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Breaking the pain barrier: how suzetrigine and selective sodium channel blockers are reshaping the future of opioid-free analgesia

Aleksandra Kaniak [AK]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
aleksandrakaniak@wp.pl
https://orcid.org/0009-0009-7775-7785

Julia Andrzejewska [JA]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
lek.julia.andrzejewska@gmail.com
https://orcid.org/0009-0001-9414-3664

Kacper Forszt [KF]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
forsztkacper@gmail.com
https://orcid.org/0009-0009-0384-7331

Eliza Gawron [EG]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
elizagawron13@gmail.com
https://orcid.org/0009-0009-9256-0366

Paula Hauzer [PH]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
hauzer.paula@gmail.com
https://orcid.org/0000-0002-3216-1525

Natalia Kulicka [NK]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
nataliakulicka@gmail.com
https://orcid.org/0009-0002-9321-1693

Agata Ogórek [AOg]
Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii,
plac Ludwika Hirszfelda 12, 53-413 Wrocław
agata.ogorek@dr.com
https://orcid.org/0009-0000-2916-5368

Alicja Osowska [AOs]
Wielospecjalistyczny Szpital Wojewódzki w Gorzowie Wielkopolskim,
ul. Dekerta 1, 66-400 Gorzów Wielkopolski
alicjaosowska13@gmail.com
https://orcid.org/0009-0002-4715-1757

Julianna Zielska [JZ]
Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii,
plac Ludwika Hirszfelda 12, 53-413 Wrocław
jzielska52@gmail.com
https://orcid.org/0000-0002-0210-5549

Dominika Ziółkowska [DZ]
Wojewódzki Szpital Specjalistyczny we Wrocławiu,
ul. H. Kamieńskiego 73a, 51-124 Wrocław
dominikagola9898@gmail.com
https://orcid.org/0009-0004-5715-9060

Abstract

Introduction:
Pain is a complex clinical challenge, with opioids traditionally used despite the risks of dependency and overdose. The need for safer alternatives has led to growing interest in voltage-gated sodium channels, particularly NaV1.7, NaV1.8, and NaV1.9, as targets for non-opioid pain management. The recent FDA approval of suzetrigine, a selective NaV1.8 inhibitor, marks a significant step forward in opioid-free pain treatment.

Aim of the Study:
This review aims to explore the role of voltage-gated sodium channels in pain transmission and evaluate their potential as therapeutic targets, highlighting suzetrigine as a promising new analgesic.

Material and Methods:
This review, based on data from PubMed, Google Scholar, and ClinicalTrials.gov, focuses on the pathophysiological role of sodium channels in pain and the latest research on selective blockers.

Results:
NaV1.7, NaV1.8, NaV1.9 play critical roles in various pain states. While clinical trials targeting NaV1.7 have delivered disappointing results, selective inhibition of NaV1.8 has shown greater promise, with suzetrigine demonstrating significant efficacy in clinical trials.

Conclusion:
Targeting voltage-gated sodium channels, especially NaV1.8, offers a promising strategy for the development of effective and safer analgesics. Suzetrigine marks a milestone, paving the way for a new class of non-opioid pain therapies with broad clinical application.

Keywords:
suzetrigine, selective voltage-gated sodium channels, pain management, NaV1.8, NaV1.7, NaV1.9

1. Introduction:

In 2020 the International Association for the Study of Pain (IASP) set a new definition of pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [1]. Pain is a complex and distressing symptom that significantly impacts the quality of life of millions of individuals worldwide.
It can arise from various sources, including injury, surgery, chronic diseases, and neurological conditions, leading to both physical and emotional suffering [2]. Given its widespread effects, the IASP advocates for chronic pain to be recognized not just as a symptom, but as a chronic condition requiring comprehensive treatment [3]. Despite advancements in medical science, effective pain management remains a challenging issue, with many patients experiencing inadequate relief or suffering from the side effects of existing treatments [4,5].

Globally, opioids have served as the foundation of pain management particularly for severe and chronic pain. However, the extensive use of opioids has led to an alarming rise
in addiction, misuse, and overdose deaths, causing a global public health crisis [6,7]. These

concerns have underscored the urgent need for alternative pain treatments that do not carry the risks associated with opioids. Consequently, there has been growing interest in the development of opioid-free pain medications, which could provide effective pain relief without the potential for addiction or other harmful side effects [8,9].

This paper aims to investigate the potential of selective sodium channel blockers, specifically those targeting NaV1.7, NaV1.8, and NaV1.9, as a promising and innovative class of analgesics in the rapidly evolving field of opioid-free pain management [10-12]. Voltage-gated sodium channels (NaVs) are crucial for initiating and transmitting pain signals in the peripheral nervous system. Among the nine known subtypes, NaV1.8 has become a particularly appealing therapeutic target due to its selective expression in nociceptive sensory neurons and its key role in pain signal transmission, especially under conditions of inflammation or neuropathy [13-15].

