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COMMENTARY

Suzetrigine Approval Breaks a 25-Year Silence: A New Era in Non-Opioid Acute Pain Management

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Abstract: Pain management remains a critical priority in clinical practice. Meanwhile, traditional analgesics, including non-opioid and opioid medications, often pose substantial risks, including adverse effects and potential for addiction. The recent approval of Suzetrigine by the US Food and Drugs Administration (FDA) represents a pivotal advancement in non-opioid analgesia for the treatment of moderate-to-severe acute pain. Suzetrigine, a selective NaV1.8 sodium channel inhibitor, provides effective pain relief by targeting peripheral pain pathways, minimizing the risk of addiction commonly associated with opioids, and has good safety profile according to clinical trials. Given the growing concerns surrounding opioid use, Suzetrigine offers a promising therapeutic alternative in acute pain management, with future research needed to assess its long-term effectiveness in diverse populations.

Keywords: analgesics, pain, drugs, opioids, pharmacology

Pain is the most common reason for physician consultations, accounting for approximately 40% of primary care visits.[1] A systematic review by (Gregory and McGowan, 2016)[2] found that hospital-wide pain prevalence among hospitalized adults ranged from 37.7% to 84%, highlighting the significant burden of pain in clinical settings. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[3] Pain is classified into acute and chronic types based on duration and cause.[3] Acute pain, lasting less than three months, often results from injury, surgery, illness, trauma, or painful medical procedures.[4,5] In contrast, chronic pain persists or recurs beyond three months and may arise from conditions such as fibromyalgia, arthritis, irritable bowel syndrome (IBS), chronic low back pain, chronic headaches or migraines, endometriosis, and chronic fatigue syndrome.[4,6]

Analgesics, broadly classified into non-opioids, opioids, and adjuvant analgesics, have long been utilized in pain management.[7] Non-opioid analgesics are primarily indicated for mild to moderate pain and include aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen. These drugs exert their analgesic effects by inhibiting cyclooxygenase (COX) enzymes, reducing prostaglandin synthesis, and subsequently decreasing inflammation, peripheral nociceptor sensitization, and central pain transmission.[8] In contrast, opioids are predominantly used for moderate to severe pain and include codeine, tramadol, morphine, oxycodone, and fentanyl. They bind to mu (μ), kappa (κ), and delta (δ) opioid receptors in the central and peripheral nervous system, inhibiting neurotransmitter release and pain signal transmission, thereby altering pain perception.[9] Adjuvant analgesics, which enhance the effects of primary analgesics or target specific pain types, include antidepressants, benzodiazepines, anticonvulsants, and corticosteroids, offering additional therapeutic benefits in pain management.[10]

Pain medications, while effective, have been associated with several drawbacks. Non-opioid analgesics, particularly NSAIDs, have been linked to gastrointestinal (GI) adverse effects, including dyspepsia, nausea, vomiting, peptic ulcer

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disease, and kidney complications such as acute kidney injury and chronic kidney disease. Acetaminophen, though generally well-tolerated, has been found to cause hepatotoxicity when taken in excessive doses.[7,11] Opioid analgesics, commonly prescribed for severe pain, have been associated with numerous central nervous system (CNS) side effects, including sedation, dizziness, confusion, and respiratory depression. GI-related side effects such as nausea, vomiting, and constipation have also been prevalent. Opioids have been shown to cause urinary retention and may exacerbate conditions like benign prostatic hyperplasia. Long-term opioid use may lead to tolerance, dependence, and addiction, with abrupt discontinuation resulting in withdrawal symptoms, including anxiety, agitation, and flu-like symptoms.[7,12] These adverse effects highlighted the need for new pain medications that are more effective and associated with fewer side effects.

In response to the escalating opioid crisis, the FDA has long supported the development of non-opioid analgesics for acute pain management as part of its Overdose Prevention Framework. On January 30, 2025, FDA approved Journavx (suzetrigine), a 50-milligram oral tablet, as the first non-opioid analgesic for treating moderate to severe acute pain in adults.[13] This marks the approval of the first drug in this novel class in 25 years. Suzetrigine works by selectively inhibiting the $Na_V1.8$ sodium channel, which plays a crucial role in transmitting pain signals from peripheral nerves to the central nervous system (Figure 1). By binding to the second voltage-sensing domain (VSD2) of NaV1.8, suzetrigine stabilizes the channel in a closed state, preventing sodium influx, which would normally trigger pain signals.[14] This targeted mechanism minimizes side effects and avoids the risks of addiction associated with opioid use, as it does not affect brain activity.

