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NARRATIVE REVIEW PAIN MANAGEMENT

Suzetrigine as a revolution in opioid-free pain relief: a review study

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ABSTRACT

The opioid epidemic, claiming over 80,000 lives in the United States in 2022, has intensified the demand for non-opioid analgesics capable of managing moderate-to-severe acute pain without the risks of addiction or overdose. Suzetrigine, a selective NaV1.8 inhibitor approved by the FDA on January 30, 2025, offers a groundbreaking alternative. This review provides an exhaustive analysis of suzetrigine's pharmacology, clinical efficacy across diverse pain models, dosing strategies, metabolism, safety profile, and its comparative advantages over traditional opioid therapies. We will explore suzetrigine's integration into perioperative care and its potential to mitigate the opioid crisis.

Keywords: Suzitrigine; Opioid Free Analgesia; Opioid epidemic; NaV1.8 Inhibitor; Analgesia; Acute Pain

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1. INTRODUCTION

Opioid-related mortality remains a critical public health crisis, with surgical patients particularly vulnerable—approximately 10% of opioid-naïve individuals develop persistent use following procedures.[1] Anesthesiologists, tasked with managing acute perioperative pain, face the dual challenge of achieving effective analgesia while minimizing opioid exposure, a balance complicated by opioids' adverse effects: respiratory depression, postoperative ileus, sedation, and dependence.[2] Non-opioid options like NSAIDs and acetaminophen, while valuable in multimodal regimens, often lack potency for severe pain and introduce risks such as gastrointestinal perforation, renal dysfunction, or hepatotoxicity.[3]

Suzetrigine, is licensed as an acute pain relief medicine, the first new class of acute pain medication in over two decades, targets the NaV1.8 sodium channel in peripheral nociceptors, offering potent analgesia without CNS penetration or addictive potential.[4] Approved for moderate-to-severe acute pain in adults, it aligns with ASA and ERAS goals of reducing opioid reliance. This article delves into suzetrigine's mechanisms, trial data, and practical implications, positioning it as a potential tool for anesthesiologists combating the opioid

epidemic. Suzitrigine got FDA approval on January 30, 2025.

2. Mechanism of Action:

Suzetrigine selectively inhibits NaV1.8, a voltage-gated sodium channel expressed predominantly in peripheral Aδ- and C-fiber nociceptors within dorsal root ganglia (DRG) and trigeminal ganglia. Its selectivity—over 31,000-fold greater for NaV1.8 than for cardiac NaV1.5 or CNS NaV1.7—stems from its unique binding to the second voltage-sensing domain (VSD2), stabilizing the channel's closed state via allosteric modulation.[5] Preclinical studies using patch-clamp electrophysiology in human DRG neurons demonstrated that suzetrigine reduces sodium currents by 85% at therapeutic concentrations, effectively silencing pain signal initiation without affecting motor or sensory pathways mediated by other NaV isoforms.[5] Preclinical studies using patch-clamp electrophysiology in human DRG neurons demonstrated that suzetrigine reduces sodium currents by 85% at therapeutic concentrations, effectively silencing pain signal initiation without affecting motor or sensory pathways mediated by other NaV isoforms. This peripheral specificity avoids the CNS effects of opioids (e.g., euphoria, respiratory suppression) and the systemic toxicities of non-selective sodium channel blockers like lidocaine.

3. Clinical Efficacy:

Suzetrigine's efficacy has been validated across multiple clinical trials, with Phase 3 data forming the cornerstone of its approval. The NAVIGATE 1 (n=1,118, abdominoplasty) and NAVIGATE 2 (n=1,073, bunionectomy) trials—randomized, double-blind, placebo- and active-controlled studies—evaluated suzetrigine (100 mg loading dose, then 50 mg every 12 hours) against hydrocodone/acetaminophen and placebo.[6] The primary endpoint, SPID48, showed significant pain reduction and non-inferiority to opioids, with a median time to perceptible relief of 1.8 hours. Rescue ibuprofen use was lower in the suzetrigine arm versus placebo, suggesting robust standalone efficacy in postoperative settings.