In January 2025, the U.S. Food and Drug Administration (FDA) approved suzetrigine (marketed as Journavx), the first selective NaV1.8 inhibitor, for the treatment of moderate to severe acute pain in adults. This milestone represents a significant advancement in the development of non-opioid analgesics [10,15]

This paper will review their mechanisms of action, clinical efficacy, and potential applications, with a focus on how these novel therapies might revolutionize pain treatment in the future.

2. The role of voltage-gated sodium channels in pain signaling: structure, function, and clinical relevance

The first reports of the existence of voltage-gated sodium channels and their role in generating action potentials date back to 1952, when Hodgkin and Huxley published their paper on "A quantitative description of membrane current and its application to conduction and excitation in nerve" which marked a significant milestone in neuroscience and pain research [11]. Voltage-gated ion channels are a type of transmembrane protein whose shape and function are influenced by changes in the membrane potential. They are essential in transforming receptor potentials into action potentials. The voltage-gated sodium channel (VGSC) family consists of nine subtypes, named NaV1.1 through NaV1.9, each encoded by

different genes and exhibiting unique patterns of expression and physiological functions [16-20].

The core of each VGSC is a large α-subunit, which forms the ion-conducting pore and determines the channel's electrophysiological characteristics. This α-subunit is organized into four homologous domains (labeled I–IV), each consisting of six transmembrane segments (S1–S6). The first four segments (S1–S4) in each domain create the voltage-sensing domain (VSD),while segments S5 and S6 contribute to the formation of the pore domain (PD), allowing sodium ions to pass selectively when the channel opens. This pore is activated by changes in membrane potential, causing a conformational shift in the protein that permits the influx of Na^+ ions. This sodium entry initiates depolarization and action potential firing, processes that are fundamental to the transmission of pain signals. Additionally, VGSCs are associated with accessory β subunits that influence gating behavior and channel surface expression, further supporting their role in neuronal excitability and nociception [16,21].

NaV1.7, NaV1.8, and NaV1.9 are three subtypes of voltage-gated sodium channels that are especially important in pain signaling, as they are primarily found in peripheral sensory neurons. These channels are highly expressed in nociceptive neurons located in the dorsal root ganglion (DRG), where they each contribute in specific ways to the process of transmitting pain signals [21].

NaV1.7, encoded by the *SCN9A* gene, plays a significant role in the initiation and propagation of pain signals. It is primarily expressed in nociceptive neurons of the dorsal root ganglion (DRG), trigeminal ganglia, olfactory epithelium, and sympathetic neurons. NaV1.7 has an ability to respond to small, subthreshold depolarizations and amplify weak stimuli to generate action potentials. This makes it crucial in deciding whether a pain signal will be transmitted to the central nervous system [16]. Genetic studies have highlighted its significance in human pain perception. Individuals with loss-of-function mutations in *SCN9A* exhibit congenital insensitivity to pain (CIP), meaning they cannot feel pain at all, although they can still perceive pressure and touch. On the contrary, gain-of-function mutations in the same gene are associated with several severe hereditary pain disorders, such as inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and small fiber neuropathy (SFN) [13,22-25].

NaV1.8, encoded by the *SCN10A* gene, is a tetrodotoxin-resistant voltage-gated sodium channel mainly expressed in peripheral sensory neurons, including small-diameter dorsal root ganglion (DRG) neurons and trigeminal ganglia [17]. It plays a central role in transmitting pain signals, particularly in inflammatory and neuropathic pain. Compared to other sodium channels, NaV1.8 activates at more depolarized membrane potentials and has slower inactivation kinetics, allowing it to remain active during prolonged or repeated stimulation even after other channels have inactivated. This unique biophysical profile enables NaV1.8 to support high-frequency firing and maintain excitability in hyperpolarized or inflamed neurons, seen during chronic pain states [21]. Functionally, NaV1.8 plays a key role
in shaping the rising phase and strength of action potentials in pain-sensing neurons. Once the electrical threshold is reached (typically set by NaV1.7), NaV1.8 helps amplify the pain signal, allowing it to be transmitted more effectively [17,21].

NaV1.9, encoded by the *SCN11A* gene, is a voltage-gated sodium channel primarily found in small-diameter sensory neurons of the dorsal root ganglia (DRG), trigeminal ganglia, and the enteric nervous system. Unlike other sodium channels, NaV1.9 produces slow, persistent sodium currents that do not initiate action potentials directly but amplify subthreshold stimuli and influence the resting membrane potential [26,27]. This makes NaV1.9 crucial in sensitizing nociceptors during inflammation and contributing to chronic pain and visceral hypersensitivity. Activating mutations in *SCN11A* can lead to hyperexcitability and painful conditions such as familial episodic pain and small fiber neuropathy [26]. NaV1.9 also plays a role in cold pain perception, as disruption of its expression has been shown to reduce sensitivity to both cold and inflammatory pain [17].

