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# MECHANISMS, EFFICACY, AND SAFETY OF SUZETRIGINE COMPARED WITH OTHER ANALGESICS IN ACUTE PAIN MANAGEMENT

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## ABSTRACT

This review aims to compare the mechanisms of action, efficacy, and safety profiles of suzetrigine with established analgesic classes, including Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, in the management of acute pain. The objective is to assess whether suzetrigine offers clinical advantages over traditional therapies and to define its potential role in modern multimodal pain strategies.

## KEYWORDS

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Opioid Analgesics, Suzetrigine, Acute Pain, Sodium Channel Inhibitors

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## 1. Introduction

Acute pain functions as a brief and intense pain sensation which develops immediately after tissue damage or surgical procedures or inflammatory conditions or medical illnesses. The body uses acute pain as a protective response to detect tissue damage and the pain disappears when the healing process finishes. (Loeser and Treede, 1999; Kent et al., 2017; Tighe et al., 2015).

Acute pain presents a major healthcare challenge because it affects numerous patients throughout the world despite being a short-term condition. The failure to properly treat pain during hospitalization results in longer hospital stays and delayed recovery times and raises the chances of developing chronic pain. (Rao and Knaus, 2008; Ozleyen et al., 2023).

Medical care depends on various analgesic drug classes which were developed to treat different pain types and severities. The World Health Organization (WHO) Pain Treatment Ladder from 1986 serves as a clinical guideline for selecting pain medications according to pain intensity which starts with non-opioid drugs before advancing to opioid-based treatments. The current pharmacological landscape faces challenges because pain medications show inadequate results in various patient groups while producing unwanted side effects and opioid dependence risks. (Ozleyen et al., 2023; Bindu et al., 2020).

The development of non-opioid analgesics has become essential because these medications deliver pain relief without opioid and NSAID-related adverse effects. The non-opioid analgesic Suzetrigine (VX-548) operates as a potent NaV1.8 voltage-gated sodium channel blocker. The NaV1.8 voltage-gated sodium channel functions as a key element in peripheral pain signal transmission so blocking this channel represents a specific pain relief approach. The peripheral action of suzetrigine distinguishes it from conventional analgesics because it decreases the chance of opioid-related side effects and central nervous system depression. (Osteen et al., 2025).

The initial phase 3 clinical trials showed suzetrigine worked well for post-surgical acute pain but it failed to deliver satisfactory results in chronic neuropathic pain cases such as sciatica according to McCoun et al. (2025).

## 2. Review Methods

The research examined how suzetrigine compares to NSAIDs and opioid analgesics through a review of their mechanisms, effectiveness and safety characteristics. The research team conducted database searches through PubMed and Scopus and Web of Science databases for studies from January 2000 to August 2025. The research included studies that used the following search terms: “suzetrigine” OR “VX-548” OR “NaV1.8 inhibitor” AND “acute pain” OR “postoperative pain” OR “analgesics” and “NSAIDs” and “opioids” and their associated terminology.

The research included studies that met these criteria: peer-reviewed English articles and randomized controlled trials and meta-analyses and systematic reviews and pharmacological studies and regulatory documents.

The review excluded studies that were case reports or conference abstracts without full publication except when pivotal trial data were missing and non-English papers and animal-only studies and narrative reviews without original data.

The review did not include a risk-of-bias assessment and it lacked preregistration status.

### 3. Results and Discussion

#### NSAIDs Analysis of Mechanisms of Action

Nonsteroidal anti-inflammatory drugs (NSAIDs) serve as common medications because they provide pain relief and reduce inflammation and fever. Their primary mechanism of action involves. The COX enzymes become blocked by NSAIDs which results in decreased prostaglandin production. The reduction of prostaglandins through this process helps to decrease both inflammation and pain and fever. COX-1 enzyme blockage by NSAIDs disrupts protective systems in the gastrointestinal tract and kidneys which results in possible adverse effects. (Ghlichloo and Gerriets, 2025). NSAIDs reduce inflammation through their impact on leukocyte function which leads to decreased production of pro-inflammatory cytokines and reactive oxygen species. The anti-inflammatory action of NSAIDs emerges from their capacity to suppress leukocyte function which results in lower pro-inflammatory cytokine and reactive oxygen species production. (Díaz-González and Sánchez-Madrid, 2015). The analgesic properties of. The pain perception of patients changes because of NSAID-induced ion channel modulation which produces analgesic effects. (Ghlichloo and Gerriets, 2025; Díaz-González and Sánchez-Madrid, 2015).

