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SUZETRIGINE AND THE FUTURE OF ANALGESIA: A NEW NON-OPIOID APPROACH TO PAIN MANAGEMENT

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ABSTRACT

Introduction: Pain remains one of the most prevalent health problems worldwide and a major cause of disability, reduced quality of life and healthcare utilization. Although opioid analgesics have long been considered the cornerstone of treatment for moderate-to-severe pain, their use is associated with substantial risks, including tolerance, dependence, addiction and overdose. Consequently, the development of effective non-opioid analgesics has become a priority in pain medicine. Suzetrigine (VX-548), a selective voltage-gated sodium channel NaV1.8 inhibitor, has recently emerged as a promising therapeutic option for acute pain management.

Purpose: The aim of this review is to evaluate the current evidence regarding suzetrigine as a novel non-opioid analgesic and to discuss its potential role in the future of pain management. Particular attention is given to the clinical burden of pain, the limitations of existing analgesic therapies, the biological rationale for targeting NaV1.8 channels, and the efficacy and safety of suzetrigine.

Methodology: A narrative review of literature was conducted using published preclinical studies, clinical trials, review articles, systematic reviews and meta-analyses concerning suzetrigine and NaV1.8 inhibition using PubMed and Clinicaltrials.gov. The reviewed literature included studies evaluating pharmacological properties, mechanism of action, clinical efficacy, safety profile and potential therapeutic applications of suzetrigine in acute and chronic pain conditions.

Conclusion: Current evidence indicates that suzetrigine represents a significant advancement in analgesic drug development. By selectively inhibiting NaV1.8 channels involved in peripheral nociceptive signaling, it provides effective pain relief without engaging opioid pathways. Clinical studies have demonstrated favorable efficacy and tolerability in patients, with moderate-to-severe acute pain, while ongoing research continues to explore its potential applications in chronic and disease-specific pain conditions. Suzetrigine may therefore contribute to reducing reliance on opioid analgesics and represents a promising step toward safer pain management strategies.

KEYWORDS

Suzetrigine, VX-548, NaV1.8, Pain Management, Non-Opioid Analgesics, Acute Pain, Analgesia, Opioid Alternatives

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1. Introduction

Pain is a universal human experience and one of the most common reasons individuals seek medical attention. Persistent or inadequately managed pain can become a debilitating condition that significantly impairs physical, physiological and social well-being. Acute pain often accompanies injury, surgery or illness and generally resolves as healing occurs. In contrast, chronic pain persists beyond normal tissue recovery and frequently develops into a complex disease state characterized by neuroplastic changes within the peripheral and central nervous system (Chen et al., 2026).

According to epidemiological estimates, chronic pain affects approximately 20% of adults worldwide, while acute pain remains one of the leading causes of emergency department visits and postoperative complications (Bradshaw et al., 2026; Yuan et al., 2026). For decades, pharmacological treatment of moderate-to-severe pain has relied heavily on opioid and analgesics. Opioids exert their effects through activation receptors within the central nervous system, producing potent analgesia but also causing numerous adverse effects, including respiratory depression, constipation, sedation, tolerance, dependence and addiction (Pham et al., 2025).

Although non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen anticonvulsants, and antidepressants are widely available these medications often demonstrate limited efficacy in moderate-to-severe pain and may be associated with significant adverse effects, including gastrointestinal bleeding, cardiovascular complications, hepatotoxicity and neurological disturbances (Mach et al., 2025). Consequently, there remains a critical need for innovative analgesics capable of providing effective pain relief without the risk associated with the drugs mentioned above.

Recent advances in molecular neuroscience and pain biology have transformed our understanding of nociception and pain signaling. Among the most promising developments has been the identification of voltage-gated sodium channels as key mediators of pain transmission. These channels regulate neuronal excitability and action potential propagation within sensory neurons. Genetic studies have highlighted the importance of specific sodium channel subtypes particularly NaV1.7, NaV1.8, and NaV1.9. in the pathophysiology of pain disorders (Koivisto, 2026; Wood et al., 2025).

Na V1.8 has emerged as an especially attractive therapeutic target because of its selective expression in peripheral nociceptive neurons and its central role in generating pain-related electrical signals. Unlike opioid receptors, NaV1.8 channels are largely absent from brain regions associated with reward and addiction, suggesting that selective inhibition could produce analgesia without abuse liability (Osteen et al., 2025). Advances in medicinal chemistry have enabled the development of highly selective NaV1.8 inhibitors, culminating in the introduction of suzetrigine.

