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Review Article

Targeting NaV1.8 for Acute Pain: Mechanism, Biomarkers, and Early Clinical Evidence

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Abstract

Acute postoperative pain remains undertreated for many patients, sustaining exposure to opioids and associated harms. Voltage-gated sodium channel NaV1.8 is a key driver of nociceptor excitability under inflammatory conditions, making it an attractive peripheral target for analgesia. This narrative review synthesizes mechanistic, translational, and clinical evidence on selective NaV1.8 inhibition, focusing on suzetrigine (VX-548). We summarize channel physiology and binding mechanisms, appraise emerging pharmacodynamic biomarkers that index small-fiber activity, and examine early clinical data that suggest analgesic benefit with the potential to reduce opioid requirements. We also outline boundaries of effect where centrally maintained pain or small-fiber loss may limit response, and we discuss safety considerations relevant to perioperative use. Taken together, the evidence supports a precision-guided approach in which selective NaV1.8 blockade is paired with standardized sensory biomarkers and clinically meaningful outcomes such as pain trajectories, functional recovery, and opioid stewardship metrics. Suzetrigine's profile positions it as a promising candidate within a broader shift toward targeted, non-opioid analgesics that act at the source of nociceptive drive while preserving cognition and motor function.

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Introduction

Acute postoperative pain remains common despite multimodal regimens and continues to prolong recovery while sustaining exposure to opioids at a moment of heightened vulnerability (Yu et al., 2025). Therefore, a mechanism-defined alternative that reduces nociceptor drive without central nervous system liabilities is attractive. Voltage-gated sodium channels in peripheral sensory neurons are central to action-potential generation; among them, NaV1.8 uniquely sustains firing under inflammatory depolarization that inactivates other channels, making it a durable driver of peripheral excitability after tissue injury (Renganathan et al., 2001). Experimental and coding studies further indicate that NaV1.8 predominates at higher, inflammation-relevant temperatures, supporting the channel's relevance in surgical inflammation and hyperalgesia (Touska et al., 2018). Immune–neural signaling can amplify this contribution by altering expression and trafficking, broadening NaV1.8's functional footprint, and biasing the system toward hypersensitivity (Pinho-Ribeiro et al., 2017). Together, these observations motivate a peripherally selective strategy that dampens nociceptive input at its source while preserving cognition, arousal, and respiration.

Suzetrigine (VX-548) operationalizes this rationale as a highly selective NaV1.8 inhibitor that binds an allosteric site on the second voltage-sensing domain to stabilize the closed state and produce tonic block in human dorsal root ganglion neurons (Osteen et al., 2025). Early clinical studies report analgesic efficacy in acute pain with a favorable tolerability profile and no signal of abuse liability within observed windows, linking target biology to

bedside outcomes (Jones et al., 2023; Osteen et al., 2025). Translational anchors can make this approach actionable: standardized quantitative sensory testing provides thermal and mechanical endpoints that index small-fiber excitability. It can be paired with pain trajectories and opioid consumption to interpret target engagement in trials and practice (Rolke et al., 2006). Framed in this way, selective NaV1.8 inhibition offers a coherent path toward adequate perioperative analgesia aligned with opioid stewardship.

Methods

We conducted a structured literature review to evaluate NaV1.8 channel biology, selective sodium channel inhibition, and the development of suzetrigine for postoperative pain. Searches were performed in PubMed, Embase, and ClinicalTrials.gov between 2019 and 2025, with earlier foundational studies included for mechanistic context. MeSH terms and keywords used in the search were limited to concepts used in the manuscript: "Pain, Postoperative," "Analgesics, Non-Narcotic," "Sodium Channels," "Dorsal Root Ganglia," "Quantitative Sensory Testing," "NaV1.8," "suzetrigine," and "opioid-sparing." Reference lists of relevant articles were also screened to identify additional sources.

Eligible studies comprised mechanistic investigations of NaV1.8, translational biomarker reports, preclinical models, and clinical trials assessing analgesic efficacy, opioid-sparing outcomes, or safety. Exclusion criteria included commentary without primary data, patents without validation, and abstracts lacking reproducible methodology. Extracted findings were synthesized narratively to connect channel physiology, biomarker endpoints, and clinical outcomes into a translational framework for safer postoperative pain management.