#### Main Representative of NSAIDs

Non-Selective COX Inhibitors: These drugs block the activity of both COX-1 and COX-2 enzymes. The medication Ibuprofen serves as a common treatment for treating light to moderate pain and inflammation and fever symptoms. Available over-the-counter. Naproxen functions as an effective treatment for arthritis pain and menstrual cramp relief. The drug stays active in the body for a longer period than ibuprofen does. COX-2 inhibitors work as targeted COX-2 blockers to reduce inflammation while they protect the stomach from adverse effects. Celecoxib serves as a medication that treats osteoarthritis and rheumatoid arthritis and provides relief for acute pain. The medication shows better safety for the stomach compared to non-selective NSAIDs. (McCoun et al., 2025; Ghlichloo and Gerriets, 2025).

#### NSAIDs Efficacy

Medical professionals select ibuprofen and naproxen as their preferred drugs to treat acute musculoskeletal pain and osteoarthritis flare-ups and back pain. Research studies together with clinical trials demonstrate NSAIDs outperform placebos in treating back pain and osteoarthritis because they deliver quick pain relief and functional enhancement (Pelletier et al., 2016).

A research study with double-blind design and single-dose administration demonstrated that naproxen sodium (440 mg) delivered extended pain relief compared to ibuprofen (400 mg) and placebo in patients with moderate-to-severe acute postoperative dental pain. The participants who received naproxen needed less pain medication and showed better pain management throughout the complete 24-hour study duration (Cooper et al., 2019).

The administration of intravenous ibuprofen before surgery helps patients need less opioid medication for postoperative pain management. The administration of IV ibuprofen at 800 mg to cervical cancer surgery patients resulted in a substantial decrease of their morphine consumption during the first 24 hours after surgery according to a randomized placebo-controlled study. IV NSAIDs including ibuprofen and ketorolac and naproxen reduce postoperative opioid use by 20–60% when used in combination with other pain management strategies according to a narrative review by Liu et al. (2018).

NSAIDs such as ibuprofen and naproxen show superior pain relief performance than placebo when treating migraine and tension-type headache patients. The meta-analysis of naproxen in migraine treatment showed that patients achieved headache relief within two hours at a risk ratio of 1.58 and reached pain-free status at two hours with a risk ratio of 2.22 compared to placebo (Nalamachu, 2013).

### **NSAIDs Side Effects and Safety Profile**

The gastrointestinal system of patients experiences severe damage from NSAIDs because these medications cause mucosal injuries throughout the entire GI tract which leads to dyspepsia and peptic ulcers and bleeding and perforation. The protective gastric lining function of mucosal prostaglandins decreases because of COX-1 inhibition which leads to these adverse effects. The combination of PPIs with non-selective NSAIDs and COX-2 selective inhibitors decreases GI complications in patients who have elevated GI risk (Borer and Simon, 2005).

The use of NSAIDs leads to an increased chance of developing cardiovascular complications. The use of COX-2 selective inhibitors leads to blood clot formation but non-selective NSAIDs including diclofenac and meloxicam increase cardiovascular risks. The cardiovascular safety profile of naproxen stands as the best among all typical NSAIDs used for treatment. The varying cardiovascular risks between NSAIDs require healthcare providers to select medications based on patient-specific cardiovascular conditions (Borer and Simon, 2005).

The long-term use of NSAIDs at high doses leads to fluid accumulation in the body which causes blood pressure elevation and worsens congestive heart failure (CHF) symptoms. The use of NSAIDs except for low-dose aspirin creates a double risk of heart failure development in patients who do not have existing heart conditions (Borer and Simon, 2005). The use of NSAIDs by patients with existing congestive heart failure (CHF) leads to higher hospitalization rates according to different drug-specific odds ratios that reach 2.1 for diclofenac (Aw et al., 2005).

