NOVEL NON-OPIOID STRATEGIES FOR ACUTE PAIN

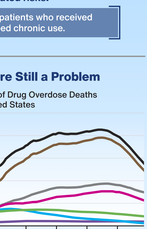
Examining the Data

Managing moderate-to-severe acute pain—especially following surgery or injury—remains a significant challenge. Although traditional therapies like NSAIDs and acetaminophen play a key role in treating mild-to-moderate pain, options for more severe cases are limited. Opioids, though effective, carry substantial risks related to tolerance, dependency, and abuse.

Advances in non-opioid strategies, including novel mechanisms like NaV1.8 sodium channel inhibition, are opening the door to safer, targeted approaches for acute pain relief.



Current Options for Management of Mild-to-Moderate Acute Pain



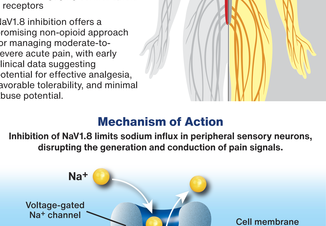
- **Acetaminophen**
- **COX-2 inhibitors** — celecoxib
- **NSAIDs** — ibuprofen, diclofenac, aspirin, naproxen
- **Sodium channel blockers** — lidocaine, mexiletine, carbamazepine

When these agents fail to provide sufficient relief, opioids are often introduced to manage more severe pain despite their associated risks.

8.6% of previously opioid-naïve patients who received a first prescription developed chronic use.

Even in 2025, Opioids Are Still a Problem

Monthly-Ending Provisional Number of Drug Overdose Deaths by Drug Class: United States



Given the limitations and risks associated with opioids, including dependency, tolerance, and AEs, there is a critical need for novel, targeted therapies.

Next in Analgesia: New Mechanisms for Pain Relief Beyond NSAIDs and Acetaminophen

NaV1.8 inhibitors fill a key therapeutic gap by targeting a specific voltage-gated sodium channel expressed predominantly in peripheral nociceptive neurons.

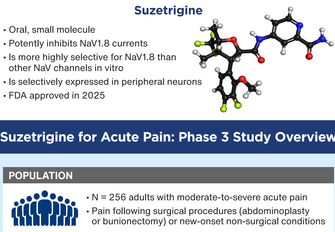
Opioids
—Act centrally
—Carry risks of sedation,depression, and addiction

NaV1.8 inhibitors
—Modulate pain transmission at its source
—Reduce neuronal excitability
—Dampen peripheral pain signaling without engaging central opioid receptors

NaV1.8 inhibition offers a promising non-opioid approach for managing moderate-to-severe acute pain, with early clinical data suggesting potential for effective analgesia, favorable tolerability, and minimal abuse potential.

Mechanism of Action

Inhibition of NaV1.8 limits sodium influx in peripheral sensory neurons, disrupting the generation and conduction of pain signals.



Suzetrigine

- Oral, small molecule
- Potently inhibits NaV1.8 currents
- Is more highly selective for NaV1.8 than other NaV channels in vitro
- Is selectively expressed in peripheral neurons
- FDA approved in 2025



Suzetrigine for Acute Pain: Phase 3 Study Overview

POPULATION

- N = 256 adults with moderate-to-severe acute pain
- Pain following surgical procedures (abdominoplasty or bunionectomy) or new-onset non-surgical conditions

TREATMENT PROTOCOL

Loading dose:
100 mg suzetrigine

Maintenance:
50 mg every 12 hours

Duration:
Up to 14 days or until pain resolution

ENDPOINTS

Primary:
Safety

Secondary:
PGA of effectiveness

SAFETY

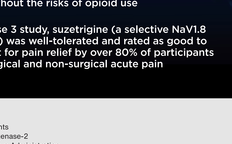
- Mild AEs: 27.7% (n = 71)
- Moderate AEs: 8.2% (n = 21)
- Nausea and headache were most common
- Well-tolerated overall



EFFICACY

83.2% of participants with moderate-to-severe pain reported **good, very good, or excellent** on the PGA at the end of suzetrigine treatment

Proportion of participants reporting good, very good, or excellent on PGA



Key Takeaways

- Traditional analgesics like acetaminophen, NSAIDs, and COX-2 inhibitors are often insufficient for managing moderate-to-severe acute pain, leading to reliance on opioids despite safety concerns
- NaV1.8 inhibitors offer a novel, targeted approach by modulating peripheral pain signaling—potentially delivering effective relief without the risks of opioid use
- In a phase 3 study, suzetrigine (a selective NaV1.8 inhibitor) was well-tolerated and rated as good to excellent for pain relief by over 80% of participants with surgical and non-surgical acute pain

Abbreviations
AEs: adverse events
COX-2: cyclooxygenase-2
FDA: Food and Drug Administration
NSAID: non-steroidal anti-inflammatory drug
PGA: Patient Global Assessment

References

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