Suzetrigine (VX-548), represents the first clinically approved selective NaV1.8 inhibitor for the treatment of moderate-to-severe acute pain (Hu et al., 2025). Developed through extensive translational research efforts, the drug selectively blocks pain signal transmission in peripheral sensory neurons while preserving normal neurological function. Clinical trials have demonstrated significant reductions in postoperative pain intensity compared with placebo and favorable comparisons with existing analgesic therapies (Bertoch et al., 2025; Jones et al., 2023).

Furthermore, emerging evidence suggests that the therapeutic potential of NaV1.8 inhibition may extend beyond acute postoperative pain. Ongoing investigations are evaluating suzetrigine in chronic pain conditions, cancer-related pain, sickle cell disease-associated vaso-occlusive crises and other pain syndromes characterized by peripheral neuronal hyperexcitability (Hasoon et al., 2026; Joudeh et al., 2026). Although these applications remain under investigation, preliminary findings indicate that NaV1.8-targeted therapies may eventually transform multiple areas of pain management.

At the time of writing (June 2026), suzetrigine has received approval from the U.S.Food and Drug Administration (FDA) for the treatment of moderate-to-severe acute pain in adults. However, it has not yet obtained marketing authorization from the European Medicines Agency (EMA), and its availability in European countries remains limited pending further regulatory evaluation.

This review aims to provide a comprehensive overview of suzetrigine as a novel non-opioid analgesic. Particular attention is given to the clinical burden of pain, current limitations of available therapies, the biological rationale for targeting NaV1.8 channels and emerging evidence regarding the efficacy and safety of suzetrigine. By examining both the scientific foundations and clinical implications of this innovative therapy, the review seeks to assess whether suzetrigine truly represents the future of analgesia.

2. Pain as a Clinical and Public Health Challenge

Pain is increasingly recognized not merely as a symptom of disease but as a significant health condition. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. This definition highlights the multidimensional nature of pain, encompassing physiological, cognitive and social components that collectively influence patient outcomes (Chen et al., 2026).

Pain is generally classified into acute and chronic forms. Acute pain is typically associated with injury, surgery, inflammation or disease and serves a protective biological function by promoting avoidance of harmful stimuli and facilitating recovery. Chronic pain, however, persist beyond normal healing processes, often lasting longer than three months and can become a disease state characterized by maladaptive neuroplastic changes (Rajasingham & Qi, 2025).

The prevalence of pain worldwide underscores its importance as a public health issue. Chronic pain affects approximately one in five adults globally and is among the leading causes of disability-adjusted life years (DALYs) lost worldwide (Yuan et al., 2026). Conditions such as osteoarthritis, low back pain, neuropathic pain, fibromyalgia, cancer-related pain and postoperative pain collectively affect hundreds of millions of individuals and place substantial demands on healthcare resources.

In addition to its physical manifestations, pain profoundly impacts mental health. Patients suffering from chronic pain frequently experience depression, anxiety, sleep disturbances, social isolation and reduced occupational functioning (Mach et al., 2025). Consequently, effective pain management requires a multidisciplinary approach addressing both physical and psychological dimensions of suffering.

The economic consequences of pain are equally significant. Direct healthcare expenditures include physician visits, hospitalizations, diagnostic testing, surgical procedures and pharmacological treatment. Indirect costs arise from work absenteeism, reduces productivity, disability benefits and informal caregiving. In many developed countries, the total economic burden of chronic pain exceeds that associated with cardiovascular disease, diabetes or cancer (Mohiuddin & Ahmed, 2025).

Acute pain remains a particularly important clinical challenge. Postoperative pain affects the majority of surgical patients and inadequate pain control is associated with delayed recovery, prolonged hospitalization, increased healthcare costs and higher risk of developic chronic postsurgical pain (Bertoch et al., 2025). Emergency departments similarly developing encounter large numbers of patients presenting with acute painful conditions, ranging from traumatic injuries to renal colic and musculoskeletal disorders (Bradshaw et al., 2026).

The growing recognition of pain as a major public health challenge has therefore created an urgent demand for innovative therapeutic approaches. As healthcare systems seeks to balance effective pain relief with patient safety, the emergence of targeted non-opiod therapies such as suzetrigine may offer a promising solution. Understanding the limitations of existing treatments and the biological basis of pain is essential for appreciating the significance of this therapeutic breakthrough.