The inhibition of renal prostaglandin synthesis by NSAIDs leads to nephrotoxic effects because these prostaglandins help maintain proper kidney blood flow during reduced blood pressure. The combination of dehydration and heart failure and chronic kidney disease and renin–angiotensin system inhibitors and diuretics with NSAID use increases the risk of acute kidney injury in patients. The use of NSAIDs results in acute interstitial nephritis and nephrotic syndrome and sometimes leads to chronic kidney disease development. The combination of hemodynamic changes with NSAIDs cause patients to develop acute interstitial nephritis and nephrotic syndrome and sometimes lead to chronic kidney disease. The combination of sodium and fluid retention with hypertension and electrolyte disturbances including hyperkalemia occurs commonly in patients taking these medications. The elderly population along with patients who have multiple health conditions face increased danger of renal damage when taking NSAIDs so doctors need to choose patients carefully and monitor their health status (Kim et al., 2025; Dixit et al., 2010). The FDA issued black box warnings for all NSAIDs because they present risks to the gastrointestinal system and cardiovascular system and kidneys when patients use them for extended periods (Borer and Simon, 2005).

### **Opioids Analysis: Mechanism of Action**

The medical field uses opioids as analgesics to treat various levels of acute pain. The drugs achieve their pain-relieving effects through their binding to particular nervous system receptors. The medical application of opioids brings along both beneficial effects and possible adverse reactions, according to Stein (2018). The primary mechanism through which opioids work involves their activation of opioid receptors which function as G-protein-coupled receptors spread across the central and peripheral nervous system and peripheral nervous system. The activation of these receptors controls how the body perceives pain and responds to it. The second primary mechanism through which opioids work involves blocking the release of neurotransmitters: When opioids connect to opioid receptors, they block adenylyl cyclase enzymes, which results in decreased cyclic adenosine monophosphate production. The decreased neurotransmitter release of glutamate and substance P occurs because of this reduction in cyclic adenosine monophosphate levels (Bovill 1997).

### **Main Opioids Present Key Characteristics**

Morphine functions as the primary opioid medication for treating intense pain conditions. The synthetic opioid Fentanyl shows strong potency levels, which doctors use for anesthesia procedures and chronic pain management. The medical community uses Oxycodone to treat patients who experience moderate to severe pain levels. Buprenorphine functions as a partial agonist at  $\mu$ -opioid receptors while treating pain and opioid dependence in patients.

### **Opioids Efficacy**

The medical community uses opioids to treat different pain types effectively, including postoperative pain and cancer-related pain, and injury-induced pain. The fast and powerful pain relief provided by opioids makes them essential for medical practice. The therapeutic benefits of opioids need to be weighed against their possible adverse effects, which become more significant when patients use them for extended periods (Stein 2020).

### **Opioids Side Effects and Safety Profile**

The analgesic properties of opioids come with multiple adverse effects, which patients experience when using these medications. The most frequent adverse effects from opioid use include nausea and vomiting alongside constipation and itching, dizziness, dry mouth, and sedation, according to Kalso et al. (2004). The severe adverse effects of opioids include respiratory depression and tolerance and dependence, and opioid-induced hyperalgesia, which causes patients to experience increased pain sensitivity after long-term use. The combination of these adverse effects has led to a major public health emergency, according to Kalso et al. (2004) and Moore and McQuay (2005).

### **Suzetrigine: Analysis of Mechanism of Action, Efficacy, and Safety Profile.**

Suzetrigine represents a new analgesic medication that scientists are testing for treating both short-term and long-term pain conditions. The pain management drug suzetrigine functions differently from standard pain medications because it blocks voltage-gated sodium channels, which transmit pain signals. The drug provides an alternative treatment option for patients who fail to respond to standard pain medications and those who face risks from opioid addiction and NSAID side effects (Osteen et al., 2025; Hu et al., 2025).

