized (Figure 2 and Table 3) (Brown et al., 2020; Sutcliffe et al., 2022). This can also be attributed to the aforementioned reasons but their inverse.

Perhaps some of the most acute examples of this idea are the uses of morphine and fentanyl. Morphine (a large, hydrophilic substance) has a much longer onset and offset when compared to fentanyl (a smaller, lipophilic substance) (refer to Figure 2 for structures) (Brown et al., 2020; Sutcliffe et al., 2022). Thus, morphine is mostly used for chronic and cancerous conditions, whilst fentanyl is reserved for general surgery under the watch of an anesthesiologist. Each has its benefits and drawbacks, making them ideal for different scenarios. Morphine lasts longer than fentanyl, increasing the risk of complications like nausea and constipation, but decreasing the risk of overdose in long-term situations, as it will be administered less often (Table 2). Fentanyl is ~50–100 times more potent than morphine, making it cheaper when diluted and given properly, but deadly if overdosed. Fentanyl may have greater reinforcement potential due to rapid onset and high potency, but if taken for prolonged periods of time, as morphine usually is, both can become extremely addictive due to euphoric effects and unregulated dopamine levels. To synthesize, morphine and fentanyl are two very different drugs, targeting the same issue but in unique ways, making them best suited for different tasks. While often discussed, these are not the only two opioid drugs that follow these principles. As mentioned earlier, medical professionals have dozens of drugs—approved, obsolete, and in development—to treat patients with (Table 3). However, especially with more recently developed opioids, most of the medical community is wary of change, with good reason, considering the recent history with OxyContin.

Thus, it is important to recognize the disparate effects (both short and long term) and tailor opioid use to the task it is performing. We can do this through clinical trials, where a near-definite assessment is reached, but even before that we are able to form a rough hypothesis based on the structure (Figure 2) and intended route of function (Table 3). Here, we will be comparing the structure, receptor, and other known factors of next generation agonists to their clinically and therapeutically established counterparts, reporting trends and inconsistencies between these factors and the drugs' effects.

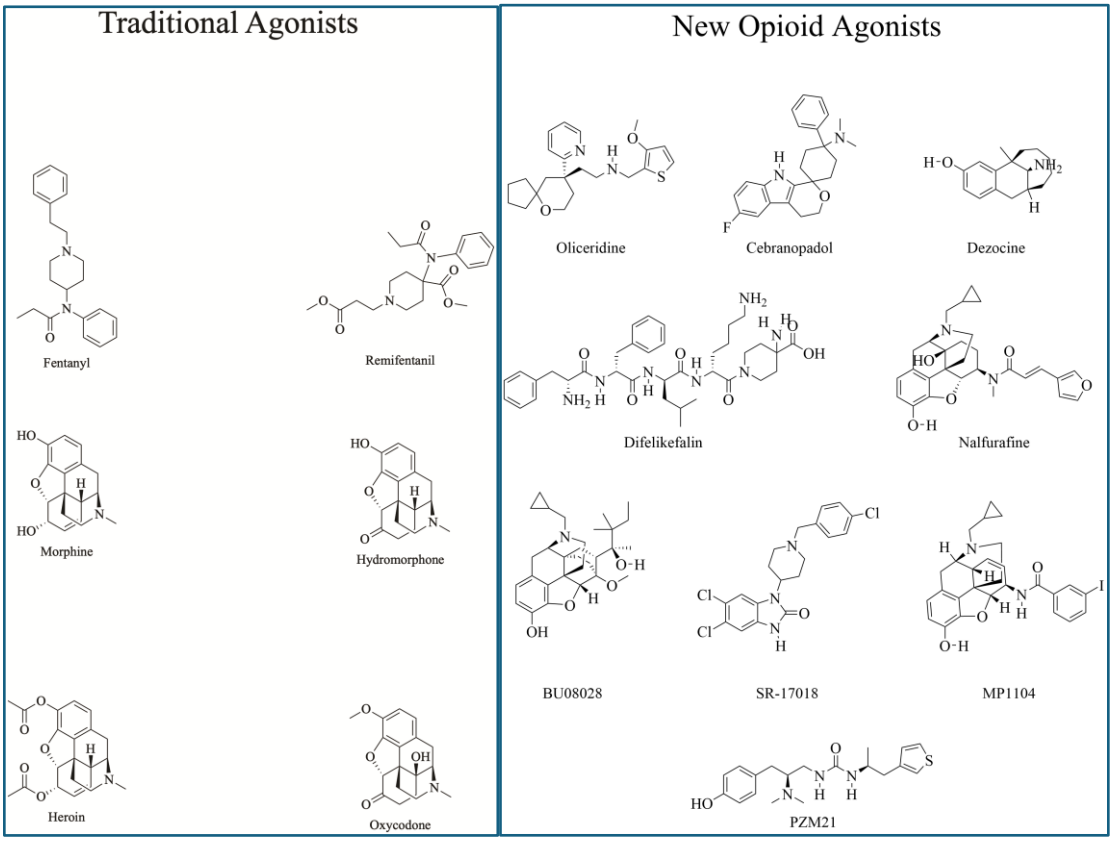

Figure 2.
Panels show structures of traditional agonists (left) and new opioid agonists (right).

Name	Common Brand Name(s)	Target	Positive Effects	Negative Effects	Stage of Development / Use
Oliceridine	Olinvyk	μ-OR – G protein–partial bias	Strong IV analgesia, slightly reduced GI and respiratory issues compared to morphine	Nausea, dizziness, respiratory depression still possible, limited duration	Approved (US) for acute pain (IV)
PZM21	–	μ-OR – low β-arrestin recruitment	Analgesia in preclinical and early human studies	Respiratory depression in later animal studies, low analgesic effects	Preclinical/early clinical
SR-17018	–	μ-OR – G protein biased	Potent, long-acting analgesia in animals, reduced tolerance issues in mice	No human data; bias claims debated, possible	Preclinical

				side effects typical of μ-OR agonists	
Dezocine	Dalgan	μ-OR partial agonist + κ-OR partial antagonist + SERT/NET inhibitor	Analgesia, possible mood elevation, lower abuse liability reports	Typical opioid adverse events, mild sedation	Approved (China); formerly marketed in US
Nalfurafine	Remitch	κ-OR full agonist + μ-OR partial agonist	Antipruritic with reduced dysphoria compared to classical κ-OR agonists	Low analgesia, Sedation, possible mild dysphoria	Approved (Japan) for uremic pruritus
Difelikefalin	Korsuva	κ-OR peripheral agonist	Pruritus relief, minimal CNS sedation/respiratory depression	Low analgesia, mild nausea, diarrhea	Approved (US) for CKD-associated pruritus; IV in dialysis
MP1104	–	κ-OR full agonist + δ-OR full agonist	Analgesia in rodents, reduced classic κ-OR aversion	Unknown human safety; possible κ-OR side effects	Preclinical
BU08028	–	μ-OR partial agonist + NOP partial agonist	Strong analgesia in NHPs, minimal respiratory depression or abuse liability	Unclear long-term safety, typical opioid effects possible	Preclinical
Cebranopadol	–	μ-OR full agonist + NOP agonist	Very long-lasting analgesia, fewer classic μ-OR adverse events	Some sedation, opioid-like side effects	FDA Fast Track Designation for chronic low back pain
Morphine	Zomorph, Sevredol, MS Contin, and Oramorph	μ-OR full agonist (balanced signaling)	Strong analgesia, sedation	Respiratory depression, constipation, histamine release, tolerance	Approved, widely used
Hydromorphone	Dilaudid	μ-OR full agonist (balanced signaling)	Potent analgesia, less histamine release than morphine	Respiratory depression, constipation, sedation	Approved, widely used
Diacetylmorphine	Heroin	μ-OR full agonist	Very rapid and strong analgesia/euphoria	High abuse liability, respiratory depression, rapid dependence, low regulation	Approved in some countries for opioid dependence; illicit in most
Oxycodone	OxyContin	μ-OR full agonist + minor κ-OR agonist	Effective oral analgesic	Abuse liability, respiratory depression, constipation	Approved, widely used
Fentanyl	Sublimaze (Intravenous), Duragesic (Transdermal patches), Actiq (Oral transmucosal lozenges), Fentora (Effervescent buccal tablets), Abstral (Sublingual tablets), Subsys (Sublingual sprays), and Lazanda (Nasal sprays)	μ-OR full agonist	Very rapid, potent analgesia and sedation	Respiratory depression, tolerance issues, addiction potential	Approved, widely used (anesthesia, severe pain)
Remifentanil	Ultiva	μ-OR full agonist	Rapid onset, rapid offset, precise titration	Respiratory depression during infusion, little residual analgesia after stop	Approved, widely used in anesthesia

Table 1.

Table showing the name, common brand name target, effects (both positive and negative), and stage of development (indicating how far a drug has advanced through testing and approval)) of different established and upcoming agonists.

***Note*. Data for Oliceridine are from Wolf et al. (2024). Data for PZM21 are from Manglik et al. (2016). Data for SR-17018 are from Pradhan et al. (2021). Data for Dezocine are from Zhou et al. (2023). Data for Nalfurafine are from Kozono et al. (2018). Data for Difelikefalin are from Fishbane et al. (2022). Data for MP1104 are from Zádor et al. (2019). Data for BU08028 are from Ding et al. (2016). Data for Cebranopadol are from Schroeder et al. (2021). Data for Morphine are from Gutstein and Akil (2025). Data for Hydromorphone are from Kharasch (2020). Data**

for Diacetylmorphine are from Darke et al. (2019). Data for Oxycodone are from Gudin and Fudin (2021). Data for Fentanyl are from Volpe (2023). Data for Remifentanil are from Egan (2019).

Based on the factors analyzed, several predictions can be drawn. It is important to note, however, that these are solely predictions, and the true effects of drugs are shown through human clinical studies and continued therapeutic use. With that said, this preemptive style of analysis can be extremely useful for researchers looking to explore very recently developed avenues of creating opioid drugs and assess which growing ideas have had the most success thus far.

Firstly, it is crucial to understand which areas of research have had the least success and least exploration with regard to opioid analgesics. To this end, we can cite the limited results of full and partial δ-OR agonists. Most drugs developed for the δ-OR either show low efficacy with analgesia, inordinate complications, or a combination of both issues (for specific examples, refer to Table 3). Thus, the data for the receptor is limited, and the results are not quite promising. Moreover, certain agonists, namely PZM21, were initially thought to be biased agonists, due to their lessened side effects (Figure 1), but it was later discovered that the effects could be attributed to low intrinsic efficacies (Hillhouse & Negus, 2016). Furthermore, the κ-OR, once considered among the most promising candidates for analgesic drug development, has shown mixed results. In many κ-OR agonists in use, low analgesic effects in ratio to dysphoric issues have been noted (Table 3). However, the antipruritic (anti-itch) benefits of κ-OR agonists such as Nalfurafine and Difelikefalin haven't gone unnoticed (Table 3). This receptor—while perhaps not as indicative of heralding the future of less issue-prone analgesic drugs—presents a unique pathway for antipruritic drugs, with a plethora of reassuring, trial-based evidence to support it (Beck et al., 2019; Liu-Chen & Huang, 2022).

More optimistically, we have a number of agonists employing a variety of strategic approaches to drug design. Not only is it important to understand which drugs are successful and unsuccessful, but the underlying mechanisms of said drugs are just as important to the field. To that end, we have seen many drugs with success, but it is still important to define and categorize that success, as different issues necessitate different criteria. The main uses for analgesic drugs are therapeutic and clinical. In outpatient therapy, the patient will be exposed to the drug for longer durations and generally at lower doses. Conversely, in clinical

procedures, higher doses are given, but far less frequently and in tightly controlled settings. Some drugs, like fentanyl (see Table 3) are even used for both cases via different routes like the fast-acting intravenous formula for surgical procedures and the slower-release transdermal patches for chronic pains (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019).

For acute clinical use, we have seen agonists at the μ-OR work the quickest and safest, but still retain some drawbacks of constipation, nausea, respiratory depression, and continually increasing tolerance. However, when biased to the G proteins $G_{\alpha i/o}$ and $G_{\beta\gamma}$, several agonists showed reduced complications, especially with tolerance, as the β-arrestin was no longer causing the internalization and degradation of the receptor. For example, Oliceridine—an agonist that preferentially activates G protein signaling over β-arrestin recruitment—is already shown to have a lower risk of several side effects in humans. Oliceridine has rapid analgesia like fentanyl and morphine, but lower respiratory depression and gastrointestinal complications at equianalgesic doses of those same traditional opioids (Table 3). This drug has shown us that G protein bias can be successful, but it is still not perfect: side effects can still occur, especially at higher doses (Faouzi et al., 2020; Stahl et al., 2021; Bateman & Levitt, 2021). Oliceridine has not been widely tested for human surgical use, mostly used to counteract moderate–severe acute pain in-clinic. Moreover, it is important to note that not all studies consistently replicate the same balance of β-arrestin versus G protein outcomes, so results should be interpreted with caution and may depend on the specific ligand and experimental system. Due to this, the community is still searching for an even better opioid analgesic to compete with fentanyl, and many feel G protein bias is the way to get there.

In chronic therapeutic development, on the other hand, many of the most promising agonists also utilize the concept of dual agonism/antagonism where agonists target multiple receptors. For example, BU08028 and Cebranopadol are both mixed agonist drugs (Table 3). BU08028 primarily targets the μ-OR and NOP, reaping analgesia via a classical opioid pathway, and also modulating pain whilst reducing side effects like addiction risk through the NOP. If hypotheses are confirmed by human trials, this drug could provide potent, long-lasting analgesia without as many complications for chronic and acute pain. Cebranopadol is a first-in-class mixed opioid receptor. The drug targets the μ-OR and NOP as a full agonist

and δ-OR and κ-OR as a partial agonist. By providing strong analgesia through the μ-OR, modulating pain through the NOP, and utilizing δ-OR & κ-OR for some neuropathic pain, this drug shows use for both acute and long-term pain management (Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017). Taking a different approach, dezocine, a drug widely used in China for chronic pain in humans, but taken off the American market (for economic, not safety concerns), is a μ-OR agonist, κ-OR antagonist, and a serotonin-norepinephrine reuptake inhibitor. By partially agonizing the μ-OR, the drug creates potent analgesia, but with a ceiling effect, lowering the risk of respiratory depression. Being a κ-OR antagonist, this opioid analgesic also reduces dysphoria and sedation risk.

Body Section 3: Opioid Antagonists: Uses, drawbacks, and new technologies

As the opioid drug crisis remains to be solved, more and more people are overdosing on opioid drugs and experiencing respiratory depression, and thus, opioid antagonists are needed increasingly more. In the United States, many school districts located in high-drug-trafficking areas keep a narcotic reversal agent on hand, usually naloxone (Narcan). However, just as fentanyl has drawbacks and welcomes alternative agonists, naloxone has sparked a new wave of innovation for better opioid antagonists.

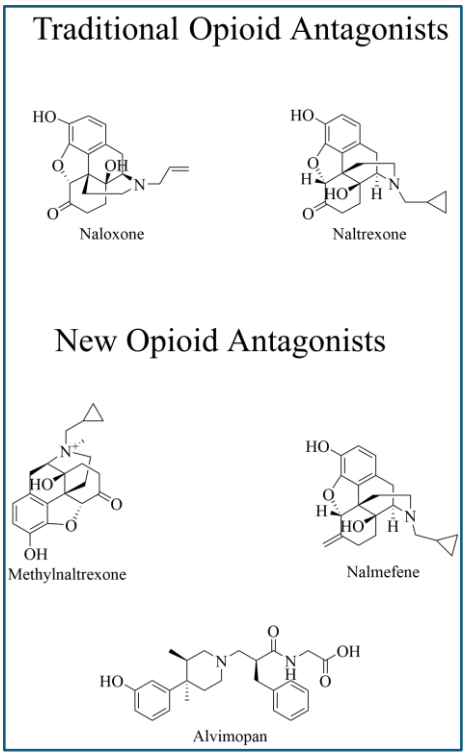

Figure 3.

Chemical structures of traditional and in-development (new) antagonists. Each structure is labeled with its name underneath.

Name / Brand(s)	Delivery Methods	Target	Positive Effects	Negative Effects	Stage of Development / Use
Naloxone (Narcan, Kloxxado, Evzio)	Intravenous (IV), Intramuscular (IM), Subcutaneous (SC), Intranasal spray	Full antagonist at μ-OR; Partial antagonist at κ-OR and δ-OR	Rapid reversal of opioid overdose, restores respiration	Short half-life (risk of re-narcotization), may cause severe withdrawal symptoms in opioid-dependent patients	Approved; gold standard emergency overdose treatment
Naltrexone (ReVia, Vivitrol, Depade)	Oral tablet, Extended-release intramuscular injection	Full antagonist at μ-OR, weak κ-OR antagonism	Prevents relapse in opioid/alcohol use disorder, longer duration than naloxone	Hepatotoxicity risk at high doses, poor adherence in oral form, precipitates withdrawal	Approved for opioid and alcohol dependence treatment
Methylnaltrexone (Relistor)	Subcutaneous injection, Oral tablet	Peripherally acting μ-opioid receptor antagonist (PAMORA); does not cross BBB	Reverses opioid-induced constipation without affecting analgesia	Abdominal pain, won't reverse overdose	Approved for opioid-induced constipation in palliative care or chronic pain
Alvimopan (Entereg)	Oral capsule	PAMORA; selective peripheral μ-opioid receptor antagonist	Reverses opioid-induced constipation without affecting analgesia	Cardiovascular risk with long-term use (restricted to short-term access)	Approved for short-term hospital use post-surgery (REMS program)
Nalmefene (Selincro, Revex)	Intravenous, Intramuscular, Subcutaneous, Oral tablet (Europe)	Full antagonist at μ-OR, partial agonist at κ-OR and δ-OR	Reversal of opioid overdose (longer duration than naloxone), reduces alcohol consumption	Nausea, dysphoria, precipitates withdrawal	Approved in some regions for alcohol dependence; approved in U.S. (IV) for overdose reversal

Table 2.

Table showing the name, common brand name target, effects (both positive and negative), and stage of development of different established and upcoming antagonists.

Note. Naloxone data are from Bailey and Wermeling (2014) and Barton et al. (2005). Naltrexone data are from Comer et al. (2018) and Mark and Jones (2022). Methylnaltrexone data are from Webster et al. (2023) and Deibert (2011). Alvimopan data are from Viscusi and Singla (2019) and Tan et al. (2008). Nalmefene data are from LiverTox (2015) and Smith et al. (2025).

Just as with agonists, antagonist drugs are present in a variety of structures, delivery routes, and mechanisms of action (Figure 3 and Table 4). Naloxone is still the gold standard emergency overdose treatment: it works with few complications and is usually life-saving. The largest issue is its short half-life, as it only works for ~30-90 minutes, whereas some opioid agonists function for hours (Table 3). This can cause re-narcotization, where overdose symptoms return after naloxone wears off, requiring repeat dosing or IV infusion. Some other issues involve rapid withdrawal symptoms in opioid dependent individuals (due to naloxone's rapid onset) and limited efficacy with ultra-potent opioids like Carfentanil. Additionally, the intravenous version of naloxone requires training to administer, but trained staff may not be available at the time of overdose (Bird et al., 2023; Beck et al., 2019; Lu et al., 2021; Cipriano et al., 2024).