3. Current approaches to pain management

Effective pain management remains one of the primary goals of modern medicine. Because pain is a multifactorial phenomenon involving biological, psychological and social components, current treatment strategies often rely on multimodal approaches that combine pharmacological and non-pharmacological interventions. Despite significant advances in pain medicine, currently available therapies continue to present substantial limitations in terms of efficacy, safety and long-term outcomes, highlighting the need for innovative analgesic solutions such as suzetrigine (Mach et al., 2025).

3.1 Non-Pharmacological Approaches

Non-pharmacological interventions play an important role in pain management, particularly in chronic pain conditions. These approaches include physical therapy, exercise programs, cognitive behavioral therapy, acupuncture, mindfulness-based interventions and interdisciplinary rehabilitation programs. Such strategies aim not to reduce pain intensity but also to improve physical function, psychological well-being and overall quality of life (Chen et al., 2026).

Although non-pharmacological treatments can be highly beneficial, especially when integrated into comprehensive pain management plans, they are often insufficient as standalone therapies for moderate-to-severe acute pain. Consequently, pharmacological treatment remains a cornerstone of pain management in majority clinical settings.

3.2. Non-Opioid Pharmacological Therapies

Non-opioid analgesics are commonly used as first-line treatment for mild-to-severe pain and as components of multimodal analgesic regimens. The most widely prescribed agents include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).

Acetaminophen remains one of the most frequently used analgesics worldwide because of its favorable safety profile at therapeutic doses. Nevertheless, its analgesic efficacy is limited in moderate-to-severe pain and excessive dosing can result in serious hepatotoxicity (Mach et al., 2025).

NSAIDs exert their analgesic effects by inhibiting cyclooxygenase enzymes and reducing the synthesis of prostaglandins involved in inflammation and pain sensitization. These medications are effective in a variety of acute and chronic pain conditions, including musculoskeletal disorders and postoperative pain. However, long-term NSAIDs use is associated with gastrointestinal bleeding, renal impairment and increased cardiovascular risk (Pham et al., 2025).

Additional non-opioid medications include anticonvulsants such as gabapentin and pregabalin, as well as antidepressants including duloxetine and amitriptyline. These agents are particularly useful in neuropathic pain syndromes, where conventional analgesics often provide inadequate relief. However, their use may be limited by adverse effects such as dizziness, sedation, cognitive impairment and weight gain (Rajasingham & Qi, 2025).

Local anesthetics constitute another important category of non-opioid analgesics. Agents such as lidocaine produce analgesia by blocking voltage-gated sodium channels and preventing the initiation and propagation of action potentials in peripheral nerves. Although highly effective for local and regional anesthesia, their clinical utility is often limited by relatively short duration of action, route-of-administration, constraints, and lack of selectivity among sodium channel subtypes (Wood et al., 2025).

3.3. Opioid Analgesics

For decades, opioids have represented the gold standard for managing moderate-to-severe acute pain. Drugs such as morphine, oxycodone, hydromorphone and fentanyl act primarily through transmission and altering pain perception.

The effectiveness of opioids in treating acute postoperative pain, cancer pain and severe traumatic injuries is well established. However, their widespread use has revealed significant limitations. Common adverse effects include nausea, vomiting, constipation, sedation, respiratory depression and cognitive dysfunction. More importantly, prolonged opioid exposure may result in tolerance, physical dependence, opioid use disorder and addiction (Sibomana et al., 2025).

The opioid epidemic has become one of the most significant public health crises of the twenty-first century. In response, healthcare systems worldwide have sought strategies to reduce opioid prescribing while maintaining adequate pain control. Nevertheless, achieving this balance remains difficult because many available non-opioid alternatives fail to provide comparable analgesic efficacy in severe pain conditions (Attal & Barrot, 2025).

3.4. Multimodal Analgesia

To address the limitations of individual therapies, contemporary pain management increasingly emphasizes multimodal analgesia. This approach combines medications with different mechanisms of action to enhance analgesic efficacy while minimizing adverse effects and opioid requirements.

Multimodal regimens may include combinations of NSAIDs, acetaminophen, local anesthetics, anticonvulsants, corticosteroids and limited opioids. Numerous studies have demonstrated that such strategies can improve postoperative pain outcomes and reduce opioid consumption (Bradshaw et al., 2026).

Despite these advances, a substantial unmet need remains. Existing therapies frequently fail to provide adequate pain relief without significant adverse effects, particularly in patients experiencing moderate-to-severe pain. Consequently, researchers have increasingly focused on developing mechanism-based analgesics that target specific components of pain signaling pathways. Among the most promising targets identified in recent years are voltage-gated sodium channels, particularly NaV1.8, which plays a critical role in nociceptive transmission (Osteen et al., 2025).