The safety of Journavx (suzetrigine) was assessed in two double-blind, placebo- and active-controlled trials with participants aged 18–80, undergoing abdominoplasty or bunionectomy. Participants with moderate-to-severe post-surgical pain were randomized to receive suzetrigine, hydrocodone bitartrate/acetaminophen (HB/APAP), or a placebo. The primary endpoint, pain intensity difference (SPID48), showed that suzetrigine significantly reduced pain compared to placebo, with a 48.4% reduction in the abdominoplasty trial ($P < 0.001$) and 29.3% in the bunionectomy trial ($P = 0.0002$). Suzetrigine also achieved a significantly quicker reduction in pain, with a median time of 119 minutes in the abdominoplasty trial, compared to 480 minutes for placebo. Although pain relief with suzetrigine was comparable to that of hydrocodone bitartrate/acetaminophen, it was generally better tolerated and associated with fewer adverse events than either HB/APAP or placebo. A third study expanded on previous trials, evaluating suzetrigine's safety and efficacy in a broader population with acute pain, showing favorable results.[13,15]

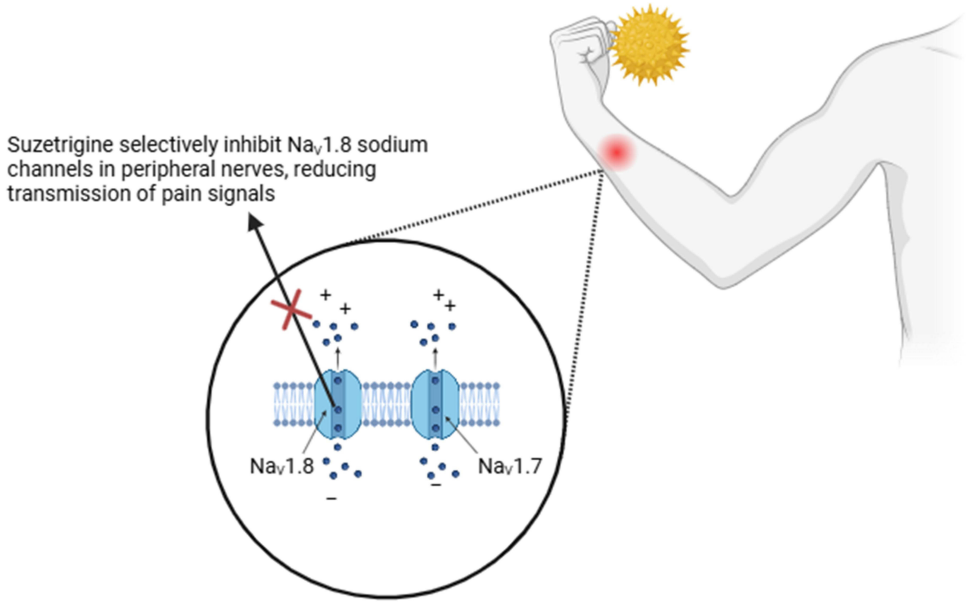

Figure 1 Mechanism of action of Suzetrigine.

The approval of Suzetrigine represents a significant milestone in non-opioid acute pain management. As a selective NaV1.8 sodium channel inhibitor, it provides effective pain relief without the risk of addiction commonly associated with opioids. With a large number of individuals suffering from acute pain each year, the demand for safer alternatives has become increasingly urgent. Suzetrigine addresses this need by targeting peripheral pain pathways, offering a promising solution for patients seeking pain relief without the concerns of dependency. In the context of the ongoing opioid crisis, Suzetrigine emerges as a groundbreaking medication that emphasizes patient safety and efficacy. It holds the potential to revolutionize the approach to acute pain treatment, making effective management more accessible and reducing the stigma and dangers linked to opioid use.

While suzetrigine avoids opioid receptors and reduces the potential for addiction, the long-term effects of NaV1.8 inhibition remain poorly understood. It is reported to carry a risk of cross-reactivity with other sodium channel subtypes, but it demonstrates over 31,000-fold selectivity for NaV1.8, significantly minimizing off-target effects.[14] Research on sodium channel blockers like lidocaine and carbamazepine has raised concerns about potential off-target effects, including neurotoxicity, cardiac arrhythmias, and altered sensory processing, highlighting the need for further investigation into the broader physiological impact of chronic NaV1.8 blockade.[16] Meanwhile, suzetrigine was approved based on the results of only two trials, which is a significant limitation, highlighting the need for further studies to validate its safety and efficacy. Additionally, issues such as cost-effectiveness, accessibility, and insurance coverage will influence Suzetrigine's clinical adoption, particularly if it is significantly more expensive than existing NSAIDs or COX-2 inhibitors. From a public health standpoint, while Suzetrigine supports opioid stewardship, it does not entirely eliminate the need for opioids in cases of severe, intractable pain. Future research and comparative effectiveness studies are crucial to assess Suzetrigine's long-term safety, effectiveness, and role in therapy, minimizing risks of over-reliance on any analgesic class.

Ethical Approval

This study did not directly include patients, so ethical approval was not required.

Consent Form

This study did not directly include patients, so consent was not required.

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Disclosure

The authors declare no conflicts of interest in this work.

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