To that end, researchers and scientists are working to develop and test several new reversal agents to hopefully solve some of naloxone's issues without sacrificing its efficacy. So far, drugs like Naltrexone and Nalmefene have been created and FDA approved for certain cases (Table 4 and Figure 3). They tend to last much longer than naloxone, but have been associated with immediate acute withdrawal symptoms, so newer opioid antagonist drugs are still in development (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Moreover, we now have several oral sprays, nasal sprays, and oral capsules to make untrained administration easier (Table 4). While some critics have argued that the widespread availability of reversal agents could embolden opioid users and agitate the issue, widespread consensus agrees that the lives saved overshadow this issue. Additionally, a new class of antagonist drugs known as PAMORAs (peripherally acting μ-opioid receptor antagonists) has emerged (Table 4). These drugs, like alvimopan and methylnaltrexone, are actually not used to treat opioid overdose.

Rather, they are utilized mainly for opioid-induced constipation. PAMORAs, unlike most antagonists, do not reduce analgesic effects, making them a great resource for patients in chronic pain or for post-operative care (Pellissier et al., 2018; Madariaga-Mazón et al., 2017).

Another issue is that while traditional antagonist drugs create a rapid reversal effect, they cannot be given preemptively, as they have a short half-life. However, a unique class of drugs known as monoclonal antibody–based opioid binders present a new way to combat the issue: the idea of opioid "vaccines". Unlike traditional antagonists, monoclonal antibodies could prevent opioid agonists from crossing the blood-brain barrier (BBB). This would effectively reduce the effects of opioids over a long period, thus "vaccinating" patients against them. Nevertheless, many concerns and debates exist over this topic. For instance, the design of these drugs is very specific, usually only targeting one or a few agonists. So, if a person suffering from opioid addiction were to get treated against heroin, thus nulling its effects, they may resort to other drugs such as fentanyl for the same euphoria. Moreover, if a patient is vaccinated against too many opioids and needs a surgical procedure, the anesthesiologist may have a difficult time finding an opioid drug to administer analgesia. This applies even more so for an emergency room (ER) case in which the patient's medical record may not be on hand. So, even though traditional antagonists and monoclonal antibody–based drugs strive to aid the same issue—the ongoing opioid crisis—both take very different routes and expect very different outcomes (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Thus, they are not in competition with each other, as neither can replace the other, but expanding our research in both areas would benefit the same problem.

Conclusion:

In synthesis, opioid pharmacology represents a path to improving both therapeutic tools and clinical medicine. Our growing understanding of opioid receptor function has revealed opportunities to separate beneficial analgesic effects from unwanted side effects, but the path toward safer and more effective drugs remains largely open. Nevertheless, historical missteps remind us that scientific innovation must not come at the cost of foregoing rigorous testing, regulation, and responsible clinical use. This evolving landscape can be summarized in three key areas. First, progress in biased and bitopic agonism has highlighted promising strategies, such as the development of biased agonists that

preferentially activate pathways linked to analgesia and the exploration of dual-acting compounds that target multiple receptors simultaneously. Second, persistent limitations remain in translating encouraging preclinical findings into reliable clinical outcomes, underscoring the need for cautious interpretation and stringent validation. Third, the outlook for rational design—integrating receptor structure and pharmacological innovation—offers a forward-looking path toward safer and more effective opioid drugs. It is important to note, however, that in the global market thus far, no opioid agonist has yet surpassed fentanyl and similarly, no opioid antagonist has yet usurped naloxone; both are remarkable innovations that have saved countless lives, regardless of their shortcomings. Ultimately, addressing the opioid crisis will not come from a single breakthrough, but rather an integrated approach. Continued research in all of these areas offers the best chance of balancing the essential role of opioids in pain relief with the urgent need to minimize their risks.

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References

Addiction Rare in Patients Treated with Narcotics. (1980). New England Journal of Medicine, 302(2), 123–123. https://doi.org/10.1056/NEJM198001103020221

Baehr, C., Kelcher, A. H., Khaimraj, A., Reed, D. E., Pandit, S. G., AuCoin, D., Averick, S., & Pravetoni, M. (2020). Monoclonal antibodies counteract opioid-induced behavioral and toxic effects in mice and rats. The Journal of Pharmacology and Experimental Therapeutics, 375(3), 469–477. https://doi.org/10.1124/jpet.120.000124

Bailey, A., & Wermeling, D. (2014). Naloxone for opioid overdose prevention: Pharmacists' role in community-based practice settings. Annals of Pharmacotherapy, 48(5), 601-606. https://doi.org/10.1177/1060028014523730

Balon, T. M., Xia, Y., McKeown, J., Wang, J., Abbott, J. J., Palettas, M., Uribe, A., Echeverria Villalobos, M., Coffman, J. C., & Hu, L.-Q. (2024). Pocket warming of bupivacaine with fentanyl to shorten onset of labor epidural analgesia: A double-blind randomized controlled clinical trial. PLOS ONE, 19(9), e0309515. https://doi.org/10.1371/journal.pone.0309515

Barton, E., Colwell, C., Wolfe, T., Fosnocht, D., Gravitz, C., Bryan, T., et al. (2005). Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. Journal of Emergency Medicine, 29(3), 265-271. https://doi.org/10.1016/j.jemermed.2005.03.007

Bateman, J. T., & Levitt, E. S. (2021). Evaluation of G protein bias and β-arrestin 2 signaling in opioid-induced respiratory depression. American Journal of Physiology-Cell Physiology, 321(4), C681–C683. https://doi.org/10.1152/ajpcell.00259.2021

Beck, T. C., Reichel, C. M., Helke, K. L., Bhadsavle, S. S., & Dix, T. A. (2019). Non-addictive orally-active kappa opioid agonists for the treatment of peripheral pain in rats. European Journal of Pharmacology, 856, 172396. https://doi.org/10.1016/j.ejphar.2019.05.025

Benet, M., Niazi, A., & Scott, J. (2017). Reciprocal evolution of opiate science from medical and cultural perspectives. Frontiers in Pharmacology, 8 (Article 782). https://doi.org/10.3389/fphar.2017.00782

Bird, H. E., Huhn, A. S., & Dunn, K. E. (2023). fentanyl Absorption, Distribution, Metabolism, and Excretion: Narrative Review and Clinical Significance Related to Illicitly Manufactured fentanyl. Journal of Addiction Medicine, 17(5), 503–508. https://doi.org/10.1097/ADM.0000000000001185

Blumenthal, D., & Shapiro, J. (2025). Policy options for the drug pricing conundrum. Proceedings of the National Academy of Sciences, 122(13), e2418540122. https://doi.org/10.1073/pnas.2418540122

Brown, J. A., Faley, S. L., Shi, Y., Hillgren, K. M., Sawada, G. A., Baker, T. K., Wikswo, J. P., & Lippmann, E. S. (2020). Advances in blood–brain barrier modeling in microphysiological systems highlight critical differences in opioid transport due to cortisol exposure. Fluids and Barriers of the CNS, 17(1), 38. https://doi.org/10.1186/s12987-020-00200-9

Chan, E. W. Y., Leung, J. C. Y., Wong, I. C. K., & others. (2021). Prescription medicine misuse in the Asia–Pacific region: An evolving issue? British Journal of Clinical Pharmacology, 87(4), 1810-1818. https://doi.org/10.1111/bcp.14638

Chatterjee, A., et al. (2023). Improving the generalizability of protein–ligand binding predictions with AI-Bind. Nature Communications, 14(1), 2347. https://doi.org/10.1038/s41467-023-37572-z

Christoph, A., Eerdekens, M.-H., Kok, M., Volkers, G., & Freynhagen, R. (2017). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience in patients with chronic low back pain in a randomized clinical trial. Pain, 158(9), 1813–1824. https://doi.org/10.1097/j.pain.0000000000000986

Cipriano, A., Kapil, R. P., Zhou, M., Shet, M. S., Whiteside, G. T., Willsie, S. K., & Harris, S. C. (2024). Safety, tolerability, and pharmacokinetics of single- and multiple-ascending doses of sunobinop in healthy participants. Clinical Pharmacology in Drug Development, 13(7), 790–800. https://doi.org/10.1002/cpdd.1394

Comer, S. D., Sullivan, M. A., Hulse, G. K., & Somoza, E. (2018). Naltrexone: A history and future directions. CNS Drugs, 32(9), 825-836.

Cook, M. E., Knoph, C. S., Fjelsted, C. A., Frøkjær, J. B., Bilgrau, A. E., Novovic, S., Jørgensen, M. T., Mortensen, M. B., Nielsen, L. B. J., Hadi, A., Berner-Hansen, M., Rutkowski, W., Vujasinovic, M., Löhr, M., Drewes, A. M., & Olesen, S. S. (2023). Effects of a peripherally acting μ-opioid receptor antagonist for the prevention of recurrent acute pancreatitis: Study protocol for an investigator-initiated, randomized, placebo-controlled, double-blind clinical trial (PAMORA-RAP trial). Trials, 24(1), 301. https://doi.org/10.1186/s13063-023-07287-z

Coombes, L., Burke, K., & Anderson, A.-K. (2017). The use of rapid onset fentanyl in children and young people for breakthrough cancer pain. Scandinavian Journal of Pain, 17(1), 256–259. https://doi.org/10.1016/j.sjpain.2017.07.010

Curran, M. P., Robins, G. W., Scott, L. J., & Perry, C. M. (2008). Alvimopan. Drugs, 68(14), 2011-2019. https://doi.org/10.2165/00003495-200868140-00006

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., Bernstein, S. L., & Fiellin, D. A. (2015). Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. JAMA, 313(16), 1636. https://doi.org/10.1001/jama.2015.3474

Darke, S., Farrell, M., & Degenhardt, L. (2019). The pharmacology of heroin. Drug and Alcohol Review, 38(1), 108–116. https://doi.org/10.1111/dar.12878

Deibert, P. (2011). Opioid-induced constipation in advanced illness. Journal of Pain and Symptom Management, 41(5), 918-929. https://doi.org/10.1038/ajg.2011.30

Ding, H., Czoty, P. W., & Nader, M. A. (2016). A novel orvinol analog, BU08028, as a safe opioid analgesic without abuse liability in primates. Proceedings of the National Academy of Sciences, 113(22), E6269–E6278. https://doi.org/10.1073/pnas.1615248113

Egan, T. D. (2019). Remifentanil pharmacokinetics and pharmacodynamics: A review and update. Anesthesia & Analgesia, 128(5), 925–937. https://doi.org/10.1213/ANE.0000000000004077

Eggleston, W., Calleo, V., Kim, M., & Wojcik, S. (2020). Naloxone Administration by Untrained Community Members. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 40(1), 84–88. https://doi.org/10.1002/phar.2352

Ehrlich, A. T., Kieffer, B. L., & Darcq, E. (2019). Current strategies toward safer mu opioid receptor drugs for pain management. Expert Opinion on Therapeutic Targets, 23(4), 315–326. https://doi.org/10.1080/14728222.2019.1586882

Escudero-Lara, A., Cabañero, D., & Maldonado, R. (2021). Kappa opioid receptor modulation of endometriosis pain in mice. Neuropharmacology, 195, 108677. https://doi.org/10.1016/j.neuropharm.2021.108677

Faouzi, A., Varga, B. R., & Majumdar, S. (2020). Biased Opioid Ligands. Molecules, 25(18), 4257. https://doi.org/10.3390/molecules25184257

Fishbane, S., Jamal, A., Nanovic, L., & Pergola, P. E. (2022). Safety and effectiveness of difelikefalin in patients with moderate-to-severe chronic kidney disease-

associated pruritus. Kidney International Reports, 7(8), 2040–2051. https://doi.org/10.1016/j.ekir.2022.06.019

Gado, F., Ferrisi, R., Polini, B., Mohamed, K. A., Ricardi, C., Lucarini, E., Carpi, S., Domenichini, F., Stevenson, L. A., Rapposelli, S., Saccomanni, G., Nieri, P., Ortore, G., Pertwee, R. G., Ghelardini, C., Di Cesare Mannelli, L., Chiellini, G., Laprairie, R. B., & Manera, C. (2022). Design, synthesis, and biological activity of new CB2 receptor ligands: From orthosteric and allosteric modulators to dualsteric/bitopic ligands. Journal of Medicinal Chemistry, 65(14), 9918–9938. https://doi.org/10.1021/acs.jmedchem.2c00582

Gavériaux-Ruff, C., & Kieffer, B. L. (2011). Delta opioid receptor analgesia: Recent contributions from pharmacology and molecular approaches. Behavioural Pharmacology, 22(5 and 6), 405–414. https://doi.org/10.1097/FBP.0b013e32834a1f2c

Glenn, J. K., & Goldman, J. (1976). Task delegation to physician extenders—Some comparisons. American Journal of Public Health, 66(1), 64–66. https://doi.org/10.2105/ajph.66.1.64

Göhler, K., Sokolowska, M., Schoedel, K. A., Nemeth, R., Kleideiter, E., Szeto, I., & Eerdekens, M.-H. (2019). Assessment of the abuse potential of cebranopadol in nondependent recreational opioid users: A phase 1 randomized controlled study. Journal of Clinical Psychopharmacology, 39(1), 46–56. https://doi.org/10.1097/JCP.0000000000000995

Gutstein, H. B., & Akil, H. (2025). Opioid analgesics. In L. Bruton, J. S. Lazo, & K. L. Parker (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics (14th ed., pp. 175–221). McGraw-Hill Education.

Gudin, J. A., & Fudin, J. (2021). Pharmacokinetics and pharmacodynamics of oxycodone: A review of the literature. Pain & Therapy, 10(1), 75–87. https://doi.org/10.1007/s40122-020-00214-3

Guo, S.-B., Meng, Y., Lin, L., Zhou, Z.-Z., Li, H.-L., Tian, X.-P., & Huang, W.-J. (2024). Artificial intelligence alphafold model for molecular biology and drug discovery: A machine-learning-driven informatics investigation. Molecular Cancer, 23(1), 223. https://doi.org/10.1186/s12943-024-02140-6

Hampsey, E., Jelen, L., & Young, A. H. (2024). Aticaprant: (A κ-opioid receptor antagonist) for major depressive disorder. Expert Opinion on Emerging Drugs, 29(3), 193–204. https://doi.org/10.1080/14728214.2024.2345645

Han, J., Zhang, J., Nazarova, A. L., Bernhard, S. M., Krumm, B. E., Zhao, L., Lam, J. H., Rangari, V. A., Majumdar, S., Nichols, D. E., Katritch, V., Yuan, P., Fay, J. F., &

Che, T. (2023). Ligand and G-protein selectivity in the κ-opioid receptor. Nature, 617(7960), 417–425. https://doi.org/10.1038/s41586-023-06030-7

Hovah, M. E., & Holzgrabe, U. (2024). Bivalent and bitopic ligands of the opioid receptors: The prospects of a dual approach. Medicinal Research Reviews, 44(6), 2545–2599. https://doi.org/10.1002/med.22050

Jang, J. S., Hwang, S. M., Kwon, Y., Tark, H., Kim, Y. J., Ryu, B. Y., & Lee, J. J. (2018). Is the transdermal fentanyl patch an efficient way to achieve acute postoperative pain control?: A randomized controlled trial. Medicine, 97(51), e13768. https://doi.org/10.1097/MD.0000000000013768

Jayakody, T., Budagoda, D. K., Mendis, K., Dilshan, W. D., Bethmage, D., Dissasekara, R., & Dawe, G. S. (2025). Biased agonism in peptide-GPCRs: A structural perspective. Pharmacology & Therapeutics, 269, 108806. https://doi.org/10.1016/j.pharmthera.2025.108806

Kelly, E., Conibear, A., & Henderson, G. (2023). Biased Agonism: Lessons from Studies of Opioid Receptor Agonists. Annual Review of Pharmacology and Toxicology, 63, 491–515. https://doi.org/10.1146/annurev-pharmtox-052120-091058

Kharasch, E. D. (2020). Hydromorphone: Clinical pharmacokinetics and pharmacodynamics. Expert Opinion on Drug Metabolism & Toxicology, 16(6), 495–507. https://doi.org/10.1080/17425255.2020.1752200

Kieffer, B. L. (1999). Opioids: First lessons from knockout mice. Trends in Pharmacological Sciences, 20(1), 19–26. https://doi.org/10.1016/S0165-6147(98)01279-6

Kliewer, A., Gillis, A., Hill, R., Schmiedel, F., Bailey, C., Kelly, E., Henderson, G., Christie, M. J., & Schulz, S. (2020). Morphine-induced respiratory depression is independent of β-arrestin2 signalling. British Journal of Pharmacology, 177(13), 2923–2931. https://doi.org/10.1111/bph.15004

Koch, E. D., Kapanadze, S., Eerdekens, M.-H., Kralidis, G., Létal, J., Sabatschus, I., & Ahmedzai, S. H. (2019). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience with cancer-related pain for up to 26 weeks. Journal of Pain and Symptom Management, 58(3), 390–399. https://doi.org/10.1016/j.jpainsymman.2019.05.012

Kozono, H., Yoshimura, M., & Tsukamoto, K. (2018). Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride for the treatment of intractable pruritus in hemodialysis patients. Therapeutics and

Clinical Risk Management, 14, 1579–1587. https://doi.org/10.2147/TCRM.S171803

Krishnamurti, C., & Rao, S. C. (2016). The isolation of morphine by Serturner. Indian Journal of Anaesthesia, 60(11), 861–862. https://doi.org/10.4103/0019-5049.193696

Lee, J. D., Nunes, E. V., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C. C., King, J., Lindblad, R., Liu, D., Matthews, A. G., May, J., Peavy, K. M., Ross, S., Salazar, D., Schkolnik, P., … Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. The Lancet, 391(10118), 309–318. https://doi.org/10.1016/S0140-6736(17)32812-X

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. (2015). Nalmefene. National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Liu-Chen, L.-Y., & Huang, P. (2022). Signaling underlying kappa opioid receptor-mediated behaviors in rodents. Frontiers in Neuroscience, 16, 964724. https://doi.org/10.3389/fnins.2022.964724

Lorch, U., Pierscionek, T., Freier, A., Spencer, C. S., & Täubel, J. (2021). Safety, tolerability, and dose proportionality of a novel transdermal fentanyl matrix patch and bioequivalence with a matrix fentanyl patch: Two phase 1 single-center open-label, randomized crossover studies in healthy Japanese volunteers. Clinical Pharmacology in Drug Development, 10(3), 260–271. https://doi.org/10.1002/cpdd.846

Lu, J. J., Polgar, W. E., Mann, A., Dasgupta, P., Schulz, S., & Zaveri, N. T. (2021). Differential in vitro pharmacological profiles of structurally diverse nociceptin receptor agonists in activating G protein and beta-arrestin signaling at the human nociceptin opioid receptor. Molecular Pharmacology, 100(1), 7–18. https://doi.org/10.1124/molpharm.120.000076

Madariaga-Mazón, A., Marmolejo-Valencia, A. F., Li, Y., Toll, L., Houghten, R. A., & Martinez-Mayorga, K. (2017). Mu-opioid receptor biased ligands: A safer and painless discovery of analgesics? Drug Discovery Today, 22(11), 1719–1729. https://doi.org/10.1016/j.drudis.2017.07.002

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of

the μ-opioid receptor bound to a morphinan antagonist. Nature, 485(7398), 321–326. https://doi.org/10.1038/nature10954

Manglik, A., Lin, H., Aryal, D. K., McCorvy, J. D., Dengler, D., Corder, G., ... & Gmeiner, P. (2016). Structure-based discovery of opioid analgesics with reduced side effects. Nature, 537(7619), 185–190. https://doi.org/10.1038/nature19112

Mark, T. L., & Jones, C. M. (2022). Assessing naltrexone prescribing and barriers to initiation for opioid use disorder. Frontiers in Psychiatry, 13, 856938.