A Phase 3 single-arm study expanded suzetrigine's scope to diverse acute pain etiologies (e.g., appendectomy, fractures, burns), with 83.2% of patients rating it "good" to "excellent" on the PGA after up to 14 days.[7] Conversely, chronic pain trials have yielded mixed results. A Phase 2 study in lumbosacral radiculopathy reported modest NPRS reduction, attributed to high placebo responses typical in neuropathic pain trials.[8] Conversely, chronic pain trials have yielded mixed results. A Phase 2 study in lumbosacral radiculopathy (LSR, n=302, completed December 2024) reported a modest NPRS reduction (2.02 vs. 1.98 for placebo), attributed to high placebo responses typical in neuropathic pain trials.[10] A redesigned Phase 3 LSR trial, launched in January 2025, incorporates stricter endpoints to address this limitation

4. Dosing and Administration:

Suzetrigine's dosing is optimized for acute pain management:

- Initial Dose: 100 mg orally once, ideally on an empty stomach to maximize bioavailability (Tmax reduced by 30 minutes).
- Maintenance Dose: 50 mg orally every 12 hours, with or without food.
- Duration: Short-term use aligned with pain resolution, not exceeding 14 days in trials.

This regimen supports perioperative protocols, with the loading dose facilitating rapid analgesia in the PACU and maintenance doses simplifying discharge planning. The wholesale cost is $15.50 per 50 mg tablet in the USA,

Table 1: Pharmacokinetics and Metabolism of Suzitrigine

Parameter	Value
Half-Life	8–10 hours
Volume of Distribution	120 L
Cmax	1.2 µg/mL
Tmax	1–2 hours (faster on empty stomach)
Metabolism	Hepatic (80% CYP3A4, minor CYP1A2/CYP2C9)
Excretion	80% renal, 15% fecal
Steady-State	Achieved within 48 hours
Drug Interactions	Increased AUC with CYP3A4 inhibitors; reduced efficacy with inducers

Table 2: Safety profile of Suzitrigine

Adverse Effect	Suzetrigine	Standard Opioids
Pruritus	2.1%	Common
Muscle Spasms	1.3%	Rare
Elevated CPK	1.1%	Not reported
Rash	2.5%	Rare
Respiratory Depression	None	4% SpO2 drop
PONV	<5%	Up to 25%
Constipation/Ileus	None	Common
QT Prolongation	None	Possible with methadone

potentially offset by reduced opioid-related complications.[9] Tablets must remain intact to preserve pharmacokinetic consistency.

5. Pharmacokinetics and Metabolism:

Suzetrigine displays linear pharmacokinetics, with a half-life of 8–10 hours and a volume of distribution of 120 L.[10] Peak plasma levels occur within 1–2 hours, enhanced by fasting. It undergoes extensive hepatic metabolism via CYP3A4, producing metabolites excreted renally (80%) and fecally (15%).[11] Steady-state concentrations are achieved within 48 hours, and no significant accumulation occurs with twice-daily dosing. Strong CYP3A4 inhibitors (e.g., clarithromycin) increase area under the curve (AUC) by 2.5-fold, while inducers (e.g., carbamazepine) reduce efficacy by 40%, necessitating careful perioperative drug reconciliation.

6. Safety Profile and Adverse Effects:

Suzetrigine's safety profile is reassuring from the current available literature. Phase 3 trials reported mild-to-moderate AEs: pruritus (2.1%), muscle spasms (1.3%), elevated CPK (1.1%), and rash (2.5%), with no dose-dependent escalation. Elevated CPK, possibly linked to NaV1.8's role in muscle afferents, lacks clinical significance in healthy patients but merits caution in myopathic conditions. Unlike opioids, suzetrigine avoids respiratory depression (SpO2 unchanged vs. 4% drop with hydrocodone), PONV (incidence <5% vs. 25%), and ileus, enhancing postoperative recovery. No QT prolongation or hepatotoxicity was observed, distinguishing it from NSAIDs' renal and gastrointestinal risks.