The development of suzetrigine represents a direct response to these unmet clinical

needs. By selectively inhibiting NaV1.8 channels involved in peripheral pain signaling, suzetrigine offers a fundamentally different approach to analgesia that may overcome many limitations associated with traditional pain medications.

4. NaV1.8 as a Therapeutic Target

4.1. Voltage-Gated Sodium Channels and Pain Signaling

Pain perception begins with the activation of specialized sensory neurons known as

nociceptors. These neurons detect potentially harmful mechanical, thermal or chemical stimuli and convert them into electrical signals that are transmitted to the spinal cord and brain. The initiation and propagation of these electrical signals depend largely on voltage-gated sodium channels (VGSCs), a family of transmembrane proteins responsible for generating action potentials in excitable tissues (Wood et al., 2025).

To date, nine major sodium channel isoforms (NaV1.1-NaV1.9) have been identified.

While several isoforms contribute to neuronal excitability, specific channels are preferentially expressed in nociceptive neurons and play critical roles in pain transmission. Genetic studies have provided compelling evidence linking sodium channel dysfunction to human pain disorders. For example, gain-of-function mutations may cause severe pain syndromes, whereas loss-of-function mutations can result in congenital insensitivity to pain (Koivisto, 2026). These findings have stimulated considerable interest in sodium channels as potential therapeutic targets for analgesic drug development.

4.2. The Role of NaV1.8 in Nociception

Among the sodium channel family, NaV1.8 has emerged as one of the most promising

targets for pain therapy. NaV1.8 is predominantly expressed in peripheral dorsal root ganglion (DRG) neurons and trigeminal ganglion neurons, where it contributes significantly to the generation and propagation of nociceptive signals (Osteen et al., 2025).

Unlike many other sodium channel isoforms, NaV1.8 remains functional under conditions of sustained depolarization and inflammation. This property enables nociceptors to maintain repetitive firing during painful stimuli, making NaV1.8 particularly important in both acute and chronic pain states (Jo et al., 2025).

Experimental studies have demonstrated that inhibition or genetic deletion of NaV1.8

substantially reduces pain behaviors in animal models without causing major neurological deficits. Furthermore, because NaV1.8 expression is largely restricted to peripheral sensory neurons, selective targeting of this channel is expected to minimize central nervous system adverse effects (Ali et al., 2025).

Recent investigations using human sensory neurons have confirmed the critical contribution of NaV1.8 to neuronal excitability and pain signal transmission. Stewart et al. (2025) demonstrated that pharmacological inhibition of NaV1.8 significantly reduced firing rates in human dorsal root ganglion neurons, supporting the translational relevance of this target.

4.3. Development of Suzetrigine

The search for selective NaV1.8 inhibitors has spanned several decades. Early compounds demonstrated proof of concept but were limited by poor selectivity, insufficient efficacy or unfavorable pharmacokinetic properties. Advances in structural biology, medicinal chemistry and electrophysiological screening ultimately enabled the development of highly selective inhibitors suitable for clinical use (Wu & Lu, 2026).

Suzetrigine (VX-548), was developed by Vertex Pharmaceuticals as a next-generation NaV1.8 inhibitor designed to provide potent analgesia while minimizing off-target effects. The compound was optimized to selectively bind NaV1.8 channels and inhibit nociceptive signal propagation without significantly affecting other sodium channel subtypes involved in cardiac, muscular or central nervous system function (Osteen et al., 2025).

The successful development of suzetrigine represents a major milestone in analgesic drug discovery and has been described as one of the most important advances in non-opioid pain management in more than two decades (Sibomana et al., 2025).

5. Mechanism of Action of Suzetrigine

Suzetrigine exerts its analgesic effect through selective inhibition of NaV1.8 sodium channels located on peripheral nociceptive neurons. By stabilizing the channel in its inactive state, the drug reduces neuronal excitability and suppresses the generation and propagation of pain-related action potentials (Osteen et al., 2025).

Importantly, this mechanism acts upstream of pain perception in the central nervous system. Rather than altering pain processing within the brain, suzetrigine reduces the transmission of nociceptive signals before they reach higher neural centers. This distinction is particularly significant because it avoids engagement of opioid receptors and associated reward pathways responsible for addiction and dependence (Rajasingham & Qi, 2025).

Electrophysiological studies have demonstrated that suzetrigine exhibits state-dependent inhibition, preferentially targeting hyperactive neurons involved in pathological pain states while exerting less influence on normally functioning neurons (Jo et al., 2025; Vaelli et al., 2024). This selectivity may contribute to its favorable safety profile and reduced likelihood of interfering with normal sensory function.