Mann, A., Illing, S., Miess, E., & Schulz, S. (2015). Different mechanisms of homologous and heterologous μ-opioid receptor phosphorylation. British Journal of Pharmacology, 172(2), 311–316. https://doi.org/10.1111/bph.12627

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature, 485(7398), 321-326. https://doi.org/10.1038/nature10954

Martinez, S., Harris, H., Chao, T., Luba, R., Pravetoni, M., Comer, S. D., & Jones, J. D. (2023). The potential role of opioid vaccines and monoclonal antibodies in the opioid overdose crisis. Expert Opinion on Investigational Drugs, 32(3), 181–185. https://doi.org/10.1080/13543784.2023.2187286

Mathur, V. S., Kumar, J., Crawford, P. W., Hait, H., Sciascia, T., & for the TR02 Study Investigators. (2017). A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. American Journal of Nephrology, 46(6), 450–458. https://doi.org/10.1159/000484573

Mark, T. L., & Jones, C. M. (2022). Assessing naltrexone prescribing and barriers to initiation for opioid use disorder. Frontiers in Psychiatry, 13, 856938.

Merivirta, R., Äärimaa, V., Aantaa, R., Koivisto, M., Leino, K., Liukas, A., & Kuusniemi, K. (2013). Postoperative fentanyl Patch versus subacromial bupivacaine infusion in arthroscopic shoulder surgery. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 29(7), 1129–1134. https://doi.org/10.1016/j.arthro.2013.04.018

Mitchell, S. G., Monico, L. B., Gryczynski, J., Fishman, M. J., O'Grady, K. E., & Schwartz, R. P. (2021). Extended-release naltrexone for youth with opioid use disorder. Journal of Substance Abuse Treatment, 130, 108407. https://doi.org/10.1016/j.jsat.2021.108407

Morales, P., Scharf, M. M., Bermudez, M., Egyed, A., Franco, R., Hansen, O. K., Jagerovic, N., Jakubík, J., Keserű, G. M., Kiss, D. J., Kozielewicz, P., Larsen, O., Majellaro, M., Mallo-Abreu, A., Navarro, G., Prieto-Díaz, R., Rosenkilde, M. M.,

Sotelo, E., Stark, H., … Wingler, L. M. (2025). Progress on the development of Class A GPCR-biased ligands. British Journal of Pharmacology, 182(14), 3249–3300. https://doi.org/10.1111/bph.17301

Mores, K. L., Cassell, R. J., & Van Rijn, R. M. (2019). Arrestin recruitment and signaling by G protein-coupled receptor heteromers. Neuropharmacology, 152, 15–21. https://doi.org/10.1016/j.neuropharm.2018.11.010

Moss, L., Hijma, H., Demitrack, M., Kim, J., Groeneveld, G. J., Van Velzen, M., Niesters, M., Olofsen, E., & Dahan, A. (2023). Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine. Anesthesiology, 139(6), 746–756. https://doi.org/10.1097/ALN.0000000000004758

Nanovic, L., Fishbane, S., Jamal, A., & Pergola, P. E. (2022). Safety and effectiveness of difelikefalin in patients with moderate-to-severe chronic kidney disease-associated pruritus. Kidney International Reports, 7(8), 2040–2051.

Ni, Y., Huang, R., Yang, S., Yang, X. Y., Zeng, S., Yao, A., Huang, J., & Yang, G. (2024). Pharmacokinetics and safety of oliceridine fumarate injection in Chinese patients with chronic non-cancer pain: A phase I, single-ascending-dose, open-label clinical trial. Drug Design, Development and Therapy, 18, 2729–2743. https://doi.org/10.2147/DDDT.S461416

Nihadha, P. M., Chugh, A., Kaur, A., Kumar, S., Naveen, K. H., Bhatia, P. K., Kumar, P., & Chaudhry, K. (2022). Transdermal fentanyl patch versus standard analgesia in postoperative oral submucous fibrosis patients: A triple blinded, randomised control trial. British Journal of Oral and Maxillofacial Surgery, 60(9), 1246–1253. https://doi.org/10.1016/j.bjoms.2022.07.002

Nunes, E. V., Bisaga, A., Krupitsky, E., Nangia, N., Silverman, B. L., Akerman, S. C., & Sullivan, M. A. (2020). Opioid use and dropout from extended-release naltrexone in a controlled trial: Implications for mechanism. Addiction, 115(2), 239–246. https://doi.org/10.1111/add.14735

Pellissier, L. P., Gandía, J., Laboute, T., Becker, J. A. J., & Le Merrer, J. (2018). μ opioid receptor, social behaviour and autism spectrum disorder: Reward matters. British Journal of Pharmacology, 175(14), 2750–2769. https://doi.org/10.1111/bph.13808

Post, A., Smart, T. S., Krikke-Workel, J., Dawson, G. R., Harmer, C. J., Browning, M., Jackson, K., Kakar, R., Mohs, R., Statnick, M., Wafford, K., McCarthy, A., Barth, V., & Witkin, J. M. (2016). A selective nociceptin receptor antagonist to treat depression: Evidence from preclinical and clinical studies.

Neuropsychopharmacology, 41(7), 1803–1812. https://doi.org/10.1038/npp.2015.348

Pradhan, A. A., Maguire, D. R., McLaughlin, J. P., & Cahill, C. M. (2021). SR-17018 stimulates atypical μ-opioid receptor phosphorylation and signaling. Frontiers in Pharmacology, 12, 721993. https://doi.org/10.3389/fphar.2021.721993

Raffaeli, W., Samolsky Dekel, B. G., Landuzzi, D., Caminiti, A., Righetti, D., Balestri, M., Montanari, F., Romualdi, P., & Candeletti, S. (2006). Nociceptin levels in the cerebrospinal fluid of chronic pain patients with or without intrathecal administration of morphine. Journal of Pain and Symptom Management, 32(4), 372–377. https://doi.org/10.1016/j.jpainsymman.2006.05.013

Reilly, R. F. (2016). Medical and surgical care during the American Civil War, 1861-1865. Proceedings (Baylor University. Medical Center), 29(2), 138–142. https://doi.org/10.1080/08998280.2016.11929390

Rosenman, E., Buck, R. K., Anjum, N., Thompson, L., Rist, J., Banuna, L., Dolgoff, E., Hartmann, S., Lelei, S., Feng, Z., & Holmes, L. M. (2025). From dealer to doctor: A case study examining how Purdue Pharma sought to leverage racial health disparities to attenuate flagging OxyContin sales. Social Science & Medicine, 382, 118132. https://doi.org/10.1016/j.socscimed.2025.118132

Rudolph, K. E., Díaz, I., Luo, S. X., Rotrosen, J., & Nunes, E. V. (2021). Optimizing opioid use disorder treatment with naltrexone or buprenorphine. Drug and Alcohol Dependence, 228, 109031. https://doi.org/10.1016/j.drugalcdep.2021.109031

Saigusa, T., Aono, Y., & Waddington, J. L. (2017). Mechanisms underlying δ- and μ-opioid receptor agonist-induced increases in extracellular dopamine level in the nucleus accumbens of freely moving rats. Journal of Oral Science, 59(2), 195–200. https://doi.org/10.2334/josnusd.16-0874

Schroeder, B., Lemieux, M., Scherbaum, N., et al. (2021). Assessment of the potential of novel and classical opioids to induce opioid use disorder-like behavior: Cebranopadol and beyond. British Journal of Pharmacology, 178(13), 2632–2648. https://doi.org/10.1111/bph.16199

Singla, N. K., Skobieranda, F., Soergel, D. G., Salamea, M., Burt, D. A., Demitrack, M. A., & Viscusi, E. R. (2019). APOLLO-2: A randomized, placebo and active-controlled phase III study investigating oliceridine (TRV 130), a G protein–biased ligand at the μ-opioid receptor, for management of moderate to

severe acute pain following abdominoplasty. Pain Practice, 19(7), 715–731. https://doi.org/10.1111/papr.12801

Smith, J., et al. (2025). New study examines nalmefene auto-injector and intranasal naloxone for reversal of respiratory depression induced by fentanyl. Purdue Pharma News.

Smith, L. C., Bremer, P. T., Hwang, C. S., Zhou, B., Ellis, B., Hixon, M. S., & Janda, K. D. (2019). Monoclonal antibodies for combating synthetic opioid intoxication. Journal of the American Chemical Society, 141(26), 10489–10503. https://doi.org/10.1021/jacs.9b04872

Stahl, E. L., Schmid, C. L., Acevedo-Canabal, A., Read, C., Grim, T. W., Kennedy, N. M., Bannister, T. D., & Bohn, L. M. (2021). G protein signaling–biased mu opioid receptor agonists that produce sustained G protein activation are noncompetitive agonists. Proceedings of the National Academy of Sciences, 118(48), e2102178118. https://doi.org/10.1073/pnas.2102178118

Stevens, R. C., Cherezov, V., Katritch, V., Abagyan, R., Kuhn, P., Rosen, H., & Wüthrich, K. (2013). The GPCR network: A large-scale collaboration to determine human GPCR structure and function. Nature Reviews Drug Discovery, 12(1), 25–34. https://doi.org/10.1038/nrd3859

Sutcliffe, K. J., Corey, R. A., Alhosan, N., Cavallo, D., Groom, S., Santiago, M., Bailey, C., Charlton, S. J., Sessions, R. B., Henderson, G., & Kelly, E. (2022). Interaction with the lipid membrane influences fentanyl pharmacology. Advances in Drug and Alcohol Research, 2, 10280. https://doi.org/10.3389/adar.2022.10280

Szumiec, L., Bugno, R., Szumiec, L., & Przewlocki, R. (2023). The differential influence of PZM21, a nonrewarding μ-opioid receptor agonist with G protein bias, on behavioural despair and fear response in mice. Behavioural Brain Research, 449, 114466. https://doi.org/10.1016/j.bbr.2023.114466

Tan, Z., et al. (2008). Management of postoperative ileus: Focus on alvimopan. Journal of Pain & Symptom Management, 35(5), 500-501.

Van Zee, A. (2009). The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. American Journal of Public Health, 99(2), 221–227. https://doi.org/10.2105/AJPH.2007.131714

Varga, B. R., Streicher, J. M., & Majumdar, S. (2023). Strategies towards safer opioid analgesics—A review of old and upcoming targets. British Journal of Pharmacology, 180(7), 975–993. https://doi.org/10.1111/bph.15760

Verbeek, J., & Brinkman, D. J. (2025). A comprehensive narrative review of protonitazene: Pharmacological characteristics, detection techniques, and toxicology. Basic & Clinical Pharmacology & Toxicology, 137(2), e70078. https://doi.org/10.1111/bcpt.70078

Viscusi, E. R., & Singla, N. K. (2019). Alvimopan for post-radical cystectomy ileus: What should we know? Therapeutic Advances in Urology, 11, 1756287218822806.

Wang, Y., et al. (2023). Structures of the entire human opioid receptor family. Cell, 186(2), 413-427.e17. https://doi.org/10.1016/j.cell.2022.12.026

Webster, L. R., Brenner, D., Israel, R. J., Stambler, N., & Slatkin, N. E. (2023). Reductions in all-cause mortality associated with the use of methylnaltrexone for opioid-induced bowel disorders: A pooled analysis. Pain Medicine, 24(3), 341-350. https://doi.org/10.1093/pm/pnx148

Wikstrom, B. D., Gellert, R., Ladefoged, S. D., Danda, Y., Akai, M., Ide, K., Ogasawara, M., Kawashima, Y., Ueno, K., Mori, A., & Ueno, Y. (2005). κ-Opioid system in uremic pruritus: Multicenter, randomized, double-blind, placebo-controlled clinical studies. Journal of the American Society of Nephrology, 16(12), 3742–3747. https://doi.org/10.1681/ASN.2005020152

Wolf, A., Unterberg, M., Witowski, A., Adamzik, M., & Wolf, A. (2024). Efficacy, safety, and side effects of oliceridine in acute postoperative pain: A protocol for a systematic review and meta-analysis. PLOS ONE, 19(2), e0299320. https://doi.org/10.1371/journal.pone.0299320

Yamaguchi, S., Uchida, E., Terahara, T., Okawa, K., Hashimoto, F., & Tanaka, Y. (2020). Efficacy and safety of fentanyl citrate patch, including a low-dose 0.5 mg formulation, in opioid-naïve patients with cancer pain. Clinical Drug Investigation, 40(11), 1041–1052. https://doi.org/10.1007/s40261-020-00965-9

Zádor, F., Zelena, D., Szegeczki, V., et al. (2019). MP1104, a mixed kappa-delta opioid receptor agonist has anti-hyperalgesic actions without abuse liability in rodents. European Journal of Pharmacology, 857, 172459. https://doi.org/10.1016/j.ejphar.2019.172459

Zhou, X., Wang, W., Fang, B., & Yu, T. (2023). A new formulation of dezocine, Cyc-dezocine, reduces oxycodone consumption in postoperative pain management. Neuroscience Letters, 813, 137486. https://doi.org/10.1016/j.neulet.2023.137486

Zhuang, Y., Wang, Y., He, B., He, X., Zhou, X. E., Guo, S., Rao, Q., Yang, J., Liu, J., Zhou, Q., Wang, X., Liu, M., Liu, W., Jiang, X., Yang, D., Jiang, H., Shen, J., Melcher, K., Chen, H., … Xu, H. E. (2022). Molecular recognition of morphine and fentanyl by the human μ-opioid receptor. Cell, 185(23), 4361-4375.e19. **https://doi.org/10.1016/j.cell.2022.09.041**

EDITOR COMMENTS AND RECOMMENDATION:

Both reviewers agree that the manuscript has strong potential and is a thorough review of opioid analgesics. Both reviewers also raise concerns, however, about the use of informal/imprecise language, lack of important in-text citations, and also advise better use and description of the included figures in the text. The editor suggests that the author particularly address points #4 and #5 raised by Reviewer 1, as well as the "Overall Feedback" section of Reviewer 2's critique for improving the manuscript. Given this feedback, I recommend a major revision prior to publication.

REVIEWER 1:

The manuscript comprehensively reviews opioid ligands, related therapeutic approaches, and clinical trials. The selection of cited studies is abundant and well-represents the current knowledge and recent advances in this field. Well-developed figures are included. The author did an excellent job walking through the mechanisms and providing their perspectives. I also love the incorporation of tables to show differences and clinical trials, pointing out certain stages of technologies. However, the overall manuscript shows notable weakness in writing style, proper word and sentence structures, and the use of in-text citations. In summary, I think the manuscript cannot be published in Convergence in the present form. A future publication depends on complete explanation/consideration of all major points raised below. A major rewrite is required to address issues in writing, and appropriate citations.

- I have never seen fentanyl written as fentaNYL. Fentanyl is the standard spelling.
    - Changed all instances to fentanyl.
- The author abbreviated many words without first writing them full in the Abstract (e.g.: μ-OR, NOP). In the main text, despite stating the abbreviation

and full name, the author continued to use the full name (e.g. Nociceptin/Orphanin Receptor, instead of NOP). For any abbreviation that is not used later, there is no point of abbreviating them (e.g. HTS).

    - Done, standardized in greek letters.

- There are errors in word capitalizations and sentence organizations. For example, the author randomly capitalized a word mid-sentence *In Ayurveda (An ancient medical practice from India), Morphine,* or *Traditional Medicine*. I also recommend adding appropriate punctuation. Random abbreviations and symbols like "&" should be written out. Spelling errors (e.g.: marijuana, anatgonist [sic]) were also spotted throughout. Please proofread the entire manuscript.
    - Fixed spelling errors and grammar.
- I recommend listing all sources where the author mentioned a fact. For example, the author talked about the history of opioids but did not list any sources. Many other facts were stated without proper in-text citations.
    - Sources were added here.
- While the author created several scientific figures, they did not mention the figures in their writing. The mention of each figure is required. Also, it is unlikely that the author drew all these figures by themselves. I suggest that they put proper citations, especially if they use Biorender.com.
    - Each figure is mentioned more, and BioRender is cited.
- Table needs to be titled as Table 1 and must be referred to in the manuscript.
    - All tables were changed from figure to table

REVIEWER 2:

Title page and abstract

- **L1–2 / Page 1, Title:** Put the title in Title Case. Replace "&" with "and." Change "therapeutic/clinical" to "therapeutic and clinical."
    - Done exactly.
- **L8–10 / Page 1, Abstract, first paragraph:** Standardize spelling to "fentanyl." Choose one abbreviation convention for receptors (μ-OR or MOR) and apply it consistently.
    - Standardized to greek spellings.
- **L10–13 / Page 1, Abstract, first paragraph:** "Fentanyl alone has led to over 80,000
  deaths last year" is too absolute. Rephrase to note fentanyl as the primary driver of opioid
  overdoses without implying it is the only cause.
    - Done exactly.
- **L15–17 / Page 1, Abstract, second paragraph:** The sentence about δ-OR, κ-OR, and NOP receptors could preview the distinct complications tied to each, helping orient the reader.
    - As this would make the abstract very long, as even 1 sentence on each opioid receptor would nearly double the length of the abstract, I felt that this was not the best option here. The opioid receptors are previewed in depth later.
- **L18–21 / Page 1, Abstract, second paragraph:** Change "biased and bitopic agonism emerge" to "biased and bitopic agonism have emerged."

Tighten the fentanyl
comparison: “No approach has yet yielded a drug that surpasses fentanyl’s potency and prevalence.”

- Both changes were made.

- **L21–24 / Page 1, Abstract, last sentence:** Fix the broken word in “clinically backed.”
  Simplify: “This review surveys new opioid drug classes and evaluates their clinical relevance, with examples that illustrate mechanisms and early efficacy signals.”
  - Both changes were made.