7. Contraindications and Use in Hepatic and Renal Impairment:

Contraindications include co-administration with strong CYP3A inhibitors and grapefruit products, which elevate suzetrigine levels. In moderate hepatic impairment (Child-Pugh B), a reduced maintenance dose (25 mg every 12 hours) is advised due to a 50% increase in AUC; severe impairment (Child-Pugh C) precludes use due to unstudied risks.[11] In severe renal dysfunction (eGFR <15 mL/min/1.73 m^2), accumulation of metabolites contraindicates suzetrigine, though mild-to-moderate impairment (eGFR ≥30) requires no adjustment. Anesthesiologists must assess liver and kidney function preoperatively, especially in elderly or polypharmacy patients.

8. Perioperative Integration and Opioid-Sparing Potential:

Suzetrigine integrates seamlessly into multimodal analgesia, reducing intraoperative opioid requirements (e.g., fentanyl boluses) and postoperative prescriptions. In NAVIGATE trials, opioid consumption dropped by 60% in suzetrigine-treated patients versus controls, aligning with ERAS goals.[13] Combining it with regional techniques (e.g., epidural analgesia) or adjuncts (e.g., ketamine, magnesium) could further optimize outcomes, particularly in high-risk surgeries like thoracotomy or joint replacement. Its lack of sedation supports same-day discharge, a priority in ambulatory settings where 70% of U.S. surgeries occur.[14]

9. Patient Selection and Monitoring:

Ideal candidates include opioid-naïve patients, those with opioid intolerance, or those at high risk for addiction (e.g., history of substance use). Monitoring focuses on AEs like rash or muscle spasms, with baseline CPK optional in at-risk groups. Perioperative teams should educate patients on avoiding grapefruit and CYP3A4 inhibitors, leveraging anesthesiologists' role in medication management.

10. Economic and Societal Impact:

At $15.50 per tablet, suzetrigine's cost may exceed generic opioids ($0.50–$1 per dose), but savings from

Table 3: Comparison of Suzitrigine and standard opioid medications

Parameter	Suzetrigine (JOURNAVX™)	Standard Opioids (e.g., Morphine)
Mechanism of Action	NaV1.8 inhibition	μ-opioid receptor agonism
Analgesic Potency	Moderate-to-severe acute pain	Moderate-to-severe pain
Addiction Potential	None observed	High (10% chronic use post-surgery)
Common Adverse Effects	Pruritus, muscle spasms, elevated CPK, rash	Respiratory depression, PONV, constipation
Dosing	100 mg initial, 50 mg q12h	Variable (e.g., 0.1 mg/kg IV morphine)
Metabolism	Hepatic CYP3A4	Hepatic glucuronidation
Use in Hepatic Impairment	Adjust in moderate; avoid in severe	Reduce dose; caution in severe
Use in Renal Impairment	Avoid in severe (eGFR <15)	Adjust dose; risk of metabolite accumulation

reduced opioid-related readmissions (e.g., overdose, ileus) could offset expenses. A 2025 cost-effectiveness analysis projected a 20% reduction in societal opioid burden with widespread adoption.[15] For anesthesiologists, its use could lower malpractice risks tied to opioid overprescribing.

11. Future Directions and Research Gaps:

Suzetrigine's success in acute pain management has established it as a transformative opioid-sparing option, yet significant research gaps remain that could shape its broader adoption and utility in anesthesiology. Ongoing trials, such as Evaluation of Efficacy and Safety of Suzetrigine for Pain Associated With Diabetic Peripheral Neuropathy will provide more insight into its increasing efficacy for chronic pain..16 These studies incorporate advanced endpoints (e.g., quantitative sensory testing, painDETECT scores) to better differentiate drug effects from psychosocial influences, addressing a key limitation in prior chronic pain research.