Preclinical studies have further shown that NaV1.8 inhibition by suzetrigine produces robust analgesic effects across multiple pain models. Notably, Ali et al. (2025) reported sustained analgesic efficacy in mice without evidence of tolerance development following repeated administration. This observation contrasts with opioid therapy, where tolerance often necessitates escalating doses over time.

5.1. Pharmacological Properties

In addition to its selectivity, suzetrigine demonstrates pharmacokinetic characteristics

suitable for clinical use. The drug is orally bioavailable and achieves therapeutic plasma concentrations capable of sustained NaV1.8 inhibition. Clinical studies have reported predictable pharmacokinetic behavior and favorable dosing characteristics, facilitating its use in acute pain management settings (Hang Kong et al., 2024).

The peripheral selectivity of suzetrigine also distinguishes it from many existing analgesics. Because the drug primarily targets sensory neurons outside the central nervous system, it is associated with a lower risk of sedation, respiratory depression, cognitive impairment and abuse potential compared with opioid analgesics (Hu et al., 2025).

5.2. Clinical Significance of NaV1.8 Inhibition

The emergence of suzetrigine validates decades of research aimed at identifying

selective sodium channel inhibitors for pain treatment. By targeting a key molecular component of nociceptive signaling, NaV1.8 inhibition represents a paradigm shift from traditional analgesic approaches that focus on inflammatory mediators or opioid receptor activation.

The approval of suzetrigine has also renewed interest in the broader therapeutic potential of sodium channel modulation. Ongoing research continues to investigate whether NaV1.8-targeted therapies may prove beneficial in chronic pain disorders, neuropathic pain, cancer-related pain and other conditions characterized by peripheral neuronal hyperexcitability (Chen et al., 2026; Yuan et al., 2026).

Collectively, the biological rationale and pharmacological characteristics of suzetrigine support its classification as a first-in-class, mechanism-based analgesic capable of addressing important limitations of existing pain therapies. Its clinical efficacy and safety profile will be examined in the following sections.

6. Efficacy of Suzetrigine

The clinical development of suzetrigine has generated considerable interest due to its novel mechanism of action and potential to address the unmet need for effective non-opioid analgesics. Following encouraging preclinical findings, multiple Phase II and Phase III clinical trials have evaluated its efficacy in patients experiencing moderate-to-severe acute pain. Collectively, the available evidence suggests that selective NaV1.8 inhibition may provide clinically meaningful analgesia while avoiding many limitations associated with opioid therapy. However, as the clinical experience with suzetrigine remains relatively recent, ongoing investigation is required to fully establish its long-term therapeutic role.

6.1. Preclinical Evidence

The rationale for clinical evaluation of suzetrigine was supported by extensive preclinical research demonstrating the critical role of NaV1.8 in nociceptive signaling. In murine models, pharmacological inhibition of NaV1.8 significantly reduced pain-related behaviors across inflammatory and neuropathic pain paradigms (Ali et al., 2025).

Importantly, repeated administration did not result in measurable analgesic tolerance, a finding that distinguishes NaV1.8 inhibition from opioid-based therapies.

Ali et al. (2025) reported that mice receiving chronic suzetrigine treatment maintained consistent analgesic responses throughout the study period without evidence of diminished efficacy. Furthermore, no significant behavioral indicators of dependence or withdrawal were observed following treatment discontinuation. These findings provided early evidence that Na V1.8 inhibition might offer sustained analgesia without some of the complications commonly associated with long-term opioid exposure.

Electrophysiological studies further strengthened the translational rationale. Stewart et al. (2025) demonstrated that suzetrigine significantly reduced firing frequency in human dorsal root ganglion neurons, confirming that NaV1.8 blockade effectively attenuates nociceptive signaling in human sensory tissue. Similar observations were reported by Jo et al. (2025), who found that suzetrigine preferentially inhibited hyperexcitable neuronal states, potentially enhancing selectivity for pathological pain conditions.