Introduction and Background

- **L28–36 / Page 2, Paragraph 1:** The phrase “An ancient medical practice” would read
  better with a lowercase “ancient.” Italicize historical terms like *Ahiphena* and *Ying Su Ke*. Add a brief parenthetical gloss (for example, what the term translates to) to help readers unfamiliar with the cultural context.
  - The italics were done, but each already has translation to English in the text.
- **L37–38 / Page 2, Paragraph 1:** Revise “culminating in the isolation of morphine… and synthesis of fentanyl” to “culminating in the 19th-century isolation of morphine and the 20th-century synthesis of fentanyl.” This makes the timeline precise.
  - Change made.
- **L40–43 / Page 2, Paragraph 2:** Instead of “Morphine, the first true opioid analgesic,” write “Morphine, the first purified opioid analgesic.”

"True" sounds subjective.

  - Change made.

- **L46–50 / Page 2, Paragraph 2:** The sentence starting with "Beyond that, however…" is long and heavy. Split it into two. Also, note specifically how the morphine era shaped receptor theory and understanding of tolerance.
  - The sentences would be difficult to split, but I have adjusted to make it less heavy.
- **L53–60 / Page 2, Paragraph 3:** The phrase "even 2 mg… lethal" is misleading. Change to "as little as about 2 mg may be lethal in opioid-naïve individuals," and note variability.
  - Change made.
- **L61–66 / Page 2, Paragraph 3:** The claim about "for-profit healthcare artificially

  inflating prices" comes across as opinionated. Reword neutrally: "High costs of treatment and medication have contributed to limited access." Support with data if retained.
  - Supported with data.
- **L68–73 / Page 2, Paragraph 4:** Instead of "Together, these issues—among many others—have plunged Americans into an opioid crisis," use "These factors have contributed to the ongoing U.S. opioid crisis." More precise and professional. Additionally, the use of em-dash is not required in this instance. Please reword.
  - Change made.
- **L74–81 / Page 2, Paragraph 5:** Phrases like "globally lambasted" feel too casual. Replace with "frequently identified as hotspots." Also ensure there are references to support geographic comparisons.

    - The phrase was changed and evidence was given.
- **L82 / Page 2, Paragraph 5:** Correct spelling to “marijuana.”
    - Done
- **L89–97 / Page 3, Paragraph 1:** Spell out GPCR at first use. Then introduce μ-OR, δ- OR, κ-OR, and NOP, and provide a short table of abbreviations for clarity.
    - Table provided
- **L102–104 / Page 3, Paragraph 2:** Replace “continues to dispel researchers” with “continues to deter researchers” or “continues to puzzle researchers.” “Dispel” is incorrect in this context.
    - Done
- **L108–111 / Page 3, Paragraph 2:** Change “next-generation pain killers” to “next- generation painkillers.”
    - Done
- **L111–118 / Page 3, Paragraph 3:** The explanation of biased vs bitopic agonism is strong. Add a short line explaining why bitopic agonists can provide finer control, such as their ability to interact with both orthosteric and allosteric sites.
    - Line added.
- **L119–127 / Page 3, Paragraph 3:** The point about infrastructure strain is good. Add a concrete example (for instance, the scale of compounds screened per year) if available.
    - No really good quantitative data given, but qualitative data was found and cited.
- **L129–131 / Page 3, Paragraph 4:** Clarify “consistent and reproducible therapeutic promise.” Do you mean replication across labs, consistency across models, or clinical reproducibility? State explicitly.

- Reworded the sentence for clarity.

Methodology

- **L135–139 / Page 3, Methodology, Paragraph 1:** The reasoning for focusing on qualitative synthesis is fine, but the explanation is vague. Specify inclusion criteria such as date ranges, receptor targets, and whether only peer-reviewed articles were included. Mention which databases were searched besides PubMed, if any.
  - All points now covered.
- **L142–146 / Page 3, Methodology, Paragraph 2:** The phrase “mitigating bias through reference of a wide breadth of sources” is awkward. Suggest: “Bias was mitigated by drawing from a wide range of studies across different labs and experimental designs.”Also, clarify whether you excluded certain study types (for example, animal-only studies, unpublished trials).
  - All points now added.

Discussion – Section 1: Receptors and Signaling

- **L151–156 / Page 4, Paragraph 1:** Good introduction to GPCR cascades. To improve clarity, you could cross-reference Figure 1 here, so the reader knows where to look for a visual representation.
  - Figure cited.
- **L158–168 / Page 4, Paragraph 2:** You frame G-protein signaling as

"positive" and arrestin signaling as "negative." This is an oversimplification. Suggest softening: "G- protein signaling is often associated with analgesic effects, while arrestin recruitment is frequently linked to adverse effects, though exceptions exist."
    - Revision made.
- **Figure 1, Caption / Page 6 (L171–177):** Replace "Both figures show" with "Panels show." Standardize phrasing to "G-protein–biased" and "β-arrestin–biased." Consider adding a legend to clarify icons used in the diagram.
    - Revision made.
- **L179–187 / Page 6, Paragraph below Fig. 1:** Change "β-arrestins biased agonists" to "β-arrestin–biased agonists." Also rephrase "becoming a G protein biased agonist" to "producing a G-protein–biased signaling profile."
    - Change made.
- **L194–204 / Page 6–7, Paragraph 1 (μ-OR/MOR):** Strong anatomical overview. When you call μ-OR the "gold standard," soften to "has long been considered the clinical standard for analgesia." Standardize spelling to **MOR** throughout to avoid issues with the Greek letter μ.
    - Standardized all spellings to Greek letters.
- **L205–216 / Page 7, Paragraph 2 (κ-OR/KOR):** Good summary of promise and liabilities. Clarify nalfurafine's approval: specify indication (for example, pruritus in dialysis patients in Japan). Preview that its analgesic effects are limited compared with its antipruritic use.
    - Revision made.
- **L217–223 / Page 7, Paragraph 3 (δ-OR/DOR):** Concise summary. Add

one sentence noting seizure risk observed in some DOR-selective agonists and why this complicates drug development.
    - Revision made.
- **L224–232 / Page 7, Paragraph 4 (NOP):** Balanced overview. The final sentence could hint at later discussion: "NOP's synergy with MOR signaling has spurred interest in dual agonists, which are discussed in a later section."
    - Revision made.

Discussion – Section 2: Biased and Dual Agonism; Clinical vs Therapeutic Use

- **L235–246 / Page 8, Paragraph 1:** The history of Purdue and OxyContin is important, but the tone is too strong. Replace "recklessly" with "aggressively" or "widely." Make clear that the NEJM letter was misinterpreted rather than malicious.
    - "Recklessly" was replaced. However, the passage makes quite clear that the NEJM was misinterpreted. I stated already that the paper was, "taken out of context".
- **L247–254 / Page 8, Paragraph 1–2:** "FDA-backed promotional marketing" needs rewording. Unless there is evidence, say "marketing campaigns were allowed despite limited evidence of safety in long-term outpatient use."
    - Evidence added
- **L255–258 / Page 8, Paragraph 2:** Replace "fentanyl-laced drugs" with "illicitly manufactured fentanyl." This is the accepted terminology in recent literature.
    - Revision made
- **L259–268 / Page 9, Paragraph 1:** Strong distinction between outpatient

and inpatient prescribing. Consider presenting this information in a comparative table that includes onset, duration, potency, and major risks.
    - Table added.
- **L270–281 / Page 9, Paragraph 2:** Be careful with the statement "fentanyl is generally considered at higher risk for addiction than morphine." A more accurate phrasing: "Fentanyl may have greater reinforcement potential due to rapid onset and high potency."
    - Revision made
- **L285–293 / Page 10, Paragraph 1:** "The recent affair with OxyContin" sounds informal. Replace "affair" with "experience" or "history." Remove the trademark symbol — scientific writing does not usually use ® or ™.
    - Thank you for letting me know about the scientific journal convention, changes made.
- **Figure 2, Caption / Page 10, L299–303:** Revise caption to "Panels show traditional agonists (left) and new opioid agonists (right)." Ensure drawings have consistent stereochemistry and resolution.
    - Revision made

- **Table under Fig. 2 / Page 11, L303–319:**
    - Correct spelling of "anatgonist" to "antagonist."
        - Revision made
    - Format multi-target entries consistently (for example, "SERT/NET inhibitor" instead of mixed styles).
        - Format standardized
    - Add a "Key references" column or footnotes.
        - Note section added based on feedback (For both large tables)

- Clarify what “Stage of development” means (preclinical, phase I, approved, etc.).
    - Definition provided

Discussion – Section 3: Advances, Limitations, and Outlook

- **L320–332 / Page 12, Paragraph 1:** Good coverage of new opioid scaffolds. Add examples of compounds in early clinical trials to make this more concrete.
    - I have cited my table here, as I felt it would be redundant to add the examples again. I have only given the most prominent examples (mainly those currently in clinical use).
- **L333–340 / Page 12, Paragraph 2:** When discussing biased agonists, acknowledge that not all studies replicate the same arrestin vs G-protein outcomes. This avoids overstating the certainty.
    - Change made.
- **L341–350 / Page 12–13, Paragraph 2–3:** When you describe preclinical successes, indicate whether these are in rodent models, non-human primates, or early human studies. This distinction is important for readers.
    - Distinction clarified.
- **L351–364 / Page 13, Paragraph 3:** The discussion of limitations is solid. You could strengthen by naming specific barriers: cost of large-scale synthesis, difficulty with receptor selectivity, or poor blood–brain barrier penetration.
    - I tried looking for a good area to insert this information, but I ultimately felt that it veered off-topic. Thus, I have left it as is.

Discussion – Section 4: Future Directions

- **L374–382 / Page 14, Paragraph 1:** The optimism about computational drug design is good. Suggest citing specific advances such as cryo-EM–guided docking or machine- learning–based ligand prediction.
- **L383–390 / Page 14, Paragraph 2:** You mention dual agonists combining MOR and NOP activity. Strengthen this by referencing examples (for instance, cebranopadol, which has advanced to late-stage trials).
- **L391–400 / Page 14–15, Paragraph 3:** The broader conclusion that "no approach has produced a drug to dethrone fentanyl" is fair, but soften the phrasing. Consider: "Despite promising new scaffolds, no candidate has yet matched fentanyl's potency and ubiquity in illicit markets

*Unfortunately, I could not find this section or anything related to the comments in this area. I think there may be an error or some comments may have been misplaced. If there is something I missed, feel free to let me know.

The revised manuscript has substantially improved and expanded, with stronger supporting citations and more compelling claims. However, several minor issues regarding formatting and references still need to be addressed before the manuscript can be accepted for publication.

1. In the Abstract, the author wrote “Mu Opioid-Receptor, Delta Opioid-Receptor, Kappa Opioid-Receptor, and Nociceptin/Orphanin Receptor”. Please change them to the preferred scientific formats: μ-opioid receptors, δ-opioid receptor, κ-opioid receptor. These names are not proper nouns and do not need to be capitalized. For the Nociceptin/Orphanin receptor (NOP), please use either Nociceptin/Orphanin FQ receptor (NOP) or Nociceptin receptor (NOP).
2. Line 36: change to Chinese traditional medicine.
3. Table 1, pg 3: Please address the similar writing style per #1.
4. Avoid using contractions in writing a scientific manuscript. For example, L 212: “It’s”. Change to “It is”.
5. The author needs to double-check that all abbreviations are used consistently throughout the manuscript. For example, in L 241, the author still uses “DOR”.
6. L 264: Change to “one-paragraph”. Keep in mind, in scientific writing, any number below ten should be spelled out, unless it is followed by a unit of measurement (*e.g.:* ten people, 10 mg). Please review “Spelling out numbers in technical, scientific, and complex writing” section https://www.grammarly.com/blog/writing-tips/when-to-spell-out-numbers/ and apply the format to your manuscript.
7. Several abbreviations have not been spelled out first. For example, L 268 “FDA”.
8. Unlike figure captions, table captions are placed on top of the table, not at the bottom. Please fix all the table captions. Only the notes are placed underneath the table, which the author has already done correctly.
9. Tables should appear and be referenced in numerical order. Currently, Table 2 is placed after Table 3, which also does not exist, and Table 1 appears last. Please ensure Table 1 appears first and is cited first in the text, followed by Tables 2, 3, and so forth.
10. The manuscript contains two Table 1s and two Table 2s. Please renumber the tables appropriately and revise all in-text references. Additionally, Tables 3 and 4 are referenced but not included in the manuscript. Please add or correct these.

The revised manuscript represents a clear effort to strengthen the scientific foundation and expand the scope of the original review. The current version is more cohesive, better supported by citations, and more balanced in how it presents the promise and limitations of new opioid pharmacology. The improvements in structure and detail are evident throughout, particularly in the sections discussing biased and bitopic agonism, the differentiation between clinical and therapeutic use, and the expanded tables comparing traditional and next-generation opioid compounds. Despite these gains, several areas still require attention to bring the manuscript into line with publication standards.

One area that needs further refinement is the consistent use of terminology. Receptor names should follow standard scientific formatting throughout the manuscript. This includes the abstract, all section headings, figure captions, and tables. There are still places where the older, capitalized forms appear. Ensuring consistency here matters because the manuscript focuses heavily on receptor-level pharmacology, so precise scientific notation is essential.

Formatting issues in the tables also require a thorough review. Several tables are mislabeled or appear out of order, and two table numbers are duplicated. Additionally, some tables that are cited in the text are either missing or appear in a different sequence than referenced. Table captions should be placed above their corresponding tables, not below, and all tables should appear in numerical order. Correcting these will make the manuscript significantly more readable and more professional.

The manuscript would also benefit from a careful pass addressing abbreviations. A number of abbreviations, such as FDA, BBB, ER, and PAMORA, appear without being spelled out at first use. Because the paper covers multiple receptor families, drug classes, and signaling pathways, any undefined abbreviation can disrupt comprehension. Adding a brief list of abbreviations at the beginning could help orient readers.

There are also some lingering stylistic issues. Contractions should be removed entirely. Sentence structure can be simplified in several locations where ideas are stacked too closely together. A few paragraphs also rely on very long sentences that would read more clearly if divided. Spelling out numbers below ten, unless followed by a unit of measurement, will help bring the writing into line with standard scientific format.

Overall, the manuscript is close to publication quality. With careful correction of formatting, abbreviation consistency, and sentence-level clarity, the scientific strength of the content will stand out more clearly. These refinements will help ensure the final version meets the expectations of peer reviewers and the scientific community.

Current and Prospective Opioid Analgesics: Assessing Their Value for Ongoing Research and Promise for Therapeutic and Clinical Use

*Name & Affiliation not given as per Blind Review guidelines

Abstract

Opioid analgesics, though among the most potent tools for pain relief at our disposal, sit at the epicenter of a growing clinical and societal crisis. Currently, most opioid analgesic drugs like fentanyl function at the μ-opioid receptor (μ-OR), which has notably been linked to respiratory depression, constipation, and high abuse potential. In fact, the abuse of fentanyl been a primary driver of opioid overdose, leading to over 80,000 deaths in the United States just in the last year. As demand for safer analgesics has surged, the field has responded with a range of innovative approaches, many involving the strategic use of other opioid receptors such as the δ opioid receptor, κ-opioid receptor, and Nociceptin/Orphanin FQ Receptor (δ-OR, κ-OR, and NOP respectively). Each of these receptors plays a role in analgesia yet also creates a unique set of complications to accompany it. To combat this issue, dozens of opioid agonists and antagonists are being developed. We have seen new concepts such as biased and bitopic agonism emerge, presenting an updated outlook on how these drugs function. Thus far, no single method has yielded a drug to outcompete fentanyl's potency and prevalence in the global market. This review not only brings to light the new classes of opioid drugs, but also discusses their relevance to the field. Moreover, many prevalent examples of opioids and their mechanisms are discussed throughout the paper, giving clinically backed insight into the drugs' varying levels of efficacy.

Introduction

Since first being recorded by the Sumerian Empire for their hypnotic properties in 3400 B.C., opioids have been employed by a myriad of civilizations, including the Egyptians, Indians, Chinese, and Greeks. There is even evidence showing two of the oldest medical systems using opium derived from poppy seeds to induce analgesia. In Ayurveda (an ancient holistic medical practice from India) *Ahiphena*—also known as poppy seeds—were used for sedation, pain relief, and gastrointestinal relief. Similarly, in Chinese traditional medicine, the same plant, though here called "*Ying Su Ke*", was used for pain and cough suppression. Through

the years, opioid use has been refined through medical, religious, and recreational contexts, ultimately culminating in the 19th-century isolation of morphine and the 20th-century synthesis of fentanyl (Benet et al., 2017).

Morphine, the first purified opioid analgesic, has been one of the most prominent drugs in medical and pharmaceutical history (Krishnamurti & Rao, 2016). Isolated by Friedrich Sertürner in Germany in 1804, this opium poppy derivative broke ground in the research of analgesics. Morphine functions by binding to the μ-opioid receptors in the brain and spinal cord to block the perception of pain (Zhuang et al., 2022). Its introduction into the clinical and therapeutic settings revolutionized pain management, saving countless lives. During the American Civil War, morphine was widely employed as an analgesic via hypodermic injection or laudanum (Reilly, 2016). Beyond that, however, it helped the scientific community understand addiction, receptor theory, and tolerance. Namely, early patterns of dose-dependent effects and diminishing efficacy with prolonged use provided some of the first evidence for discrete receptor sites and the adaptive changes of tolerance. These ramifications have made morphine both a medical breakthrough and cautionary tale, sparking the development of newer, safer, and more potent opioid analgesics.

This undertaking eventually gave rise to a new breed of opioid analgesics optimized for the clinical field: synthetic opioids. The most notable of which is fentanyl, an opioid-based drug first synthesized in Belgium by Dr. Paul Janssen in 1959. This drug is widely accepted as the greatest discovery in the field since the introduction of morphine, of which it is 50–100 times more potent (Zhuang et al., 2022). Originally developed for surgical anesthesia and severe pain management, fentanyl's high lipid solubility and rapid onset coupled with its relatively low cost have made it one of the most universal analgesics of the modern world. However, its high potency and rapid onset could make even as little as about 2 mg lethal in opioid-naïve individuals, underscoring the need for precaution and safety when in use (Bird et al., 2023). Nevertheless, as of now, fentanyl is still favored in most developed nations for analgesia.

In America, the for-profit healthcare and pharmacological system artificially inflate the price of life-saving medicines, making them inaccessible to most Americans living under the poverty line (Blumenthal & Shapiro, 2025). Thus, many Americans are forced to resort to unlicensed distributors to attain their

prescriptions at a reasonable price. Unfortunately, however, this results in many preventable deaths every year. The issue is exacerbated by the recreational use of opioids and high mental health crisis rates (usually resulting in substance abuse) among American youths. Moreover, many medical professionals are encouraged to use opioids to treat pain therapeutically, creating high addiction rates in many chronic pain patients. Together, these factors—among many others—have contributed to the ongoing U.S. opioid crisis.