Postoperative Pain Burden and the Case for Peripheral NaV1.8 Blockade

Postoperative and acute pain continue to be a significant clinical and public health issue. Notwithstanding the strategic use of multimodal analgesic regimens (NSAIDs, acetaminophen, adjuvants, etc.), a large portion of patients undergo inadequate pain control, prolonging discomfort, slowing functional recovery, and driving unplanned health care use. The consequence is continued exposure to opioid prescriptions with attendant risk of dependence and opioid harm. Latest reviews suggest a stubborn void in efficacy and limitations in the current non opioid modalities for moderate to severe acute postoperative pain (Yu et al., 2025), a gap that keeps perioperative care tethered to opioids and leaves clinicians with few credible routes to spare them without sacrificing analgesia.

Voltage-gated sodium (Nav) channels are vital in transmitting neuron action potentials. The NaV1.8 voltage-gated sodium channel, found in peripheral nociceptive neurons, is implicated in transmitting nociceptive signals (Jones et al., 2023). In nociceptors, NaV1.8 contributes a significant majority (80–90%) of the inward membrane current flowing during the rising phase of the action potential. This quantitative role positions the channel as a principal driver of excitability under inflammatory conditions. Fast TTX-sensitive Na+ channels are capable of producing all-or-none action potentials in some NaV1.8 (−/−) neurons, but, consistent with steady-state inactivation, electrogenesis in NaV1.8 (−/−) neurons is more depolarization-sensitive than in NaV1.8 (+/+) neurons, and in the absence of NaV1.8 is diminished with even modest depolarization. These results indicate that NaV1.8 is critically involved in action potential electrogenesis in C-type DRG neurons, pointing to a peripheral target where selective modulation could quiet nociceptive input at its source while limiting central nervous system exposure (Renganathan et al., 2001).

Suzetrigine (VX-548) is a potent and selective NaV1.8 inhibitor that has shown clinical efficacy and safety in several acute pain trials. Suzetrigine is ≥ 31,000-fold selective over all other NaV subtypes and 180 other molecular targets, a profile that aligns with the need for predictable perioperative use without broad off-target effects. Suzetrigine inhibits NaV1.8 by binding to the protein's second voltage-sensing domain (VSD2) to stabilize the channel in the closed state. The unique allosteric mechanism results in a tonic block of NaV1.8 and reduces pain signaling in primary human DRG sensory neurons, a mechanistic throughline from target to tissue that fits the clinical aim of steady, peripheral analgesia. Safety studies of suzetrigine reveal no adverse CNS, cardiovascular, or behavioral effects and no evidence of addictive potential or dependence, suggesting compatibility with enhanced recovery pathways that emphasize opioid minimization (Osteen et al., 2025).

Several physiological endpoints in nonhuman primates were employed to evaluate the analgesic and pharmacodynamic action of the NaV1.8 inhibitor compound, MSD199. Such pharmacodynamic biomarkers deliver substantial evidence on the in vivo action of NaV1.8 inhibition on peripheral pain fibers in primates. This work carries clear translational weight, linking target engagement to functional readouts in a species closer to humans and providing tools to inform dose selection, response assessment, and potentially patient stratification in clinical studies. Such findings could thus facilitate the success of translational drug discovery programs for superior pain therapeutics, while also providing insight into the primate biology of NaV1.8 inhibition (Vardigan et al., 2025).

In summary, the convergence of postoperative pain burden, the shortcomings of current regimens, and the necessity to reduce opioid exposure sets the stage for innovation. Suzetrigine, via peripherally selective NaV1.8 blockade and plausible biomarker-driven precision use, represents an advanced connecting mechanism to bedside practice, offering a route to adequate acute analgesia better aligned with safety, recovery, and public health goals.

NaV1.8 Upregulation in Inflammation and Nerve Injury

In inflammatory or nerve-injury contexts, NaV1.8 expression, trafficking, or functional contribution may rise or extend to larger sensory neurons, increasing peripheral excitability (Pinho-Ribeiro, Verri, & Chiu, 2017). As excitability escalates at the periphery, the pain generator becomes more accessible to selective modulation, bringing the therapeutic focus to the site where nociceptive drive is established and sustained. These peripherally targeted expression patterns affirm the proposal that selective inhibition of NaV1.8 will suppress nociceptive input without creating substantial CNS liabilities, aligning pharmacology with the clinical goal of reducing pain while preserving cognition, arousal, and respiration. NaV1.9 is the hallmark NaV subtype in S-type CMH fibers and is required to preserve responses to fast (1°C/s), but not slow (0.1°C/s), temperature rises. At the same time, NaV1.8 gains function above 46°C and promptly encodes the heat-resistant action potential (Touska et al., 2018). This division of labor across temperature ranges situates NaV1.8 as a key contributor when thermal and inflammatory stressors dominate, the very conditions that amplify postoperative and injury-related pain.