6.2. Early Clinical Development

The first major evidence supporting the clinical efficacy of suzetrigine emerged from two Phase II randomized, double-blind, placebo- and active-controlled trials in patients undergoing abdominoplasty or bunionectomy, two established models of acute postoperative pain. A total of 303 patients were enrolled in the abdominoplasty trial and 274 in the bunionectomy trial. The primary endpoint was the time-weighted sum of pain intensity differences over 48 hours (SPID48), a measure integrating both the magnitude and duration of analgesic effect. Patients receiving high-dose VX-548 experienced significantly greater pain reduction than those receiving placebo, with least-squares mean differences in SPID48 of 37.8(95% Cl,9.2-66.4) after abdominoplasty and 36.8(95% Cl, 4.6-69.0) after bunionectomy (both $p<0.001$). In contrast, the lower X-548 dose produced results comparable to placebo, suggesting a dose-dependent effect. Although superiority over hydrocodone-acetaminophen was not demonstrated, the analgesic efficacy of high-dose VX-548 approached that of the opioid comparator. Adverse events were generally mild to moderate, with headache and constipation reported most frequently. These findings provided the first clinical proof-of-concept that selective NaV1.8 inhibition can produce meaningful pain relief in humans (Jones et al., 2023).

6.3. Phase III Clinical Trials

The strongest evidence for suzetrigine efficacy comes from two pivotal Phase Ill randomized, double-blind trials in patients with moderate-to-severe postoperative pain following abdominoplasty or bunionectomy. Using SPID48 as the primary endpoint, suzetrigine demonstrated statistically significant superiority over placebo in both studies, with least-squares mean differences of 48.4 (95% CI, 33.6-63.1; $p < 0.0001$) and 29.3 (95% CI, 14.0-44.6; $p = 0.0002$), respectively. Suzetrigine also produced a rapid onset of analgesia, reducing the median time to a clinically meaningful ≥2-point (in NRS) reduction in pain intensity from 480 to 119 minutes in the abdominoplasty trial and from 480 to 240 minutes in the bunionectomy trial (nominal $p < 0.0001$ and $p = 0.0016$, respectively). Importantly, the drug met the first key secondary endpoint of superiority over hydrocodone-acetaminophen with respect to SPID48, indicating analgesic efficacy comparable to or exceeding that of the opioid-containing regimen. Adverse events were generally mild to moderate, supporting a favorable safety profile and the potential role of suzetrigine as an effective non-opioid alternative for acute pain management (Bertoch et al., 2025).

Additional evidence was provided by the Phase Ill single-arm VX-548-107 study, which evaluated suzetrigine in adults with moderate-to-severe acute pain arising from a broad range of surgical and non-surgical conditions (McCoun et al., 2025). A total of 256 participants received suzetrigine for up to 14 days or until pain resolution. The study demonstrated a favorable safety profile, with most adverse events being mild (27.7%) or moderate (8.2%) in severity. Importantly, patient-reported outcomes indicated high treatment satisfaction, with 83.2% of participants rating the effectiveness of suzetrigine as good, very good, or excellent on a global assessment scale. These findings support the safety, tolerability, and broad applicability of NaV1.8 inhibition across diverse acute pain conditions, extending the potential utility of suzetrigine beyond traditional postoperative pain models.

6.4. Evidence from Systematic Reviews and Meta-Analyses

As the number of clinical studies increased, several systematic reviews and meta-analyses attempted to synthesize the available evidence. Bansal et al. (2026) analyzed randomized controlled trials evaluating suzetrigine for acute pain management and concluded that the drug produced significantly greater pain reduction than placebo while maintaining an acceptable safety profile. Similarly, Alvarez-Aguilar & Picado-Loaiza (2026) reported that pooled analyses demonstrated statistically significant improvements in postoperative pain outcomes among patients receiving suzetrigine. The meta-analysis by Alvarez-Aguilar and Picado-Loaiza (2026) found that patients treated with suzetrigine were significantly more likely to achieve clinically meaningful pain relief compared with placebo-treated individuals.

The authors noted moderate heterogeneity among studies but concluded that the overall evidence supported the efficacy of selective NaV1.8 inhibition in acute postoperative pain.

However, both reviews emphasized that direct comparisons with established opioid regimens remain relatively limited and that additional studies will be necessary to better define the comparative effectiveness of suzetrigine in routine clinical practice.

6.5. Emerging Applications Beyond Acute Pain

Although suzetrigine has primarily been developed for acute pain, several early

investigations have explored its potential utility in chronic and disease-specific pain conditions. Hasoon et al. (2026) described three patients with cancer-related bone pain who experienced clinically meaningful symptom improvement following suzetrigine administration. Similarly, Joudeh et al. (2026) reported encouraging findings in three patients with vaso-occlusive pain associated with sickle cell disease. While these case series cannot establish efficacy, they suggest that Na V1.8 inhibition may warrant further investigation in chronic pain syndromes characterized by peripheral nociceptor hyperexcitability.