This problem, however, is not uniform throughout the world. Nations like Switzerland, Rwanda, Saudi Arabia, New Zealand, China, Japan, South Korea, and Singapore have been able to keep drug abuse rates low through strict pharmaceutical monitoring and low prescription medication costs (Chan et al., 2021). In stark contrast, regions like Latin America, Eastern Europe, Central & South Asia, and Africa are frequently identified as illicit drug hotspots & trafficking routes. Overall, this disparity can be attributed to an array of factors from cultural taboos to geopolitical connections to government regulations.

Opioids, unlike other substances like marijuana or nicotine products, can be immediately fatal. While most addicting substances create long-term issues sometimes leading to cancer, opioid drugs create respiratory depression in overdose, thus making them fatal in minutes if not counteracted with an antagonist drug. To combat this, many disparate approaches are being taken by researchers and corporations alike. One prevalent avenue involves exploring the different opioid receptors.

Table 1.

This table outlines the abbreviations used in lieu of standard terminology throughout the paper.

Standard Terminology	Abbreviation Used
G protein-coupled receptor	GPCR
μ-opioid receptor	μ-OR
κ-opioid receptor	κ-OR
δ-opioid receptor	δ-OR
Nociceptin/Orphanin FQ receptor	NOP
U.S. Federal Drug Administration	FDA

Opioid receptors are a specific type of GPCR located throughout the brain, spinal cord, and peripheral nervous system. Currently, we know of four main types of these receptors: μ-OR, κ-OR, δ-OR, and NOP (Refer to table 1) (Wang et al., 2023). Each plays a distinct role in analgesia, pain management, and the effects of both endogenous and synthetic opioids. The μ-OR has historically been used for the majority of analgesic drugs, including morphine, heroin, oxycodone, and fentanyl. It governs euphoria and analgesia, but its use also often leads to respiratory depression and addiction (Zhuang et al., 2022). The κ-OR also deals in the domain of analgesia, but comes with the complications of dysphoria and hallucinations. Whilst it has historically been overshadowed by the μ-OR, and disregarded due to its hallucinogenic properties, it has had renewed interest in recent years for non-addictive therapies (Beck et al., 2019). On the other hand, the δ-OR continues to deter researchers due to its low selectivity and efficacy. For while it may be another route to drug discovery, it lacks significant promise, and thus intrigue in the receptor is scarce. More recently, an opioid-like receptor has taken the international stage. The NOP, being the newest of the four, has been shown to play a part in stress, mood regulation, and pain. As it has shown reduced side effects in comparison to its counterparts, it represents a promising target for next-generation painkillers (Lu et al., 2021; Cipriano et al., 2024).

In addition to exploring the use of different receptors, two major pathways to mitigating side effects have emerged in the field: bitopic and biased ligands. Bitopic ligands interact with both allosteric and orthosteric sites, offering enhanced control over receptor signaling. By engaging the allosteric site in addition to the orthosteric site, they enable finer modulation of receptor activity. This dual binding confers greater differentiation between receptor subtypes and, consequently, more precise control over receptor activation (Gado et al., 2022). Biased ligands present a way to activate only certain signaling pathways preferentially. They aim to retain therapeutic effects while minimizing complications (Stahl et al., 2021). Until now, opioid drug design focused primarily on orthosteric sites, but recent efforts with biased and bitopic signaling have yielded some positive results, making them a popular topic for continued research.

These discoveries have sparked a surge of interest in the field. Soon after they arose, we saw innumerable researchers begin leveraging these concepts to address the opioid crisis. When hundreds of ligands entered the screening pipeline at once, they quickly overwhelmed existing infrastructure and techniques, underscoring the

need for faster, more scalable approaches (Chatterjee et al., 2023). With aid from new technologies like high-throughput screening, scientists are now able to test thousands of compounds simultaneously at a fraction of the cost, significantly accelerating drug discovery.

Alas, with such a vast repertoire of recent innovation in the field, pinpointing promising candidates has become a highly time-intensive task for researchers new to the field. Fortunately, this review aims to sift through the growing body of opioid ligand candidates to identify those demonstrating the most consistent and reproducible therapeutic and clinical promise across clinical studies.

Methodology:

To report the trends in the field of opioid analgesic drugs, this review utilized primarily qualitative data drawn from open-access sources through PubMed. As the focus of this paper covers next-generation opioid agonists and antagonists, and sources of quantitative data varied greatly between labs for many of these drugs, it would have been counterproductive and scientifically irresponsible to include data collected through such heterogenous methods. The most accurate method of discussing the various opioid agonists and antagonists was by reviewing clinical studies and reporting trends and inconsistencies in the current data. The inclusion criteria consisted of studies published between 2017 and 2025, with some exceptions made for historical data critical to contextualizing newer developments. Moreover, only peer-reviewed articles were included. Study types were selected with a preference for human clinical trials; however, in cases where such studies were unavailable, particularly for newer opioid drugs, animal studies were included to fill in important knowledge gaps. By using this methodology, bias was mitigated by drawing from a wide range of studies across different labs and experimental designs, accurately displaying the current landscape of the field of opioid agonists and antagonists.

Discussion:

Body Section 1: Analysis & Overview of μ-OR, κ-OR, δ-OR, and NOP

The main opioid receptors—μ-OR, κ-OR, δ-OR, and NOP—are part of the Class A G protein-coupled receptor (GPCR) family. GPCRs are a large group of cell-surface receptors that transmit signals into the cell via the activation of intracellular G proteins (Wang et al., 2023). When discussing opioid receptors and their agonists/antagonists, a cascade of intricate processes must occur to create the desired, and undesired, effects that we're familiar with.

As per our current understanding of said processes, we focus on three main proteins within the body: $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. While their respective roles in the system are not yet fully understood, recent findings have linked G protein subunits ($G_{\alpha i/o}$ and $G_{\beta\gamma}$) to primarily positive effects (i.e. analgesia and sedation) and β-arrestin to mainly negative effects (i.e. respiratory depression, constipation, and tolerance development), though exceptions exist (Bateman & Levitt, 2021; Faouzi et al., 2020; Mores et al., 2019). Opioids usually activate $G\alpha_{i/o}$ and $G_{\beta\gamma}$, subsequently phosphorylating the receptor, causing β-arrestin to bind to it. Thus, we receive nearly every effect, every time. To that end, many researchers believe that creating ligands biased to G proteins—or even just one subunit of G protein—over β-arrestins could be the foundation for many next generation opioid drugs, hopefully aiding the opioid addiction crisis by mitigating tolerance issues (Figure 1).

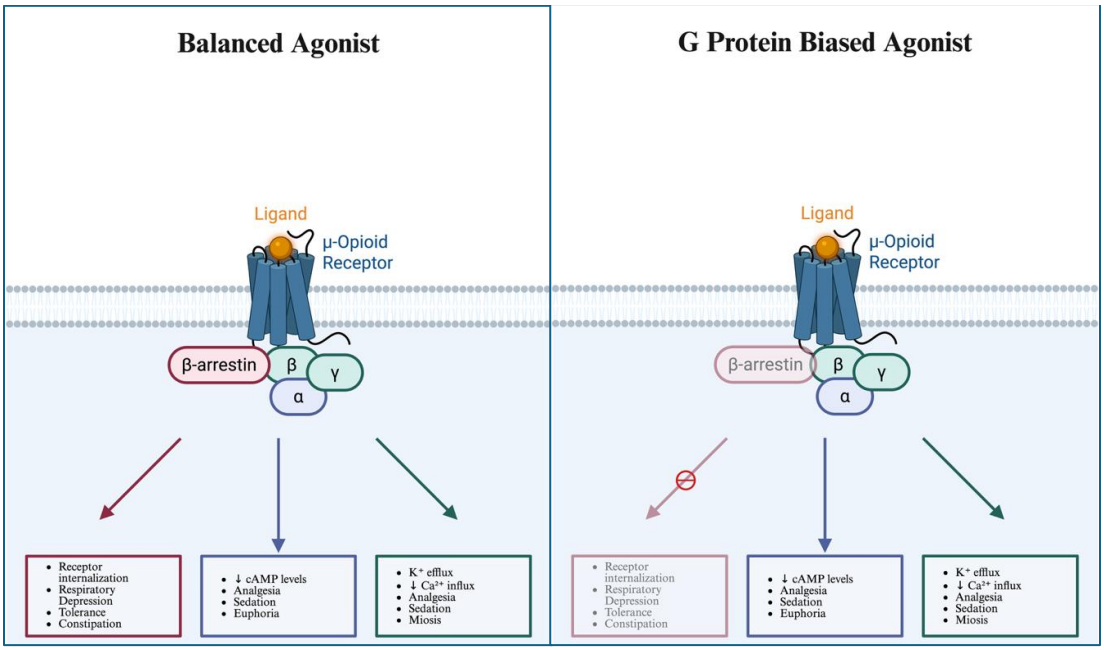

Figure 1.
Both panels show the proteins activated by agonists at the μ-OR. These are the $G_{\alpha i/o}$, $G_{\beta\gamma}$, and β-arrestin. Additionally, a set of common effects associated with each protein type is shown in the boxes below. The balanced agonists (shown left) activate both G protein signaling and β-arrestin pathways to a similar extent. In contrast, G protein-biased agonists (shown right) preferentially activate G protein signaling while minimizing β-arrestin recruitment. The figure was created using BioRender (Roy, A. 2025).

Biased agonists have become increasingly prominent in our ongoing pharmacological search for a drug with the aforementioned qualities. They function primarily through the controlled phosphorylation of the opioid receptor. By preventing phosphorylation, they reduce the recruitment of β-arrestins, producing a G protein-biased agonist (Figure 1 shown right). Inversely, by increasing the recruitment of β-arrestins, they become β-arrestin-biased agonists. Each is hypothesized to take on solely the properties of their protein, thus giving researchers greater governance over the opioid functions (Jayakody et al., 2025). Generally, scientists favor the G protein activity due to its more desirable analgesic effect, however, both routes have some exploration as the concept is a very recent development.

While the information and processes mentioned can be generalized to all the opioid receptors, there also lie distinct pharmacological profiles, therapeutic and clinical potentials, and sets of complications among the μ-OR, κ-OR, δ-OR, and NOP. Understanding and exploiting these factors is vital for the development of more effective opioid agonists and antagonists. For any researcher looking to do so, it is crucial to acknowledge these disparities.

The μ-OR, encoded by the OPRM1 gene, is primarily involved in the analgesic and euphoric effects of opioids. It s predominantly expressed in the periaqueductal gray, thalamus, dorsal horn of the spinal cord, nucleus accumbens, and brainstem respiratory centers, allowing it a great degree of control over pain management. This receptor has strong supraspinal and spinal analgesia, making it effective for acute pain. Thus far, it has long been considered the clinical standard for analgesia due to our longstanding knowledge of its nature and its effectiveness. However, especially in recent years, it has become infamous due to its high risk of respiratory depression, constipation, tolerance, dependence, and euphoria-driven abuse

(Pellissier et al., 2018; Madariaga-Mazón et al., 2017; Ehrlich et al., 2019; Mann et al., 2015).

The κ-OR is encoded by the OPRK1 gene, and while perhaps overshadowed by the μ-OR, has consistently shown promise in analgesia. It produces potent spinal analgesia, antipruritic effects, and minimal respiratory depression. Dense in hypothalamus, amygdala, periaqueductal gray, spinal cord dorsal horn, and pituitary, this receptor has become increasingly valuable as we search for a replacement to traditional μ-OR drugs like fentanyl. Alas, it is also known to cause dysphoria, hallucinations, sedation, and aversion in many patients. For this reason, it has historically been avoided for opioid use. Recently, however, significant promise with the receptor has been shown. In Japan, a κ-OR drug, nalfurafine, has even been conditionally approved for certain therapeutic prescriptions like pruritus in dialysis patients (Table 3), showing net positive effects in many patients thus far (Liu-Chen & Huang, 2022; Hampsey et al., 2024; Escudero-Lara et al., 2021; Han et al., 2023).

On the other hand, the δ-OR, encoded by the OPRD1 gene, is predominantly expressed in the cortex, olfactory bulb, dorsal root ganglia, hippocampus, and limbic regions. In general consensus, it has shown little promise compared to its counterparts. While it does show some mild analgesic, antidepressant, and anxiolytic effects, its risk of seizure is high and potency for pain relief is low. Generally, the risk of seizures alongside analgesia is not a tradeoff viewed favorably in drug development. To that end, δ-OR selective agonists have been largely passed over by researchers in the field (Gavériaux-Ruff & Kieffer, 2011; Saigusa et al., 2017).

More recently, the atypical NOP has come into play. Encoded by the OPRL1 gene, this receptor is widespread at the cerebral cortex, amygdala, spinal cord, locus coeruleus, and dorsal root ganglia. It has shown great promise in the production of spinal and peripheral analgesia without the creation of respiratory depression, euphoria, or extreme tolerance issues. However, due to its often dual analgesic/anti-analgesic behavior, many feel it to be counterintuitive. Regardless, it has shown significant promise in the field, especially in combination with other receptors. Notably, NOP's synergy with μ-OR signaling has spurred interest in dual agonists, which will be discussed in a later section (examples can be seen in Table 3) (Post et al., 2016; Raffaeli et al., 2006; Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017).

Body Section 2: The Rise of New Classes of Opioid Agonists: Biased and Dual Agonism

Until the late 1990s medical professionals and researchers alike were wary of opioid drugs, using them only when absolutely necessary (i.e. late-stage cancer) and in small quantities, but in 1996 the company Purdue Pharma produced OxyContin, a drug that would change the opioid landscape for decades to come. OxyContin, a brand name for an extended-release formulation of oxycodone, was introduced by Purdue Pharma to treat moderate–severe pain over long periods of time. As opioids had long-since been considered addictive and having many complications, most care providers were averse to their use. Nevertheless, Purdue Pharma confidently cited a one-paragraph letter from the renowned *New England Journal of Medicine* (Porter & Jick, 1980). This report—using a small test group of hospitalized patients—was taken out of context by Purdue Pharma, cited as definite proof that opioids were safe and non-addicting for long-term outpatient use. When coupled with more influential clinical papers; aggressive, misleading, and FDA-backed promotional marketing (Table 1) (Van Zee, 2009); and pressure from the "Pain as the 5th vital sign marketing", doctors' fears were assuaged, and the mass prescription of opioids began (Rosenman et al., 2025). In 2020, Purdue Pharma pleaded guilty to their false advertising, taking OxyContin's extended-release form off the market. Unfortunately, by then, the damage was done, leaving us with an opioid crisis we don't have a solution to. Even today, while under closer security and restriction, opioids are being prescribed to those with chronic pain-causing afflictions, as they are currently thought to be the best method of pain-mitigation. However, even when medical professionals stop the opioid prescription, there is a high likelihood of addiction, tempting patients to continue their use through non-controlled substances like diacetylmorphine (heroin), illicit morphine, or illicitly manufactured fentanyl (Refer to Figure 2 for structures).

Table 2.

Table detailing common characteristics of therapeutic and clinical opioid usage.

	Duration	Risk of Addiction	Level of Supervision
Therapeutic (Outpatient) Use	~2 Months – Indefinite	Usually **higher risk** than clinical	Initially prescribed by medical professional, generally with occasional updates

Clinical (Inpatient) Use	~2 Hours – 24 Hours	Usually **lower risk** than therapeutic	Near-constant monitoring and adjusting by medical professional

Currently, for outpatient therapeutic use (Table 2), we have a variety of opioids at our disposal. For this purpose, we tend to use longer-acting drugs such as morphine (Zhuang et al., 2022; Krishnamurti & Rao, 2016; Reilly, 2016), oxycodone, hydromorphone, methadone, and fentanyl transdermal patches (Figure 2 and Table 3) (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019). We do this for several reasons including duration of action, potency, overdose risk, abuse risk, cost, and government regulation. Conversely, for inpatient clinical care (Table 2), shorter-acting drugs with faster onset and offset, like fentanyl and remifentanil, are often utilized (Figure 2 and Table 3) (Brown et al., 2020; Sutcliffe et al., 2022). This can also be attributed to the aforementioned reasons but their inverse.

Perhaps some of the most acute examples of this idea are the uses of morphine and fentanyl. Morphine (a large, hydrophilic substance) has a much longer onset and offset when compared to fentanyl (a smaller, lipophilic substance) (refer to Figure 2 for structures) (Brown et al., 2020; Sutcliffe et al., 2022). Thus, morphine is mostly used for chronic and cancerous conditions, whilst fentanyl is reserved for general surgery under the watch of an anesthesiologist. Each has its benefits and drawbacks, making them ideal for different scenarios. Morphine lasts longer than fentanyl, increasing the risk of complications like nausea and constipation, but decreasing the risk of overdose in long-term situations, as it will be administered less often (Table 2). Fentanyl is ~50–100 times more potent than morphine, making it cheaper when diluted and given properly, but deadly if overdosed. Fentanyl may have greater reinforcement potential due to rapid onset and high potency, but if taken for prolonged periods of time, as morphine usually is, both can become extremely addictive due to euphoric effects and unregulated dopamine levels. To synthesize, morphine and fentanyl are two very different drugs, targeting the same issue but in unique ways, making them best suited for different tasks. While often discussed, these are not the only two opioid drugs that follow these principles. As mentioned earlier, medical professionals have dozens of drugs—approved, obsolete, and in development—to treat patients with (Table 3). However, especially with more recently developed opioids, most of the medical community is

wary of change, with good reason, considering the recent history with OxyContin. Thus, it is important to recognize the disparate effects (both short and long term) and tailor opioid use to the task it is performing. We can do this through clinical trials, where a near-definite assessment is reached, but even before that we are able to form a rough hypothesis based on the structure (Figure 2) and intended route of function (Table 3). Here, we will be comparing the structure, receptor, and other known factors of next generation agonists to their clinically and therapeutically established counterparts, reporting trends and inconsistencies between these factors and the drugs' effects.