Beyond chronic pain, long-term safety data beyond the 14-day trial limit are absent, posing a challenge for anesthesiologists managing extended postoperative pain (e.g., after major oncologic or spinal surgeries). Preclinical models suggest NaV1.8 inhibition is well-tolerated chronically, but human studies are needed to assess risks like tachyphylaxis or compensatory upregulation of other NaV channels (e.g., NaV1.7), which could diminish efficacy over time. Similarly, the potential for rare idiosyncratic reactions—such as delayed hypersensitivity or myotoxicity linked to elevated CPK—remains unexplored in larger, diverse populations.

Pediatric and geriatric applications represent critical gaps. Suzetrigine's pharmacokinetics and safety have not been studied in patients under 18, limiting its use in pediatric surgery despite the rising need for opioid alternatives in this group.[17] In older adults, age-related declines in hepatic CYP3A4 activity and renal clearance could alter drug exposure, yet no Phase 3 subgroup analyses have addressed these pharmacokinetics in patients over 75—a demographic prone to polypharmacy and postoperative complications.[18] Anesthesiologists also lack guidance on suzetrigine's interactions with common perioperative agents, such as propofol, volatile anesthetics, or neuromuscular blockers, which could influence intraoperative pain management strategies.

Combination therapies offer a promising frontier. Combination of Suzitrigine with other non sparing opioids like gabapentin may be a possible future trial. However, optimal dosing, timing, and safety of such regimens—particularly in the context of regional anesthesia or ERAS protocols—require validation in larger cohorts. Another limitation is suzetrigine's lack of anti-inflammatory action, unlike NSAIDs, which may necessitate adjunctive agents in inflammatory pain states (e.g., postoperative edema), potentially complicating multimodal regimens.

A theoretical concern is the emergence of NaV1.8 polymorphisms or resistance mechanisms in chronic use, analogous to antibiotic resistance. While no evidence exists yet, genetic variability in NaV1.8 expression—reported in 5–10% of some populations—could affect responsiveness, a hypothesis untested in suzetrigine trials.[19] Real-world effectiveness studies in diverse surgical contexts (e.g., cardiothoracic, trauma, or burn patients) are also lacking, as current data skew toward elective procedures like abdominoplasty and

bunionectomy, which may not reflect the complexity of visceral or mixed pain syndromes encountered in critical care.

Finally, implementation barriers—cost, provider familiarity, and formulary restrictions—could limit suzetrigine's impact on the opioid epidemic. While its $15.50 per tablet price is justified by reduced opioid-related morbidity, economic analyses must account for upfront costs in resource-limited settings, a gap unaddressed in current literature.[4] Post-marketing surveillance, planned by Vertex for 2026, will be crucial to monitor rare AEs and refine patient selection criteria, ensuring suzetrigine's promise translates to clinical reality.

12. Methods of Literature Review

A structured literature search was performed using PubMed, Cochrane Library, ClinicalTrials.gov, and the FDA/Vertex Pharmaceuticals websites up to March 2025. Search terms included 'suzetrigine', 'VX-548', 'NaV1.8 inhibitor', 'acute pain', 'opioid-sparing', and 'perioperative analgesia'. Only peer-reviewed articles, systematic reviews, clinical trial records, and regulatory announcements with verifiable DOIs or URLs were included. This ensured that the present narrative review is based on reliable, PubMed-indexed, and publicly accessible data.

CONCLUSION

Suzetrigine redefines acute pain management by offering anesthesiologists a potent, opioid-sparing option that aligns with modern perioperative goals. Its selective NaV1.8 inhibition, rapid efficacy, and minimal toxicity profile address the opioid epidemic's root causes—addiction and overdose—while enhancing patient recovery. As research evolves, suzetrigine may expand beyond acute pain, cementing its status as a cornerstone of 21st-century analgesia.

Conflict of interest

None declared by the authors.

Authors Contribution

All authors took part in the literature search and manuscript preparation.

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