Chen et al. (2026) further argued that the biological rationale supporting NaV1.8

inhibition extends beyond acute nociception and may potentially apply to selected neuropathic and inflammatory pain disorders. Nevertheless, current evidence remains preliminary, and definitive conclusions cannot yet be drawn.

Overall, the available clinical evidence suggests that suzetrigine provides meaningful

analgesic efficacy in moderate-to-severe acute pain. Randomized controlled trials consistently demonstrated superiority over placebo and clinically relevant reductions in pain intensity. Although available data do not yet establish superiority over opioid therapy, the observed efficacy combined with the absence of opioid receptor engagement makes suzetrigine a potentially important advancement in pain management.

At present, the strongest evidence supports its use in acute postoperative pain. Future

studies will determine whether the therapeutic benefits observed in these settings can be extended to chronic pain conditions and broader patient populations.

7. Safety and Tolerability

The safety profile of any novel analgesic is a critical consideration, particularly in the context of ongoing efforts to reduce opioid-related harms. While analgesic efficacy remains essential, the development of safer alternatives has become an equally important objective in pain medicine. Available evidence suggests that suzetrigine is generally well tolerated and may offer several safety advantages compared with traditional opioid therapies. Nevertheless, as clinical experience remains relatively limited, continued pharmacovigilance and long-term studies are necessary.

Across Phase II and Phase III studies, suzetrigine demonstrated a favorable tolerability profile. The most frequently reported adverse events were generally mild to moderate in severity and included nausea, headache, dizziness, constipation and pruritus (Bertoch et al., 2025; Jones et al., 2023).

In the Phase III trials conducted by Bertoch et al. (2025), the overall incidence of treatment-emergent adverse events was comparable between the suzetrigine and placebo groups. Most reported events resolved spontaneously and rarely resulted in treatment discontinuation. Importantly, serious adverse events were uncommon and did not appear to occur at substantially higher frequencies than observed in placebo-treated patients. Investigators found no evidence of major organ toxicity, clinically significant laboratory abnormalities or unexpected safety signals.

Similarly, McCoun et al. (2025) reported high treatment completion rates in their broad acute pain cohort, further supporting the tolerability of the drug across diverse clinical settings.

One of the most notable features of suzetrigine is the absence of direct opioid receptor activity. Because the drug exerts its effects through peripheral NaV1.8 inhibition rather than central opioid receptor activation, many classic opioid-associated adverse effects are theoretically avoided. Clinical studies have not identified evidence of opioid-induced respiratory depression, a complication that remains one of the most serious risks associated with opioid therapy (Hu et al., 2025). Likewise, substantial sedation, euphoria and cognitive impairment have not emerged as prominent safety concerns.

The potential for abuse and dependence represents a major concern in contemporary pain management. The opioid epidemic has demonstrated that even highly effective analgesics can pose significant public health risks when associated with addictive properties. Because NaV1.8 channels are primarily located in peripheral sensory neurons rather than brain reward circuits, suzetrigine is not expected to produce the reinforcing effects typically associated with opioids (Osteen et al., 2025). Preclinical studies support this expectation. Ali et al. (2025) found no evidence of behavioral dependence or withdrawal phenomena in animal models following prolonged exposure. Similarly, clinical trials have not reported signals suggestive of drug-seeking behavior, misuse or psychological dependence.

However, it should be noted that post-marketing experience remains limited.

Consequently, definitive conclusions regarding abuse liability should be approached cautiously until larger real-world datasets become available.

Historically, sodium channel inhibitors have raised concerns regarding potential cardiovascular and neurological adverse effects due to the widespread physiological importance of sodium channels. Suzetrigine was specifically engineered to minimize interactions with sodium channel isoforms expressed in cardiac and central nervous system tissues. Available evidence suggests that this selectivity has been largely successful. Clinical trials have not identified clinically meaningful effects on cardiac conduction, electrocardiographic parameters or cardiovascular outcomes (Peshin et al., 2025). Likewise, significant neurological toxicity has not been observed.

Despite these encouraging findings, several limitations should be acknowledged. First, most clinical studies have evaluated short-term treatment in acute pain settings. Consequently, the long-term safety of chronic NaV1.8 inhibition remains incompletely understood. Second, patient populations enrolled in clinical trials may not fully represent individuals encountered in routine clinical practice. Elderly patients, individuals with multiple comorbidities and those receiving complex medication regimens may exhibit different safety outcomes. Finally, rare adverse events may not become apparent until substantially larger numbers of patients have been exposed to the drug following widespread clinical adoption.