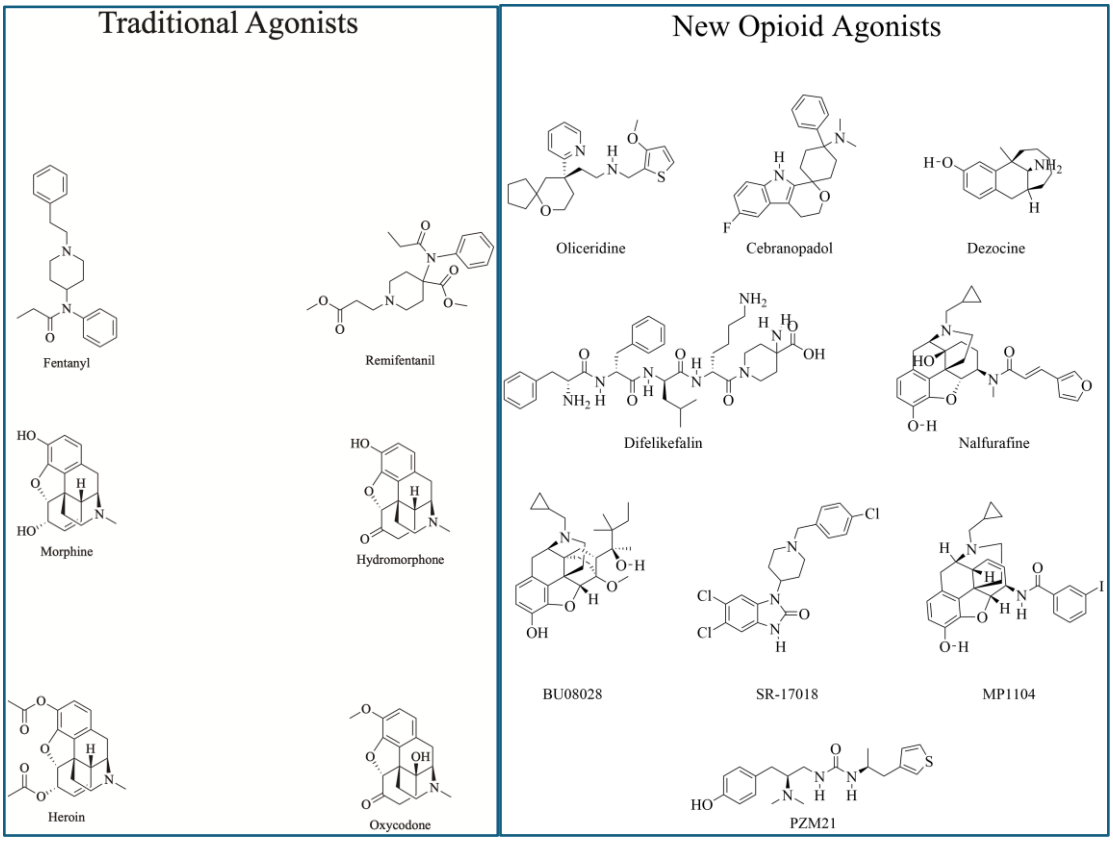

Figure 2.

Panels show structures of traditional agonists (left) and new opioid agonists (right).

Table 3.

Table showing the name, common brand name target, effects (both positive and negative), and stage of development (indicating how far a drug has advanced through testing and approval) of different established and upcoming agonists.

Name	Common Brand Name(s)	Target	Positive Effects	Negative Effects	Stage of Development / Use
Oliceridine	Olinvyk	μ-OR – G protein–partial bias	Strong IV analgesia, slightly reduced GI and respiratory issues compared to morphine	Nausea, dizziness, respiratory depression still possible, limited duration	Approved (US) for acute pain (IV)
PZM21	–	μ-OR – low β-arrestin recruitment	Analgesia in preclinical and early human studies	Respiratory depression in later animal studies, low analgesic effects	Preclinical/early clinical
SR-17018	–	μ-OR – G protein biased	Potent, long-acting analgesia in animals, reduced tolerance issues in mice	No human data; bias claims debated, possible side effects typical of μ-OR agonists	Preclinical
Dezocine	Dalgan	μ-OR partial agonist + κ-OR partial antagonist + SERT/NET inhibitor	Analgesia, possible mood elevation, lower abuse liability reports	Typical opioid adverse events, mild sedation	Approved (China); formerly marketed in US
Nalfurafine	Remitch	κ-OR full agonist + μ-OR partial agonist	Antipruritic with reduced dysphoria compared to classical κ-OR agonists	Low analgesia, Sedation, possible mild dysphoria	Approved (Japan) for uremic pruritus
Difelikefalin	Korsuva	κ-OR peripheral agonist	Pruritus relief, minimal CNS sedation/respiratory depression	Low analgesia, mild nausea, diarrhea	Approved (US) for CKD-associated pruritus; IV in dialysis
MP1104	–	κ-OR full agonist + δ-OR full agonist	Analgesia in rodents, reduced classic κ-OR aversion	Unknown human safety; possible κ-OR side effects	Preclinical
BU08028	–	μ-OR partial agonist + NOP partial agonist	Strong analgesia in NHPs, minimal respiratory depression or abuse liability	Unclear long-term safety, typical opioid effects possible	Preclinical
Cebranopadol	–	μ-OR full agonist + NOP agonist	Very long-lasting analgesia, fewer classic μ-OR adverse events	Some sedation, opioid-like side effects	FDA Fast Track Designation for chronic low back pain
Morphine	Zomorph, Sevredol, MS Contin, and Oramorph	μ-OR full agonist (balanced signaling)	Strong analgesia, sedation	Respiratory depression, constipation, histamine release, tolerance	Approved, widely used
Hydromorphone	Dilaudid	μ-OR full agonist (balanced signaling)	Potent analgesia, less histamine release than morphine	Respiratory depression, constipation, sedation	Approved, widely used
Diacetylmorphine	Heroin	μ-OR full agonist	Very rapid and strong analgesia/euphoria	High abuse liability, respiratory depression, rapid dependence, low regulation	Approved in some countries for opioid dependence; illicit in most
Oxycodone	OxyContin	μ-OR full agonist + minor κ-OR agonist	Effective oral analgesic	Abuse liability, respiratory depression, constipation	Approved, widely used
Fentanyl	Sublimaze (Intravenous), Duragesic (Transdermal patches), Actiq (Oral transmucosal lozenges), Fentora (Effervescent buccal tablets), Abstral (Sublingual tablets), Subsys (Sublingual sprays), and Lazanda (Nasal sprays)	μ-OR full agonist	Very rapid, potent analgesia and sedation	Respiratory depression, tolerance issues, addiction potential	Approved, widely used (anesthesia, severe pain)
Remifentanil	Ultiva	μ-OR full agonist	Rapid onset, rapid offset, precise titration	Respiratory depression during infusion, little residual analgesia after stop	Approved, widely used in anesthesia

Note. Data for Oliceridine are from Wolf et al. (2024). Data for PZM21 are from Manglik et al. (2016). Data for SR-17018 are from Pradhan et al. (2021). Data for Dezocine are from Zhou et al. (2023). Data for Nalfurafine are from Kozono et al. (2018). Data for Difelikefalin are from Fishbane et al. (2022). Data for MP1104 are from Zádor et al. (2019). Data for BU08028 are from Ding et al. (2016). Data for Cebranopadol are from Schroeder et al. (2021). Data for Morphine are from Gutstein

and Akil (2025). Data for Hydromorphone are from Kharasch (2020). Data for Diacetylmorphine are from Darke et al. (2019). Data for Oxycodone are from Gudin and Fudin (2021). Data for Fentanyl are from Volpe (2023). Data for Remifentanil are from Egan (2019).

Based on the factors analyzed, several predictions can be drawn. It is important to note, however, that these are solely predictions, and the true effects of drugs are shown through human clinical studies and continued therapeutic use. With that said, this preemptive style of analysis can be extremely useful for researchers looking to explore very recently developed avenues of creating opioid drugs and assess which growing ideas have had the most success thus far.

Firstly, it is crucial to understand which areas of research have had the least success and least exploration with regard to opioid analgesics. To this end, we can cite the limited results of full and partial δ-OR agonists. Most drugs developed for the δ-OR either show low efficacy with analgesia, inordinate complications, or a combination of both issues (for specific examples, refer to Table 3). Thus, the data for the receptor is limited, and the results are not quite promising. Moreover, certain agonists, namely PZM21, were initially thought to be biased agonists, due to their lessened side effects (Figure 1), but it was later discovered that the effects could be attributed to low intrinsic efficacies (Hillhouse & Negus, 2016). Furthermore, the κ-OR, once considered among the most promising candidates for analgesic drug development, has shown mixed results. In many κ-OR agonists in use, low analgesic effects in ratio to dysphoric issues have been noted (Table 3). However, the antipruritic (anti-itch) benefits of κ-OR agonists such as Nalfurafine and Difelikefalin haven't gone unnoticed (Table 3). This receptor—while perhaps not as indicative of heralding the future of less issue-prone analgesic drugs—presents a unique pathway for antipruritic drugs, with a plethora of reassuring, trial-based evidence to support it (Beck et al., 2019; Liu-Chen & Huang, 2022).

More optimistically, we have a number of agonists employing a variety of strategic approaches to drug design. Not only is it important to understand which drugs are successful and unsuccessful, but the underlying mechanisms of said drugs are just as important to the field. To that end, we have seen many drugs with success, but it is still important to define and categorize that success, as different issues necessitate different criteria. The main uses for analgesic drugs are therapeutic and clinical. In outpatient therapy, the patient will be exposed to the

drug for longer durations and generally at lower doses. Conversely, in clinical procedures, higher doses are given, but far less frequently and in tightly controlled settings. Some drugs, like fentanyl (see Table 3) are even used for both cases via different routes like the fast-acting intravenous formula for surgical procedures and the slower-release transdermal patches for chronic pains (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019).

For acute clinical use, we have seen agonists at the μ-OR work the quickest and safest, but still retain some drawbacks of constipation, nausea, respiratory depression, and continually increasing tolerance. However, when biased to the G proteins $G_{\alpha i/o}$ and $G_{\beta\gamma}$, several agonists showed reduced complications, especially with tolerance, as the β-arrestin was no longer causing the internalization and degradation of the receptor. For example, Oliceridine—an agonist that preferentially activates G protein signaling over β-arrestin recruitment—is already shown to have a lower risk of several side effects in humans. Oliceridine has rapid analgesia like fentanyl and morphine, but lower respiratory depression and gastrointestinal complications at equianalgesic doses of those same traditional opioids (Table 3). This drug has shown us that G protein bias can be successful, but it is still not perfect: side effects can still occur, especially at higher doses (Faouzi et al., 2020; Stahl et al., 2021; Bateman & Levitt, 2021). Oliceridine has not been widely tested for human surgical use, mostly used to counteract moderate–severe acute pain in-clinic. Moreover, it is important to note that not all studies consistently replicate the same balance of β-arrestin versus G protein outcomes, so results should be interpreted with caution and may depend on the specific ligand and experimental system. Due to this, the community is still searching for an even better opioid analgesic to compete with fentanyl, and many feel G protein bias is the way to get there.

In chronic therapeutic development, on the other hand, many of the most promising agonists also utilize the concept of dual agonism/antagonism where agonists target multiple receptors. For example, BU08028 and Cebranopadol are both mixed agonist drugs (Table 3). BU08028 primarily targets the μ-OR and NOP, reaping analgesia via a classical opioid pathway, and also modulating pain whilst reducing side effects like addiction risk through the NOP. If hypotheses are confirmed by human trials, this drug could provide potent, long-lasting analgesia without as many complications for chronic and acute pain. Cebranopadol is a first-

in-class mixed opioid receptor. The drug targets the μ-OR and NOP as a full agonist and δ-OR and κ-OR as a partial agonist. By providing strong analgesia through the μ-OR, modulating pain through the NOP, and utilizing δ-OR & κ-OR for some neuropathic pain, this drug shows use for both acute and long-term pain management (Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017). Taking a different approach, dezocine, a drug widely used in China for chronic pain in humans, but taken off the American market (for economic, not safety concerns), is a μ-OR agonist, κ-OR antagonist, and a serotonin-norepinephrine reuptake inhibitor. By partially agonizing the μ-OR, the drug creates potent analgesia, but with a ceiling effect, lowering the risk of respiratory depression. Being a κ-OR antagonist, this opioid analgesic also reduces dysphoria and sedation risk.

Body Section 3: Opioid Antagonists: Uses, drawbacks, and new technologies

As the opioid drug crisis remains to be solved, more and more people are overdosing on opioid drugs and experiencing respiratory depression, and thus, opioid antagonists are needed increasingly more. In the United States, many school districts located in high-drug-trafficking areas keep a narcotic reversal agent on hand, usually naloxone (Narcan). However, just as fentanyl has drawbacks and welcomes alternative agonists, naloxone has sparked a new wave of innovation for better opioid antagonists.

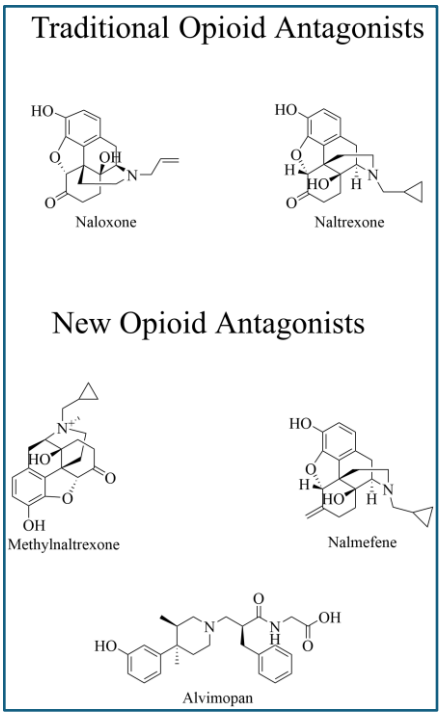

Figure 3.
Chemical structures of traditional and in-development (new) antagonists. Each structure is labeled with its name underneath.

Table 4.
Table showing the name, common brand name target, effects (both positive and negative), and stage of development of different established and upcoming antagonists.

Name / Brand(s)	Delivery Methods	Target	Positive Effects	Negative Effects	Stage of Development / Use
Naloxone (Narcan, Kloxxado, Evzio)	Intravenous (IV), Intramuscular (IM), Subcutaneous (SC), Intranasal spray	Full antagonist at μ-OR; Partial antagonist at κ-OR and δ-OR	Rapid reversal of opioid overdose, restores respiration	Short half-life (risk of re-narcotization), may cause severe withdrawal symptoms in opioid-dependent patients	Approved; gold standard emergency overdose treatment
Naltrexone (ReVia, Vivitrol, Depade)	Oral tablet, Extended-release intramuscular injection	Full antagonist at μ-OR, weak κ-OR antagonism	Prevents relapse in opioid/alcohol use disorder, longer duration than naloxone	Hepatotoxicity risk at high doses, poor adherence in oral form, precipitates withdrawal	Approved for opioid and alcohol dependence treatment
Methylnaltrexone (Relistor)	Subcutaneous injection, Oral tablet	Peripherally acting μ-opioid receptor antagonist (PAMORA); does not cross BBB	Reverses opioid-induced constipation without affecting analgesia	Abdominal pain, won't reverse overdose	Approved for opioid-induced constipation in palliative care or chronic pain
Alvimopan (Entereg)	Oral capsule	PAMORA; selective peripheral μ-opioid receptor antagonist	Reverses opioid-induced constipation without affecting analgesia	Cardiovascular risk with long-term use (restricted to short-term access)	Approved for short-term hospital use post-surgery (REMS program)
Nalmefene (Selincro, Revex)	Intravenous, Intramuscular, Subcutaneous, Oral tablet (Europe)	Full antagonist at μ-OR, partial agonist at κ-OR and δ-OR	Reversal of opioid overdose (longer duration than naloxone),	Nausea, dysphoria, precipitates withdrawal	Approved in some regions for alcohol dependence; approved in

			reduces alcohol consumption		U.S. (IV) for overdose reversal

Note. Naloxone data are from Bailey and Wermeling (2014) and Barton et al. (2005). Naltrexone data are from Comer et al. (2018) and Mark and Jones (2022). Methylnaltrexone data are from Webster et al. (2023) and Deibert (2011). Alvimopan data are from Viscusi and Singla (2019) and Tan et al. (2008). Nalmefene data are from LiverTox (2015) and Smith et al. (2025).

Just as with agonists, antagonist drugs are present in a variety of structures, delivery routes, and mechanisms of action (Figure 3 and Table 4). Naloxone is still the gold standard emergency overdose treatment: it works with few complications and is usually life-saving. The largest issue is its short half-life, as it only works for ~30-90 minutes, whereas some opioid agonists function for hours (Table 3). This can cause re-narcotization, where overdose symptoms return after naloxone wears off, requiring repeat dosing or IV infusion. Some other issues involve rapid withdrawal symptoms in opioid dependent individuals (due to naloxone's rapid onset) and limited efficacy with ultra-potent opioids like Carfentanil. Additionally, the intravenous version of naloxone requires training to administer, but trained staff may not be available at the time of overdose (Bird et al., 2023; Beck et al., 2019; Lu et al., 2021; Cipriano et al., 2024).

To that end, researchers and scientists are working to develop and test several new reversal agents to hopefully solve some of naloxone's issues without sacrificing its efficacy. So far, drugs like Naltrexone and Nalmefene have been created and FDA approved for certain cases (Table 4 and Figure 3). They tend to last much longer than naloxone, but have been associated with immediate acute withdrawal symptoms, so newer opioid antagonist drugs are still in development (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Moreover, we now have several oral sprays, nasal sprays, and oral capsules to make untrained administration easier (Table 4). While some critics have argued that the widespread availability of reversal agents could embolden opioid users and agitate the issue, widespread consensus agrees that the lives saved overshadow this issue. Additionally, a new class of antagonist drugs known as PAMORAs (peripherally acting μ-opioid receptor antagonists) has emerged (Table 4). These drugs, like alvimopan and methylnaltrexone, are actually not used to treat opioid overdose. Rather, they are utilized mainly for opioid-induced constipation. PAMORAs, unlike most antagonists, do not reduce analgesic effects, making them a great resource for

patients in chronic pain or for post-operative care (Pellissier et al., 2018; Madariaga-Mazón et al., 2017).

Another issue is that while traditional antagonist drugs create a rapid reversal effect, they cannot be given preemptively, as they have a short half-life. However, a unique class of drugs known as monoclonal antibody–based opioid binders present a new way to combat the issue: the idea of opioid "vaccines". Unlike traditional antagonists, monoclonal antibodies could prevent opioid agonists from crossing the blood-brain barrier (BBB). This would effectively reduce the effects of opioids over a long period, thus "vaccinating" patients against them. Nevertheless, many concerns and debates exist over this topic. For instance, the design of these drugs is very specific, usually only targeting one or a few agonists. So, if a person suffering from opioid addiction were to get treated against heroin, thus nulling its effects, they may resort to other drugs such as fentanyl for the same euphoria. Moreover, if a patient is vaccinated against too many opioids and needs a surgical procedure, the anesthesiologist may have a difficult time finding an opioid drug to administer analgesia. This applies even more so for an emergency room (ER) case in which the patient's medical record may not be on hand. So, even though traditional antagonists and monoclonal antibody–based drugs strive to aid the same issue—the ongoing opioid crisis—both take very different routes and expect very different outcomes (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Thus, they are not in competition with each other, as neither can replace the other, but expanding our research in both areas would benefit the same problem.

Conclusion:

In synthesis, opioid pharmacology represents a path to improving both therapeutic tools and clinical medicine. Our growing understanding of opioid receptor function has revealed opportunities to separate beneficial analgesic effects from unwanted side effects, but the path toward safer and more effective drugs remains largely open. Nevertheless, historical missteps remind us that scientific innovation must not come at the cost of foregoing rigorous testing, regulation, and responsible clinical use. This evolving landscape can be summarized in three key areas. First, progress in biased and bitopic agonism has highlighted promising strategies, such as the development of biased agonists that preferentially activate pathways linked to analgesia and the exploration of dual-acting compounds that target multiple receptors simultaneously. Second, persistent limitations remain

in translating encouraging preclinical findings into reliable clinical outcomes, underscoring the need for cautious interpretation and stringent validation. Third, the outlook for rational design—integrating receptor structure and pharmacological innovation—offers a forward-looking path toward safer and more effective opioid drugs. It is important to note, however, that in the global market thus far, no opioid agonist has yet surpassed fentanyl and similarly, no opioid antagonist has yet usurped naloxone; both are remarkable innovations that have saved countless lives, regardless of their shortcomings. Ultimately, addressing the opioid crisis will not come from a single breakthrough, but rather an integrated approach. Continued research in all of these areas offers the best chance of balancing the essential role of opioids in pain relief with the urgent need to minimize their risks.