### **Suzetrigine: Mechanism of Action**

The analgesic properties of suzetrigine (VX-548) stem from its specific blocking action on Na<sub>v</sub>1.8 voltage-gated sodium channels, which primarily exist in peripheral nociceptive dorsal root ganglion (DRG) neurons to initiate and transmit noxious stimulus-evoked action potentials (Osteen et al., 2025; Hu et al., 2025; Jones et al., 2023). The drug blocks sodium entry through Na<sub>v</sub>1.8 channels, which stops the fundamental electrical process that causes nociceptor hyperexcitability and blocks pain signal transmission.

Suzetrigine binds to the second voltage-sensing domain (VSD2) of Na<sub>v</sub>1.8 channels through its interaction with the extracellular S3–S4 loop according to Osteen et al. (2025). The drug creates a stable closed state of the channel through allosteric binding, which stops the S4 segment from moving outward to trigger depolarization-induced gating charge displacement and pore opening. The drug action of suzetrigine leads to a rightward shift in activation voltage dependence, which makes channel opening impossible during normal nociceptive stimuli (Catterall, 2012; Jones et al., 2023).

The drug stabilizes sodium channels in DRG neurons, which results in continuous blocking of sodium currents and decreased excitability of pain-transmitting pathways (Stewart et al., 2025). The mechanism of suzetrigine differs from traditional pore blockers because it modulates channel gating without blocking the channel completely, which protects normal physiological signals in non-nociceptive neurons. The drug shows exceptional selectivity for Na<sub>v</sub>1.8 channels with a ratio exceeding 31,000, which protects cardiac and central nervous system sodium channels from unwanted effects (Osteen et al., 2025; Stewart et al., 2025).

Studies using electrophysiology have shown that suzetrigine demonstrates reverse use-dependent behavior because the drug temporarily releases from channels during high-frequency depolarizations but quickly rebinds when membrane potentials return to rest (Jones et al., 2023; Stewart et al., 2025). The drug maintains continuous suppression of Na<sub>v</sub>1.8 channel activity through its dynamic mechanism. The drug enables adaptive changes in response to different neuronal activity patterns, which helps achieve optimal results while preserving safety benefits (Catterall, 2012; Stewart et al., 2025; Peshin et al., 2025).

### **Pharmacokinetics of Suzetrigine**

The oral half-life of suzetrigine amounts to 23.6 hours while its main active metabolite M6-SUZ maintains a half-life of 33.0 hours. The pharmacokinetic characteristics of suzetrigine support a twice-daily dosing schedule to maintain continuous drug levels in the body (Osteen et al., 2025; U.S. Food and Drug Administration, 2025).

The peak concentration of suzetrigine occurs at 3 hours after oral intake, but M6-SUZ reaches its peak at 10 hours following drug administration. The drug shows a large apparent volume of distribution at 495 L and high protein binding at 99% while its metabolite shows similar protein binding at 96% (U.S. Food and

Drug Administration, 2025; Jones et al., 2025). Suzetrigine undergoes CYP3A enzyme metabolism to produce M6-SUZ, which shows 3.7 times lower potency than the parent compound in blocking NaV1.8 channels. The drug is eliminated through both fecal ( $\approx 50\%$ ) and urinary ( $\approx 44\%$ ) pathways, with the parent compound making up most of the fecal elimination ( $\approx 9.1\%$ ) (U.S. Food and Drug Administration, 2025; Jones et al., 2025).

### Suzetrigine's Side Effects

The dizziness, nausea, headache, and brief paraesthesia. The medication does not cause opioid-like respiratory depression. Clinical trials demonstrate that Suzetrigine has good tolerance because the most common adverse reactions consist of light, and it lacks gastrointestinal and cardiovascular side effects, which are typical of NSAIDs. (U.S. Food and Drug Administration, 2025; McCoun et al., 2025; Peshin et al., 2025).