8. Discussion

The FDA approval of suzetrigine represents an important milestone in analgesic drug development and may constitute one of the most significant advances in non-opioid pain management in recent decades. Unlike conventional analgesics that primarily target inflammatory mediators or opioid receptors, suzetrigine was developed through a mechanism-based approach focused on selective inhibition of the NaV1.8 sodium channel, a key mediator of peripheral nociceptive transmission. This strategy reflects a broader shift toward targeted therapies designed to address specific biological mechanisms underlying pain.

The growing interest in suzetrigine should be considered within the context of the ongoing opioid crisis. Although opioid analgesics remain highly effective for the treatment of moderate-to-severe acute pain, their use is associated with substantial risks, including respiratory depression, tolerance, dependence, addiction, and overdose (Pham et al., 2025). Consequently, the development of effective non-opioid alternatives has become a major priority in both clinical practice and pharmaceutical research.

Current evidence suggests that suzetrigine provides clinically meaningful analgesic efficacy in patients experiencing acute postoperative pain. Phase II and Phase III clinical trials consistently demonstrated significantly greater reductions in pain intensity compared with placebo and clinically relevant improvements in postoperative pain control (Bertoch et al., 2025; Jones et al., 2023). Although opioid-containing comparator regimens generally produced numerically greater analgesic effects, the observed differences were relatively modest. Therefore, suzetrigine appears capable of providing effective pain relief while potentially reducing the need for opioid exposure in selected patient populations.

In addition to its efficacy, the safety profile of suzetrigine appears particularly promising. Across clinical studies, the incidence of adverse events was generally low, and most reported events were mild to moderate in severity. Importantly, no evidence of opioid-related respiratory depression, significant sedation or euphoria has emerged thus far (Hu et al., 2025; Rejeev et al., 2025). Furthermore, preclinical studies did not demonstrate tolerance development following repeated administration, raising the possibility that NaV1.8 inhibition may provide more stable analgesic effects over time compared with conventional opioid therapy (Ali et al., 2025). However, because long-term clinical data remain limited, these findings should be interpreted with caution.

Despite these encouraging results, several important limitations should be acknowledged. Most available evidence originates from acute postoperative pain models and the efficacy of suzetrigine in chronic pain conditions remains uncertain. Chronic pain involves complex pathophysiological mechanisms, including central sensitization, neuroimmune interactions and psychosocial factors, which may not be fully addressed by peripheral NaV1.8 inhibition alone (Chen et al., 2026). In addition, direct comparisons with established multimodal analgesic protocols remain limited, making it difficult to precisely define the position of suzetrigine within current treatment algorithms.

Emerging evidence suggests that the therapeutic potential of suzetrigine may extend beyond acute pain. Preliminary reports have described beneficial outcomes in patients with cancer-related bone pain and vaso-occlusive pain associated with sickle cell disease (Hasoon et al., 2026; Joudeh et al., 2026). However, these

findings are based on small case series and should be considered exploratory until confirmed by larger randomized controlled trials.

Overall, the currently available evidence suggests that suzetrigine is a promising addition to the analgesic armamentarium. Its combination of clinically relevant efficacy, a favorable safety profile and the absence of direct opioid receptor activity may represent an important step toward safer pain management strategies. Nevertheless, further studies evaluating long-term safety, comparative effectiveness, cost-effectiveness and efficacy in chronic pain populations will be necessary to fully determine its future role in clinical practice.

8. Conclusions

Pain remains a major clinical challenge worldwide, creating a substantial burden for

patients and healthcare systems. Although opioids remain effective for the treatment of moderate-to-severe pain, concerns regarding dependence, addiction and other serious adverse effects have increased the demand for safer alternatives.

Suzetrigine, the first selective NaV1.8 inhibitor approved for clinical use, represents a

novel mechanism-based approach to pain management. Current evidence suggests that it provides clinically meaningful analgesia in patients with acute pain while maintaining a favorable safety profile and avoiding many opioid-related adverse effects. Its peripheral mechanism of action and lack of direct opioid receptor activity make it a particularly promising non-opioid therapeutic option.

However, important limitations remain. Most available data originate from acute postoperative pain studies, and evidence regarding long-term use and chronic pain conditions is still limited. Overall, suzetrigine appears to be a promising addition to current analgesic therapies, although further research is needed to fully establish its long-term clinical role and broader therapeutic potential.

Conflict of Interest Statement: The authors declare no conflicts of interest

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