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References

Addiction Rare in Patients Treated with Narcotics. (1980). New England Journal of Medicine, 302(2), 123–123. https://doi.org/10.1056/NEJM198001103020221

Baehr, C., Kelcher, A. H., Khaimraj, A., Reed, D. E., Pandit, S. G., AuCoin, D., Averick, S., & Pravetoni, M. (2020). Monoclonal antibodies counteract opioid-induced behavioral and toxic effects in mice and rats. The Journal of Pharmacology and Experimental Therapeutics, 375(3), 469–477. https://doi.org/10.1124/jpet.120.000124

Bailey, A., & Wermeling, D. (2014). Naloxone for opioid overdose prevention: Pharmacists' role in community-based practice settings. Annals of Pharmacotherapy, 48(5), 601-606. https://doi.org/10.1177/1060028014523730

Balon, T. M., Xia, Y., McKeown, J., Wang, J., Abbott, J. J., Palettas, M., Uribe, A., Echeverria Villalobos, M., Coffman, J. C., & Hu, L.-Q. (2024). Pocket warming of bupivacaine with fentanyl to shorten onset of labor epidural analgesia: A double-blind randomized controlled clinical trial. PLOS ONE, 19(9), e0309515. https://doi.org/10.1371/journal.pone.0309515

Barton, E., Colwell, C., Wolfe, T., Fosnocht, D., Gravitz, C., Bryan, T., et al. (2005). Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. Journal of Emergency Medicine, 29(3), 265-271. https://doi.org/10.1016/j.jemermed.2005.03.007

Bateman, J. T., & Levitt, E. S. (2021). Evaluation of G protein bias and β-arrestin 2 signaling in opioid-induced respiratory depression. American Journal of Physiology-Cell Physiology, 321(4), C681–C683. https://doi.org/10.1152/ajpcell.00259.2021

Beck, T. C., Reichel, C. M., Helke, K. L., Bhadsavle, S. S., & Dix, T. A. (2019). Non-addictive orally-active kappa opioid agonists for the treatment of peripheral pain in rats. European Journal of Pharmacology, 856, 172396. https://doi.org/10.1016/j.ejphar.2019.05.025

Benet, M., Niazi, A., & Scott, J. (2017). Reciprocal evolution of opiate science from medical and cultural perspectives. Frontiers in Pharmacology, 8 (Article 782). https://doi.org/10.3389/fphar.2017.00782

Bird, H. E., Huhn, A. S., & Dunn, K. E. (2023). fentanyl Absorption, Distribution, Metabolism, and Excretion: Narrative Review and Clinical Significance Related to Illicitly Manufactured fentanyl. Journal of Addiction Medicine, 17(5), 503–508. https://doi.org/10.1097/ADM.0000000000001185

Blumenthal, D., & Shapiro, J. (2025). Policy options for the drug pricing conundrum. Proceedings of the National Academy of Sciences, 122(13), e2418540122. https://doi.org/10.1073/pnas.2418540122

Brown, J. A., Faley, S. L., Shi, Y., Hillgren, K. M., Sawada, G. A., Baker, T. K., Wikswo, J. P., & Lippmann, E. S. (2020). Advances in blood–brain barrier modeling in microphysiological systems highlight critical differences in opioid transport due to cortisol exposure. Fluids and Barriers of the CNS, 17(1), 38. https://doi.org/10.1186/s12987-020-00200-9

Chan, E. W. Y., Leung, J. C. Y., Wong, I. C. K., & others. (2021). Prescription medicine misuse in the Asia–Pacific region: An evolving issue? British Journal of Clinical Pharmacology, 87(4), 1810-1818. https://doi.org/10.1111/bcp.14638

Chatterjee, A., et al. (2023). Improving the generalizability of protein–ligand binding predictions with AI-Bind. Nature Communications, 14(1), 2347. https://doi.org/10.1038/s41467-023-37572-z

Christoph, A., Eerdekens, M.-H., Kok, M., Volkers, G., & Freynhagen, R. (2017). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience in patients with chronic low back pain in a randomized clinical trial. Pain, 158(9), 1813–1824. https://doi.org/10.1097/j.pain.0000000000000986

Cipriano, A., Kapil, R. P., Zhou, M., Shet, M. S., Whiteside, G. T., Willsie, S. K., & Harris, S. C. (2024). Safety, tolerability, and pharmacokinetics of single- and multiple-ascending doses of sunobinop in healthy participants. Clinical Pharmacology in Drug Development, 13(7), 790–800. https://doi.org/10.1002/cpdd.1394

Comer, S. D., Sullivan, M. A., Hulse, G. K., & Somoza, E. (2018). Naltrexone: A history and future directions. CNS Drugs, 32(9), 825-836.

Cook, M. E., Knoph, C. S., Fjelsted, C. A., Frøkjær, J. B., Bilgrau, A. E., Novovic, S., Jørgensen, M. T., Mortensen, M. B., Nielsen, L. B. J., Hadi, A., Berner-Hansen, M., Rutkowski, W., Vujasinovic, M., Löhr, M., Drewes, A. M., & Olesen, S. S. (2023). Effects of a peripherally acting μ-opioid receptor antagonist for the prevention of recurrent acute pancreatitis: Study protocol for an investigator-initiated, randomized, placebo-controlled, double-blind clinical trial (PAMORA-RAP trial). Trials, 24(1), 301. https://doi.org/10.1186/s13063-023-07287-z

Coombes, L., Burke, K., & Anderson, A.-K. (2017). The use of rapid onset fentanyl in children and young people for breakthrough cancer pain. Scandinavian Journal of Pain, 17(1), 256–259. https://doi.org/10.1016/j.sjpain.2017.07.010

Curran, M. P., Robins, G. W., Scott, L. J., & Perry, C. M. (2008). Alvimopan. Drugs, 68(14), 2011-2019. https://doi.org/10.2165/00003495-200868140-00006

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., Bernstein, S. L., & Fiellin, D. A. (2015). Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. JAMA, 313(16), 1636. https://doi.org/10.1001/jama.2015.3474

Darke, S., Farrell, M., & Degenhardt, L. (2019). The pharmacology of heroin. Drug and Alcohol Review, 38(1), 108–116. https://doi.org/10.1111/dar.12878

Deibert, P. (2011). Opioid-induced constipation in advanced illness. Journal of Pain and Symptom Management, 41(5), 918-929. https://doi.org/10.1038/ajg.2011.30

Ding, H., Czoty, P. W., & Nader, M. A. (2016). A novel orvinol analog, BU08028, as a safe opioid analgesic without abuse liability in primates. Proceedings of the National Academy of Sciences, 113(22), E6269–E6278. https://doi.org/10.1073/pnas.1615248113

Egan, T. D. (2019). Remifentanil pharmacokinetics and pharmacodynamics: A review and update. Anesthesia & Analgesia, 128(5), 925–937. https://doi.org/10.1213/ANE.0000000000004077

Eggleston, W., Calleo, V., Kim, M., & Wojcik, S. (2020). Naloxone Administration by Untrained Community Members. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 40(1), 84–88. https://doi.org/10.1002/phar.2352

Ehrlich, A. T., Kieffer, B. L., & Darcq, E. (2019). Current strategies toward safer mu opioid receptor drugs for pain management. Expert Opinion on Therapeutic Targets, 23(4), 315–326. https://doi.org/10.1080/14728222.2019.1586882

Escudero-Lara, A., Cabañero, D., & Maldonado, R. (2021). Kappa opioid receptor modulation of endometriosis pain in mice. Neuropharmacology, 195, 108677. https://doi.org/10.1016/j.neuropharm.2021.108677

Faouzi, A., Varga, B. R., & Majumdar, S. (2020). Biased Opioid Ligands. Molecules, 25(18), 4257. https://doi.org/10.3390/molecules25184257

Fishbane, S., Jamal, A., Nanovic, L., & Pergola, P. E. (2022). Safety and effectiveness of difelikefalin in patients with moderate-to-severe chronic kidney disease-

associated pruritus. Kidney International Reports, 7(8), 2040–2051. https://doi.org/10.1016/j.ekir.2022.06.019

Gado, F., Ferrisi, R., Polini, B., Mohamed, K. A., Ricardi, C., Lucarini, E., Carpi, S., Domenichini, F., Stevenson, L. A., Rapposelli, S., Saccomanni, G., Nieri, P., Ortore, G., Pertwee, R. G., Ghelardini, C., Di Cesare Mannelli, L., Chiellini, G., Laprairie, R. B., & Manera, C. (2022). Design, synthesis, and biological activity of new CB2 receptor ligands: From orthosteric and allosteric modulators to dualsteric/bitopic ligands. Journal of Medicinal Chemistry, 65(14), 9918–9938. https://doi.org/10.1021/acs.jmedchem.2c00582

Gavériaux-Ruff, C., & Kieffer, B. L. (2011). Delta opioid receptor analgesia: Recent contributions from pharmacology and molecular approaches. Behavioural Pharmacology, 22(5 and 6), 405–414. https://doi.org/10.1097/FBP.0b013e32834a1f2c

Glenn, J. K., & Goldman, J. (1976). Task delegation to physician extenders—Some comparisons. American Journal of Public Health, 66(1), 64–66. https://doi.org/10.2105/ajph.66.1.64

Göhler, K., Sokolowska, M., Schoedel, K. A., Nemeth, R., Kleideiter, E., Szeto, I., & Eerdekens, M.-H. (2019). Assessment of the abuse potential of cebranopadol in nondependent recreational opioid users: A phase 1 randomized controlled study. Journal of Clinical Psychopharmacology, 39(1), 46–56. https://doi.org/10.1097/JCP.0000000000000995

Gutstein, H. B., & Akil, H. (2025). Opioid analgesics. In L. Bruton, J. S. Lazo, & K. L. Parker (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics (14th ed., pp. 175–221). McGraw-Hill Education.

Gudin, J. A., & Fudin, J. (2021). Pharmacokinetics and pharmacodynamics of oxycodone: A review of the literature. Pain & Therapy, 10(1), 75–87. https://doi.org/10.1007/s40122-020-00214-3

Guo, S.-B., Meng, Y., Lin, L., Zhou, Z.-Z., Li, H.-L., Tian, X.-P., & Huang, W.-J. (2024). Artificial intelligence alphafold model for molecular biology and drug discovery: A machine-learning-driven informatics investigation. Molecular Cancer, 23(1), 223. https://doi.org/10.1186/s12943-024-02140-6

Hampsey, E., Jelen, L., & Young, A. H. (2024). Aticaprant: (A κ-opioid receptor antagonist) for major depressive disorder. Expert Opinion on Emerging Drugs, 29(3), 193–204. https://doi.org/10.1080/14728214.2024.2345645

Han, J., Zhang, J., Nazarova, A. L., Bernhard, S. M., Krumm, B. E., Zhao, L., Lam, J. H., Rangari, V. A., Majumdar, S., Nichols, D. E., Katritch, V., Yuan, P., Fay, J. F., &

Che, T. (2023). Ligand and G-protein selectivity in the κ-opioid receptor. Nature, 617(7960), 417–425. https://doi.org/10.1038/s41586-023-06030-7

Hovah, M. E., & Holzgrabe, U. (2024). Bivalent and bitopic ligands of the opioid receptors: The prospects of a dual approach. Medicinal Research Reviews, 44(6), 2545–2599. https://doi.org/10.1002/med.22050

Jang, J. S., Hwang, S. M., Kwon, Y., Tark, H., Kim, Y. J., Ryu, B. Y., & Lee, J. J. (2018). Is the transdermal fentanyl patch an efficient way to achieve acute postoperative pain control?: A randomized controlled trial. Medicine, 97(51), e13768. https://doi.org/10.1097/MD.0000000000013768

Jayakody, T., Budagoda, D. K., Mendis, K., Dilshan, W. D., Bethmage, D., Dissasekara, R., & Dawe, G. S. (2025). Biased agonism in peptide-GPCRs: A structural perspective. Pharmacology & Therapeutics, 269, 108806. https://doi.org/10.1016/j.pharmthera.2025.108806

Kelly, E., Conibear, A., & Henderson, G. (2023). Biased Agonism: Lessons from Studies of Opioid Receptor Agonists. Annual Review of Pharmacology and Toxicology, 63, 491–515. https://doi.org/10.1146/annurev-pharmtox-052120-091058

Kharasch, E. D. (2020). Hydromorphone: Clinical pharmacokinetics and pharmacodynamics. Expert Opinion on Drug Metabolism & Toxicology, 16(6), 495–507. https://doi.org/10.1080/17425255.2020.1752200

Kieffer, B. L. (1999). Opioids: First lessons from knockout mice. Trends in Pharmacological Sciences, 20(1), 19–26. https://doi.org/10.1016/S0165-6147(98)01279-6

Kliewer, A., Gillis, A., Hill, R., Schmiedel, F., Bailey, C., Kelly, E., Henderson, G., Christie, M. J., & Schulz, S. (2020). Morphine-induced respiratory depression is independent of β-arrestin2 signalling. British Journal of Pharmacology, 177(13), 2923–2931. https://doi.org/10.1111/bph.15004

Koch, E. D., Kapanadze, S., Eerdekens, M.-H., Kralidis, G., Létal, J., Sabatschus, I., & Ahmedzai, S. H. (2019). Cebranopadol, a novel first-in-class analgesic drug candidate: First experience with cancer-related pain for up to 26 weeks. Journal of Pain and Symptom Management, 58(3), 390–399. https://doi.org/10.1016/j.jpainsymman.2019.05.012

Kozono, H., Yoshimura, M., & Tsukamoto, K. (2018). Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride for the treatment of intractable pruritus in hemodialysis patients. Therapeutics and

Clinical Risk Management, 14, 1579–1587. https://doi.org/10.2147/TCRM.S171803

Krishnamurti, C., & Rao, S. C. (2016). The isolation of morphine by Serturner. Indian Journal of Anaesthesia, 60(11), 861–862. https://doi.org/10.4103/0019-5049.193696

Lee, J. D., Nunes, E. V., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C. C., King, J., Lindblad, R., Liu, D., Matthews, A. G., May, J., Peavy, K. M., Ross, S., Salazar, D., Schkolnik, P., … Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. The Lancet, 391(10118), 309–318. https://doi.org/10.1016/S0140-6736(17)32812-X

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. (2015). Nalmefene. National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Liu-Chen, L.-Y., & Huang, P. (2022). Signaling underlying kappa opioid receptor-mediated behaviors in rodents. Frontiers in Neuroscience, 16, 964724. https://doi.org/10.3389/fnins.2022.964724

Lorch, U., Pierscionek, T., Freier, A., Spencer, C. S., & Täubel, J. (2021). Safety, tolerability, and dose proportionality of a novel transdermal fentanyl matrix patch and bioequivalence with a matrix fentanyl patch: Two phase 1 single-center open-label, randomized crossover studies in healthy Japanese volunteers. Clinical Pharmacology in Drug Development, 10(3), 260–271. https://doi.org/10.1002/cpdd.846

Lu, J. J., Polgar, W. E., Mann, A., Dasgupta, P., Schulz, S., & Zaveri, N. T. (2021). Differential in vitro pharmacological profiles of structurally diverse nociceptin receptor agonists in activating G protein and beta-arrestin signaling at the human nociceptin opioid receptor. Molecular Pharmacology, 100(1), 7–18. https://doi.org/10.1124/molpharm.120.000076

Madariaga-Mazón, A., Marmolejo-Valencia, A. F., Li, Y., Toll, L., Houghten, R. A., & Martinez-Mayorga, K. (2017). Mu-opioid receptor biased ligands: A safer and painless discovery of analgesics? Drug Discovery Today, 22(11), 1719–1729. https://doi.org/10.1016/j.drudis.2017.07.002

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of

the μ-opioid receptor bound to a morphinan antagonist. Nature, 485(7398), 321–326. https://doi.org/10.1038/nature10954

Manglik, A., Lin, H., Aryal, D. K., McCorvy, J. D., Dengler, D., Corder, G., ... & Gmeiner, P. (2016). Structure-based discovery of opioid analgesics with reduced side effects. Nature, 537(7619), 185–190. https://doi.org/10.1038/nature19112

Mark, T. L., & Jones, C. M. (2022). Assessing naltrexone prescribing and barriers to initiation for opioid use disorder. Frontiers in Psychiatry, 13, 856938.

Mann, A., Illing, S., Miess, E., & Schulz, S. (2015). Different mechanisms of homologous and heterologous μ-opioid receptor phosphorylation. British Journal of Pharmacology, 172(2), 311–316. https://doi.org/10.1111/bph.12627

Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Mathiesen, J. M., Sunahara, R. K., Pardo, L., Weis, W. I., Kobilka, B. K., & Granier, S. (2012). Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature, 485(7398), 321-326. https://doi.org/10.1038/nature10954

Martinez, S., Harris, H., Chao, T., Luba, R., Pravetoni, M., Comer, S. D., & Jones, J. D. (2023). The potential role of opioid vaccines and monoclonal antibodies in the opioid overdose crisis. Expert Opinion on Investigational Drugs, 32(3), 181–185. https://doi.org/10.1080/13543784.2023.2187286

Mathur, V. S., Kumar, J., Crawford, P. W., Hait, H., Sciascia, T., & for the TR02 Study Investigators. (2017). A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. American Journal of Nephrology, 46(6), 450–458. https://doi.org/10.1159/000484573

Mark, T. L., & Jones, C. M. (2022). Assessing naltrexone prescribing and barriers to initiation for opioid use disorder. Frontiers in Psychiatry, 13, 856938.