NaV1.8 vs Central Agents: Mechanistic Contrast

Selective NaV1.8 inhibition is expected to provide analgesia with minimal sedation, minor effect on respiratory drive, and low abuse liability because it modulates peripheral nociceptor excitability rather than directly engaging mesolimbic reward circuitry (Osteen et al., 2025; Kingwell, 2024). This profile contrasts with opioids and centrally acting sedatives such as benzodiazepines or some α2-adrenergic agents, which produce dose-dependent central nervous system depression, impaired ventilatory control, cognitive slowing, and addiction risk (Stein, 2016; Volkow & McLellan, 2016). In perioperative pathways that prioritize early mobilization and preservation of cognition, a peripherally restricted NaV1.8 inhibitor aligns with enhanced recovery goals by targeting the generator of nociceptive input while leaving arousal and motor function largely intact (Osteen et al., 2025).

Differences in the site of action and intracellular signaling explain both the therapeutic potential and the safety boundaries. NaV1.8 blockers act at peripheral nociceptors—including axon terminals, axons, and dorsal root ganglion somata—reducing sodium influx and preventing action potential initiation and propagation before signals enter the central nervous system (Jarvis et al., 2007; Renganathan et al., 2001). Opioids alleviate pain primarily through μ-opioid receptors within central networks; the same central activation underlies respiratory depression, sedation, and euphoria that drive misuse and dependence (Stein, 2016; Volkow & McLellan, 2016). At the cellular level, NaV1.8 blockade produces a direct biophysical reduction in excitability rapidly reversible with local drug clearance. In contrast, opioids signal through G-protein pathways that alter neurotransmitter release and network state across multiple brain regions (Williams et al., 2013). This contrast clarifies why selective channel inhibition is a plausible route to opioid-sparing analgesia in acute and postoperative settings.

Clinical Translation of NaV1.8 Selectivity

Selective peripheral NaV1.8 blockade is expected to relieve pain by decreasing stimulus-driven hypersensitivity to touch and heat, and ongoing or spontaneous pain caused by the continuous firing of peripheral pain-sensing neurons. In practical terms, that means fewer exaggerated responses to routine stimuli such as dressing changes or mobilization, alongside attenuation of background firing that prolongs discomfort at rest. Preclinical pharmacology and genetic knockout models show reduction of inflammatory and some neuropathic pain behaviors without apparent motor or cardiac conduction effects, which is congruent with the limited expression of NaV1.8 in these tissues (Jarvis et al., 2007; Renganathan et al., 2001). This selectivity narrows the safety calculus in settings where motor block or conduction abnormalities would otherwise limit use, making peripheral sodium channel modulation a more natural fit for enhanced recovery pathways. However, the extent of effectiveness may vary depending on the pain's mechanism. Syndromes driven by central sensitization or by ongoing central drivers (in the absence of peripheral nociceptor input) may be less sensitive. Sensory distortions (e.g., abnormal sensation of cold or reduced sensation of very high and low temperatures) can occur in specific patient groups (Luiz et al., 2019; Touska et al., 2018). Finally, as inflammatory signaling controls NaV1.8 activity, biomarker-directed selection (identification of patients with active peripheral sensitization) could increase responders and maximize opioid sparing clinical effects (Pinho-Ribeiro et al., 2017; Osteen et al., 2025). These boundaries argue for phenotype-guided deployment and clear patient counseling, so peripheral inhibitors are used where peripheral generators dominate and expectations reflect the biology being treated.

Discussion

Linking Mechanism, Biomarkers, and Meaningful Clinical Benefit

Selective NaV1.8 inhibition offers a mechanistic thread that runs from nociceptor physiology to endpoints that matter at the bedside. Target engagement in small fibers can be captured with quantitative sensory testing and related assays, which should map to reductions in pain intensity, improved tolerance of routine stimuli such as mobilization and dressing changes, and lower opioid requirements (Renganathan et al., 2001; Rolke et al., 2006). Treating mechanism, measurement, and outcome as a single continuum avoids siloing biology from practice and clarifies why this class has a credible route to opioid sparing in acute settings where peripheral generators dominate (Jones et al., 2023; Osteen et al., 2025).