### Efficacy, Safety, and Non-Addictive Profile

Suzetrigine stands as the first medication from a new class of non-opioid analgesics that targets peripheral sodium channels. The U.S. Food and Drug Administration approved suzetrigine through breakthrough therapy, fast-track, and priority review programs, which resulted in its January 2025 approval for treating moderate to severe acute pain. The available evidence supporting suzetrigine's effectiveness stems mainly from postoperative pain studies involving bunionectomy and abdominoplasty patients, although these results might not translate to other acute pain scenarios (Jones et al., 2023; McCoun et al., 2025). The drug shows no better results than a placebo when treating chronic neuropathic pain, specifically in lumbosacral radiculopathy (sciatica). The phase 2 randomized controlled trial showed no difference in pain intensity scores between treatment and control groups which indicates suzetrigine works best for short-term postoperative pain management instead of chronic neuropathic pain (U.S. Food and Drug Administration, 2025).

**Table 1.** Comparison of suzetrigine, NSAIDs, and opioids.

Summary of pharmacological mechanisms, clinical efficacy, benefits, side effects, and safety profiles of the three main classes of analgesics in acute pain management

Feature	Suzetrigine	NSAIDs (e.g., Ibuprofen, Aspirin)	Opioids (e.g., Morphine, Oxycodone)
Mechanism of Action	Selective inhibitor of NaV1.8 sodium channels, blocking pain signals in peripheral neurons without affecting the central nervous system (CNS)	Inhibits COX-1 and COX-2 enzymes, reducing prostaglandin synthesis, which mediates pain and inflammation	Binds to opioid receptors in the CNS, modulating pain perception and increasing endorphin release
Type of Pain Treated	Acute pain (e.g., postoperative pain), potentially neuropathic pain	Inflammatory pain (e.g., arthritis, musculoskeletal pain)	Moderate to severe pain, including post-surgical, chronic, and cancer-related pain
Efficacy	Effective in acute pain management, but mixed results in chronic pain conditions like sciatica	Highly effective for mild to moderate inflammatory pain, but less so for neuropathic pain	Very effective for severe pain, but long-term use is limited by tolerance and dependence
Key Benefits	Non-opioid, non-addictive, minimal CNS side effects	Anti-inflammatory properties, widely available, no addiction risk	Powerful analgesic effects, essential for severe pain cases (e.g., cancer pain)
Side Effects	Well-tolerated, no sedation, no addiction risk	GI bleeding, renal toxicity, increased cardiovascular risk	Sedation, respiratory depression, nausea, constipation, high risk of dependence and addiction
Safety Profile	Favorable, no risk of respiratory depression or addiction	Generally safe for short-term use but associated with GI and cardiovascular risks	High risk of dependence, overdose, and other serious side effects

#### 4. Conclusions

Suzetrigine brings a new treatment option for acute pain management, specifically for patients with moderate to severe postoperative pain. The drug works by blocking NaV1.8 sodium channels in peripheral neurons to provide pain relief without opioid-related side effects, including sedation, respiratory depression, and addiction potential. The drug operates independently of COX pathways, which prevents it from causing gastrointestinal and cardiovascular adverse effects like NSAIDs do. The drug shows strong pain relief in bunionectomy and abdominoplasty studies, but its effectiveness for chronic pain management, including neuropathic pain, remains unclear because it failed to outperform placebo in clinical trials. The available research indicates that suzetrigine could become a useful tool for treating acute surgical pain through multimodal pain management approaches. Additional extensive research involving large patient groups, extended observation periods, and head-to-head comparisons will establish the exact position of suzetrigine in modern pain treatment protocols.

#### Disclosure

##### Author's Contributions Statement:

Conceptualization: J.Ž., M.Z., W.S., Methodology: J.Ž., W.S., M.Z., Software: J.Ž., M.B., W.C., L.C., Check: J.Ž., Z.C., A.C., K.K., Formal analysis: J.Ž., L.C., K.G., A.R., Investigation: J.Ž., A.C., W.C., K.W., Resources: J.Ž., K.K., A.R., B.R., Data curation: J.Ž., K.W., M.B., K.K., Writing – rough preparation: J.Ž., A.R., Z.C., B.R., Writing – review and editing: J.Ž., K.G., M.B., W.C., Visualization: J.Ž., K.W., Z.C., A.C., Supervision: J.Ž., K.G., L.C., W.S., Project administration: J.Ž., B.R.

All authors have read and agreed with the published version of the manuscript.

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