Merivirta, R., Äärimaa, V., Aantaa, R., Koivisto, M., Leino, K., Liukas, A., & Kuusniemi, K. (2013). Postoperative fentanyl Patch versus subacromial bupivacaine infusion in arthroscopic shoulder surgery. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 29(7), 1129–1134. https://doi.org/10.1016/j.arthro.2013.04.018

Mitchell, S. G., Monico, L. B., Gryczynski, J., Fishman, M. J., O'Grady, K. E., & Schwartz, R. P. (2021). Extended-release naltrexone for youth with opioid use disorder. Journal of Substance Abuse Treatment, 130, 108407. https://doi.org/10.1016/j.jsat.2021.108407

Morales, P., Scharf, M. M., Bermudez, M., Egyed, A., Franco, R., Hansen, O. K., Jagerovic, N., Jakubík, J., Keserű, G. M., Kiss, D. J., Kozielewicz, P., Larsen, O., Majellaro, M., Mallo-Abreu, A., Navarro, G., Prieto-Díaz, R., Rosenkilde, M. M.,

Sotelo, E., Stark, H., … Wingler, L. M. (2025). Progress on the development of Class A GPCR-biased ligands. British Journal of Pharmacology, 182(14), 3249–3300. https://doi.org/10.1111/bph.17301

Mores, K. L., Cassell, R. J., & Van Rijn, R. M. (2019). Arrestin recruitment and signaling by G protein-coupled receptor heteromers. Neuropharmacology, 152, 15–21. https://doi.org/10.1016/j.neuropharm.2018.11.010

Moss, L., Hijma, H., Demitrack, M., Kim, J., Groeneveld, G. J., Van Velzen, M., Niesters, M., Olofsen, E., & Dahan, A. (2023). Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine. Anesthesiology, 139(6), 746–756. https://doi.org/10.1097/ALN.0000000000004758

Nanovic, L., Fishbane, S., Jamal, A., & Pergola, P. E. (2022). Safety and effectiveness of difelikefalin in patients with moderate-to-severe chronic kidney disease-associated pruritus. Kidney International Reports, 7(8), 2040–2051.

Ni, Y., Huang, R., Yang, S., Yang, X. Y., Zeng, S., Yao, A., Huang, J., & Yang, G. (2024). Pharmacokinetics and safety of oliceridine fumarate injection in Chinese patients with chronic non-cancer pain: A phase I, single-ascending-dose, open-label clinical trial. Drug Design, Development and Therapy, 18, 2729–2743. https://doi.org/10.2147/DDDT.S461416

Nihadha, P. M., Chugh, A., Kaur, A., Kumar, S., Naveen, K. H., Bhatia, P. K., Kumar, P., & Chaudhry, K. (2022). Transdermal fentanyl patch versus standard analgesia in postoperative oral submucous fibrosis patients: A triple blinded, randomised control trial. British Journal of Oral and Maxillofacial Surgery, 60(9), 1246–1253. https://doi.org/10.1016/j.bjoms.2022.07.002

Nunes, E. V., Bisaga, A., Krupitsky, E., Nangia, N., Silverman, B. L., Akerman, S. C., & Sullivan, M. A. (2020). Opioid use and dropout from extended-release naltrexone in a controlled trial: Implications for mechanism. Addiction, 115(2), 239–246. https://doi.org/10.1111/add.14735

Pellissier, L. P., Gandía, J., Laboute, T., Becker, J. A. J., & Le Merrer, J. (2018). μ opioid receptor, social behaviour and autism spectrum disorder: Reward matters. British Journal of Pharmacology, 175(14), 2750–2769. https://doi.org/10.1111/bph.13808

Post, A., Smart, T. S., Krikke-Workel, J., Dawson, G. R., Harmer, C. J., Browning, M., Jackson, K., Kakar, R., Mohs, R., Statnick, M., Wafford, K., McCarthy, A., Barth, V., & Witkin, J. M. (2016). A selective nociceptin receptor antagonist to treat depression: Evidence from preclinical and clinical studies.

Neuropsychopharmacology, 41(7), 1803–1812. https://doi.org/10.1038/npp.2015.348

Pradhan, A. A., Maguire, D. R., McLaughlin, J. P., & Cahill, C. M. (2021). SR-17018 stimulates atypical μ-opioid receptor phosphorylation and signaling. Frontiers in Pharmacology, 12, 721993. https://doi.org/10.3389/fphar.2021.721993

Raffaeli, W., Samolsky Dekel, B. G., Landuzzi, D., Caminiti, A., Righetti, D., Balestri, M., Montanari, F., Romualdi, P., & Candeletti, S. (2006). Nociceptin levels in the cerebrospinal fluid of chronic pain patients with or without intrathecal administration of morphine. Journal of Pain and Symptom Management, 32(4), 372–377. https://doi.org/10.1016/j.jpainsymman.2006.05.013

Reilly, R. F. (2016). Medical and surgical care during the American Civil War, 1861-1865. Proceedings (Baylor University. Medical Center), 29(2), 138–142. https://doi.org/10.1080/08998280.2016.11929390

Rosenman, E., Buck, R. K., Anjum, N., Thompson, L., Rist, J., Banuna, L., Dolgoff, E., Hartmann, S., Lelei, S., Feng, Z., & Holmes, L. M. (2025). From dealer to doctor: A case study examining how Purdue Pharma sought to leverage racial health disparities to attenuate flagging OxyContin sales. Social Science & Medicine, 382, 118132. https://doi.org/10.1016/j.socscimed.2025.118132

Rudolph, K. E., Díaz, I., Luo, S. X., Rotrosen, J., & Nunes, E. V. (2021). Optimizing opioid use disorder treatment with naltrexone or buprenorphine. Drug and Alcohol Dependence, 228, 109031. https://doi.org/10.1016/j.drugalcdep.2021.109031

Saigusa, T., Aono, Y., & Waddington, J. L. (2017). Mechanisms underlying δ- and μ-opioid receptor agonist-induced increases in extracellular dopamine level in the nucleus accumbens of freely moving rats. Journal of Oral Science, 59(2), 195–200. https://doi.org/10.2334/josnusd.16-0874

Schroeder, B., Lemieux, M., Scherbaum, N., et al. (2021). Assessment of the potential of novel and classical opioids to induce opioid use disorder-like behavior: Cebranopadol and beyond. British Journal of Pharmacology, 178(13), 2632–2648. https://doi.org/10.1111/bph.16199

Singla, N. K., Skobieranda, F., Soergel, D. G., Salamea, M., Burt, D. A., Demitrack, M. A., & Viscusi, E. R. (2019). APOLLO-2: A randomized, placebo and active-controlled phase III study investigating oliceridine (TRV 130), a G protein–biased ligand at the μ-opioid receptor, for management of moderate to

severe acute pain following abdominoplasty. Pain Practice, 19(7), 715–731. https://doi.org/10.1111/papr.12801

Smith, J., et al. (2025). New study examines nalmefene auto-injector and intranasal naloxone for reversal of respiratory depression induced by fentanyl. Purdue Pharma News.

Smith, L. C., Bremer, P. T., Hwang, C. S., Zhou, B., Ellis, B., Hixon, M. S., & Janda, K. D. (2019). Monoclonal antibodies for combating synthetic opioid intoxication. Journal of the American Chemical Society, 141(26), 10489–10503. https://doi.org/10.1021/jacs.9b04872

Stahl, E. L., Schmid, C. L., Acevedo-Canabal, A., Read, C., Grim, T. W., Kennedy, N. M., Bannister, T. D., & Bohn, L. M. (2021). G protein signaling–biased mu opioid receptor agonists that produce sustained G protein activation are noncompetitive agonists. Proceedings of the National Academy of Sciences, 118(48), e2102178118. https://doi.org/10.1073/pnas.2102178118

Stevens, R. C., Cherezov, V., Katritch, V., Abagyan, R., Kuhn, P., Rosen, H., & Wüthrich, K. (2013). The GPCR network: A large-scale collaboration to determine human GPCR structure and function. Nature Reviews Drug Discovery, 12(1), 25–34. https://doi.org/10.1038/nrd3859

Sutcliffe, K. J., Corey, R. A., Alhosan, N., Cavallo, D., Groom, S., Santiago, M., Bailey, C., Charlton, S. J., Sessions, R. B., Henderson, G., & Kelly, E. (2022). Interaction with the lipid membrane influences fentanyl pharmacology. Advances in Drug and Alcohol Research, 2, 10280. https://doi.org/10.3389/adar.2022.10280

Szumiec, L., Bugno, R., Szumiec, L., & Przewlocki, R. (2023). The differential influence of PZM21, a nonrewarding μ-opioid receptor agonist with G protein bias, on behavioural despair and fear response in mice. Behavioural Brain Research, 449, 114466. https://doi.org/10.1016/j.bbr.2023.114466

Tan, Z., et al. (2008). Management of postoperative ileus: Focus on alvimopan. Journal of Pain & Symptom Management, 35(5), 500-501.

Van Zee, A. (2009). The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. American Journal of Public Health, 99(2), 221–227. https://doi.org/10.2105/AJPH.2007.131714

Varga, B. R., Streicher, J. M., & Majumdar, S. (2023). Strategies towards safer opioid analgesics—A review of old and upcoming targets. British Journal of Pharmacology, 180(7), 975–993. https://doi.org/10.1111/bph.15760

Verbeek, J., & Brinkman, D. J. (2025). A comprehensive narrative review of protonitazene: Pharmacological characteristics, detection techniques, and toxicology. Basic & Clinical Pharmacology & Toxicology, 137(2), e70078. https://doi.org/10.1111/bcpt.70078

Viscusi, E. R., & Singla, N. K. (2019). Alvimopan for post-radical cystectomy ileus: What should we know? Therapeutic Advances in Urology, 11, 1756287218822806.

Wang, Y., et al. (2023). Structures of the entire human opioid receptor family. Cell, 186(2), 413-427.e17. https://doi.org/10.1016/j.cell.2022.12.026

Webster, L. R., Brenner, D., Israel, R. J., Stambler, N., & Slatkin, N. E. (2023). Reductions in all-cause mortality associated with the use of methylnaltrexone for opioid-induced bowel disorders: A pooled analysis. Pain Medicine, 24(3), 341-350. https://doi.org/10.1093/pm/pnx148

Wikstrom, B. D., Gellert, R., Ladefoged, S. D., Danda, Y., Akai, M., Ide, K., Ogasawara, M., Kawashima, Y., Ueno, K., Mori, A., & Ueno, Y. (2005). κ-Opioid system in uremic pruritus: Multicenter, randomized, double-blind, placebo-controlled clinical studies. Journal of the American Society of Nephrology, 16(12), 3742–3747. https://doi.org/10.1681/ASN.2005020152

Wolf, A., Unterberg, M., Witowski, A., Adamzik, M., & Wolf, A. (2024). Efficacy, safety, and side effects of oliceridine in acute postoperative pain: A protocol for a systematic review and meta-analysis. PLOS ONE, 19(2), e0299320. https://doi.org/10.1371/journal.pone.0299320

Yamaguchi, S., Uchida, E., Terahara, T., Okawa, K., Hashimoto, F., & Tanaka, Y. (2020). Efficacy and safety of fentanyl citrate patch, including a low-dose 0.5 mg formulation, in opioid-naïve patients with cancer pain. Clinical Drug Investigation, 40(11), 1041–1052. https://doi.org/10.1007/s40261-020-00965-9

Zádor, F., Zelena, D., Szegeczki, V., et al. (2019). MP1104, a mixed kappa-delta opioid receptor agonist has anti-hyperalgesic actions without abuse liability in rodents. European Journal of Pharmacology, 857, 172459. https://doi.org/10.1016/j.ejphar.2019.172459

Zhou, X., Wang, W., Fang, B., & Yu, T. (2023). A new formulation of dezocine, Cyc-dezocine, reduces oxycodone consumption in postoperative pain management. Neuroscience Letters, 813, 137486. https://doi.org/10.1016/j.neulet.2023.137486

Zhuang, Y., Wang, Y., He, B., He, X., Zhou, X. E., Guo, S., Rao, Q., Yang, J., Liu, J., Zhou, Q., Wang, X., Liu, M., Liu, W., Jiang, X., Yang, D., Jiang, H., Shen, J., Melcher, K., Chen, H., … Xu, H. E. (2022). Molecular recognition of morphine and fentanyl by the human μ-opioid receptor. Cell, 185(23), 4361-4375.e19. **https://doi.org/10.1016/j.cell.2022.09.041**

The revised manuscript has substantially improved and expanded, with stronger supporting citations and more compelling claims. However, several minor issues regarding formatting and references still need to be addressed before the manuscript can be accepted for publication.

- In the Abstract, the author wrote "Mu Opioid-Receptor, Delta Opioid-Receptor, Kappa Opioid-Receptor, and Nociceptin/Orphanin Receptor". Please change them to the preferred scientific formats: μ-opioid receptors, δ-opioid receptor, κ-opioid receptor. These names are not proper nouns and do not need to be capitalized. For the Nociceptin/Orphanin receptor (NOP), please use either Nociceptin/Orphanin FQ receptor (NOP) or Nociceptin receptor (NOP).
  - I have added them in their greek letter formats and standardized the NOP notation to Nociceptin/Orphanin FQ receptor.
- Line 36: change to Chinese traditional medicine.
  - Revised
- Table 1, pg 3: Please address the similar writing style per #1.
  - I have added them in their greek letter formats and standardized the NOP notation to Nociceptin/Orphanin FQ receptor.
- Avoid using contractions in writing a scientific manuscript. For example, L 212: "It's". Change to "It is".

➢ Revised for correct scientific grammar.

❖ The author needs to double-check that all abbreviations are used consistently throughout the manuscript. For example, in L 241, the author still uses "DOR".

➢ Entire paper proofread for this error and fixed

❖ L 264: Change to "one-paragraph". Keep in mind, in scientific writing, any number below ten should be spelled out, unless it is followed by a unit of measurement (*e.g.:* ten people, 10 mg). Please review "Spelling out numbers in technical, scientific, and complex writing" section https://www.grammarly.com/blog/writing-tips/when-to-spell-out-numbers/ and apply the format to your manuscript.

➢ Revised for APA formatting with regard to numerals

❖ Several abbreviations have not been spelled out first. For example, L 268 "FDA".

➢ Full notation written out in Table 1 and referenced later in text

❖ Unlike figure captions, table captions are placed on top of the table, not at the bottom. Please fix all the table captions. Only the notes are placed underneath the table, which the author has already done correctly.

➢ Table captions revised

- Tables should appear and be referenced in numerical order. Currently, Table 2 is placed after Table 3, which also does not exist, and Table 1 appears last. Please ensure Table 1 appears first and is cited first in the text, followed by Tables 2, 3, and so forth. The manuscript contains two Table 1s and two Table 2s. Please renumber the tables appropriately and revise all in-text references. Additionally, Tables 3 and 4 are referenced but not included in the manuscript. Please add or correct these.
  - Revised error in manuscript, the last 2 tables were supposed to be labeled Table 3 & Table 4. They are already referenced as such throughout the manuscript. Revision made.

The revised manuscript represents a clear effort to strengthen the scientific foundation and expand the scope of the original review. The current version is more cohesive, better supported by citations, and more balanced in how it presents the promise and limitations of new opioid pharmacology. The improvements in structure and detail are evident throughout, particularly in the sections discussing biased and bitopic agonism, the differentiation between clinical and therapeutic use, and the expanded tables comparing traditional and next-generation opioid compounds. Despite these gains, several areas still require attention to bring the manuscript into line with publication standards.

- One area that needs further refinement is the consistent use of terminology. Receptor names should follow standard scientific formatting throughout the manuscript. This includes the abstract, all section headings, figure captions, and tables. There are still places where the older, capitalized forms appear. Ensuring consistency here matters because the manuscript focuses heavily on receptor-level pharmacology, so precise scientific notation is essential.
    - The receptor names have been standardized to Greek letters throughout the manuscript. The only remaining place I had included them was the abstract (For ease of pronunciation). However, I have now changed those as well to the accepted format.

- ❖ Formatting issues in the tables also require a thorough review. Several tables are mislabeled or appear out of order, and two table numbers are duplicated. Additionally, some tables that are cited in the text are either missing or appear in a different sequence than referenced. Table captions should be placed above their corresponding tables, not below, and all tables should appear in numerical order. Correcting these will make the manuscript significantly more readable and more professional.
    - ➢ Revised error in manuscript, the last 2 tables were supposed to be labeled Table 3 & Table 4. They are already referenced as such throughout the manuscript. Revision made. Additionally, the table captions were moved to above their corresponding tables.
- ❖ The manuscript would also benefit from a careful pass addressing abbreviations. A number of abbreviations, such as FDA, BBB, ER, and PAMORA, appear without being spelled out at first use. Because the paper covers multiple receptor families, drug classes, and signaling pathways, any undefined abbreviation can disrupt comprehension. Adding a brief list of abbreviations at the beginning could help orient readers.
    - ➢ BBB (Blood-Brain Barrier), ER (Emergency room), and PAMORA (Peripherally acting μ-opioid receptor antagonist) are all already

spelled out before the abbreviation is used. FDA (US Food and Drug Administration) is now included at the abbreviation table (Table 1).

- ❖ There are also some lingering stylistic issues. Contractions should be removed entirely. Sentence structure can be simplified in several locations where ideas are stacked too closely together. A few paragraphs also rely on very long sentences that would read more clearly if divided. Spelling out numbers below ten, unless followed by a unit of measurement, will help bring the writing into line with standard scientific format.
    - ➢ Contractions were removed entirely. Revised the document for sentence structure and lengthy sentences. However, no numbers below 10 were written using arabic numerals unless followed by a unit of measurement (i.e. 2 hours).

Overall, the manuscript is close to publication quality. With careful correction of formatting, abbreviation consistency, and sentence-level clarity, the scientific strength of the content will stand out more clearly. These refinements will help ensure the final version meets the expectations of peer reviewers and the scientific community.

Final Approval Feedback

The revised manuscript demonstrates a strong and thorough response to all prior reviewer comments and is now suitable for publication. The author has successfully addressed issues related to terminology, formatting, and clarity, resulting in a polished and well organized review. Receptor nomenclature is now consistent throughout the manuscript, abbreviations are clearly defined at first use, and the overall tone is appropriate for a scientific review. The addition of supporting citations and clearer explanations of signaling bias and dual receptor strategies has strengthened both the credibility and readability of the paper.

The structure of the manuscript is clear and logical. The Introduction provides appropriate historical and scientific context, and the Methodology is sufficiently transparent about the scope and limitations of the review. The Discussion sections demonstrate a solid understanding of opioid receptor pharmacology and translational challenges, and the author avoids overstating claims while still highlighting meaningful advances in the field. Figures and tables are properly labeled, appear in the correct order, and are well integrated into the text. The comparative tables in particular add value by clearly summarizing development stage, mechanism, and clinical relevance.

The Conclusion effectively synthesizes the major themes of the manuscript and reflects a balanced perspective on the current state of opioid drug development. The acknowledgment that no single therapeutic approach has yet surpassed existing standards is appropriately framed and supported by the analysis presented. Overall, the manuscript meets the standards expected for publication, and no further substantive revisions are required.

While the manuscript is approved in its current form, there are a few optional refinements the author may consider if time permits. A final consistency sweep for capitalization, pluralization, and abbreviation usage could help prevent minor copyediting corrections during production. The author may also wish to review figure and table citations to ensure page references remain accurate after final layout formatting. In a few places, longer sentences in the Discussion could be shortened slightly to improve readability, particularly where multiple mechanisms are introduced in a single sentence. The Conclusion could optionally include one sentence explicitly stating how this review differs from prior work in the field, which may help reinforce its contribution. Finally, a brief check of reference formatting and keywords for discoverability may further improve presentation.

These points are suggestions only and do not affect the acceptance of the manuscript. The paper is approved for publication.