Generalizability and Boundaries of Effect

Evidence to date is most substantial in acute nociceptive contexts where peripheral drivers are prominent. Extrapolation to chronic or centrally maintained pain states requires caution, since central sensitization or nerve loss may limit the leverage of a peripherally selective approach (Faber et al., 2023). Programs should prespecify phenotypes most likely to benefit and be explicit about settings where effect sizes may be smaller, including conditions marked by primary central mechanisms or prominent sensory distortions such as abnormal heat or cold perception (Luiz et al., 2019; Touska et al., 2018). Because benefit is most likely where peripheral generators dominate, trial endpoints should be chosen to reflect that biology.

Trial Design Priorities: Coprimary Biological and Clinical Endpoints

A practical next step is to pair a pharmacodynamic biomarker with a clinical endpoint in the same protocol. Coprimary testing can align a small-fiber measure, such as heat pain detection or temporal summation (standardized and z-scored against reference ranges), with a clinical outcome, such as pain-intensity area under the curve in the first 48–72 hours, time to independent mobilization, or total morphine milligram equivalents (Rolke et al., 2006). This structure keeps the program anchored to the mechanism while answering the clinical question most relevant to stewardship. It also reduces the risk that a signal is dismissed as nonspecific, since the biological readout and the bedside outcome rise or fall together (Jones et al., 2023).

Managing Heterogeneity in Sensory Biomarkers

Quantitative sensory testing is informative yet sensitive to site, device, and demographic factors. Reference datasets show region-specific norms and age and sex effects that can blur case-control contrasts when methods vary (Rolke et al., 2006). A coherent approach is to prespecify stimulus parameters, centralize device calibration, train raters, and analyze results as standardized scores against a locked normative set. Multi-domain panels can help, combining thermal with mechanical measures to reduce single-channel noise and better reflect small-fiber excitability's distributed physiology (Rolke et al., 2006). This improves the interpretability of pharmacodynamic shifts and lowers the risk of false positives or missed effects when devices or thresholds differ across sites.

Safety Characterization Beyond Early Trials

Short, well-controlled studies have shown encouraging tolerability for selective NaV1.8 inhibition, with no clear signals for central nervous system or cardiovascular toxicity in early work and no evidence of abuse liability in available reports (Jones et al., 2023; Osteen et al., 2025). Small samples and brief exposures cannot exclude rarer or delayed events. Longer observation windows and active surveillance are warranted to detect cardiac conduction changes, autonomic effects, or interactions in medically complex surgical populations. Trials should include scheduled electrocardiography, systematic neurologic and autonomic assessments, and follow-up beyond the acute postoperative period, with predefined stopping and adjudication rules for arrhythmia or neurocognitive concerns (Hinckley et al., 2020).

Publication Transparency and Evidentiary Balance

Because many NaV1.8 programs are industry-sponsored, selective visibility of favorable findings remains risky. Prospective registration with publicly accessible protocols, complete reporting of prespecified outcomes, and routine publication of negative and neutral studies are essential to avoid inflated effect estimates and delayed recognition of adverse events. Data sharing that permits independent reanalysis of responder definitions and biomarker cut points will strengthen the signal and speed consensus on how best to deploy these agents in practice (Faber et al., 2023; Rolke et al., 2006).

From Evidence to Use: A Practical Deployment Pathway

Taken together, these considerations support a pragmatic sequence for clinical adoption: identify phenotypes with peripheral hyperexcitability, confirm target engagement with a standardized small-fiber panel, and track linked clinical outcomes that include both pain control and opioid-stewardship metrics such as inpatient morphine milligram equivalents, discharge prescribing, refills, and new persistent use (Jones et al., 2023; Osteen et al., 2025;

Rolke et al., 2006). This pathway aligns mechanism with bedside needs and clarifies how a peripherally selective NaV1.8 inhibitor can be integrated into enhanced recovery protocols without compromising safety or masking heterogeneity in response.

Conclusion

Selective NaV1.8 inhibition with suzetrigine illustrates how a peripherally focused, mechanism-based approach can address acute postoperative pain while aligning with opioid stewardship. By dampening nociceptor excitability without impairing motor or tactile function, this strategy offers analgesia that targets the generator of pain rather than its downstream perception. Evidence supports analgesic benefit and a favorable tolerability profile, with the most significant promise in phenotypes where peripheral drivers are prominent. Important boundaries remain, including conditions characterized by central sensitization or small-fiber loss, and these warrant clear patient selection, standardized sensory biomarkers to verify target engagement, and careful safety surveillance. Moving forward, trials that pair pharmacodynamic markers with clinical endpoints such as pain trajectories, functional recovery, and opioid exposure will clarify where suzetrigine adds the most value. Framed in this way, NaV1.8 blockade represents a credible step toward more precise, safer perioperative analgesia and a measured contribution to reducing unnecessary opioid use.

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