3. A review of efficacy, and challenges in the development of NaV1.7 inhibitors for pain management

Genetic studies have established a strong link between SCN9A mutations and pain disorders, with null mutations associated with congenital insensitivity to pain and activating mutations linked to conditions such as inherited erythromelalgia and paroxysmal extreme pain disorder [13]. This genetic evidence initially positioned NaV1.7 as a highly promising target for non-opioid pain therapies, generating significant interest in the pharmaceutical sector. However,

clinical investigations into NaV1.7 as a therapeutic target for pain management have produced a mixed picture, offering both promising insights and notable challenges [28].

Several compounds, including vixotrigine (BIIB074) and PF-05089771, advanced into clinical trials but ultimately failed to meet efficacy endpoints. Vixotrigine, although granted orphan drug status by the FDA for trigeminal neuralgia in 2013, did not demonstrate sufficient analgesic benefit in Phase II trials, leading to its discontinuation [13,28]. Similarly, PF-05089771, developed by Pfizer, was a highly selective NaV1.7 inhibitor designed to stabilize the inactivated state of the channel by interacting with its voltage-sensing domain. Despite promising preclinical data, it failed to significantly improve pain scores in
a randomized clinical trial for diabetic neuropathy, and its development was terminated [28,29]. Lacosamide is an FDA-approved drug that reduces nerve excitability by stabilizing the slow-inactivated state of Nav1.7 channels. Its effectiveness in treating small fiber neuropathy has been inconsistent, likely due to individual differences in how the sodium channels respond [28,30].

The limited clinical success of NaV1.7 inhibitors highlights several challenges in pain management. Chronic pain involves complex signaling networks, where NaV1.7 interacts with modulators like SUMOylation and PKC phosphorylation, which are not well-represented in preclinical models [17,31]. In models where the sodium channel NaV1.7 is knocked out, nociceptors remain active, but pain relief is achieved through increased signaling by the body's natural opioids. This enhanced opioid signaling reduces neurotransmitter release from nociceptor terminals, effectively dampening pain transmission [32]. This suggests a potential synergy between NaV1.7 inhibitors and low-dose opioids, offering new opportunities for more effective pain treatments while minimizing opioid-related risks. However, as treatment shifts towards targeting other sodium channels like NaV1.8 or NaV1.9, it becomes more complex due to the body's adaptive responses. This highlights the importance of developing combination therapies that take these changes into account.

Advances in structural biology have offered renewed optimism. In 2022, a high-resolution cryo-electron microscopy (cryo-EM) study of the human NaV1.7 channel provided detailed insights into its structure and the specific sites where toxins and small molecules bind [33]. These insights are expected to facilitate the development of next-generation NaV1.7 inhibitors,

which will more effectively modulate pain signaling while minimizing off-target effects. Ultimately, this progress is anticipated to lead to more effective pain treatments with fewer side effects.

4. A review of efficacy, challenges, and future directions in the development of NaV1.8 inhibitors for pain management: focus on suzetrigine

Voltage-gated sodium channel NaV1.8 plays a crucial role in transmitting pain signals from peripheral sensory neurons. Its selective expression in nociceptors and absence in the central nervous system (CNS) make it an attractive therapeutic target for developing non-opioid analgesics without affecting motor function or causing addiction [34]. Over the past two decades, multiple pharmaceutical companies have developed NaV1.8-selective inhibitors, but many failed to reach approval. Early attempts included compounds such as A-803467 by Abbott Laboratories, which demonstrated analgesic effects in preclinical models but was stopped due to poor pharmacokinetics and toxicity. Pfizer's PF-04531083 and PF-06305591 similarly showed promise in vitro but failed to progress in early clinical trials due to limited efficacy or adverse events [21,28]. Vertex Pharmaceuticals' first-generation inhibitor VX-150 progressed into Phase II trials and demonstrated proof-of-concept analgesia, but issues with high dosing requirements and tolerability, specifically dizziness and headaches, led to its discontinuation. The setbacks with VX-961 and VX-128 further illustrated the translational challenges of targeting NaV1.8 [17,28].

A turning point came with the development of suzetrigine (VX-548), a second-generation oral NaV1.8 inhibitor that combines potent and highly selective binding with improved pharmacokinetics. Mechanistically, suzetrigine distinguishes itself from traditional sodium channel blockers, which typically target open or inactivated states of the channel. Instead, it binds allosterically to the second voltage-sensing domain (VSD2) of NaV1.8 and preferentially stabilizes the channel in its closed state. This prevents the conformational shift required for channel opening during depolarization, thereby blocking the influx of sodium ions that initiates action potentials in nociceptors [15]. Suzetrigine is designed to reduce peripheral neuronal excitability without affecting the central nervous system. Notably, unlike opioids, it does not cross the blood-brain barrier, and both preclinical and human studies have shown no evidence of CNS-related side effects or addictive potential [15]. Clinical trials

involving over 2,400 participants have underscored its potential. In two Phase III trials, suzetrigine effectively reduced moderate-to-severe pain after abdominoplasty and bunionectomy surgeries, showing clear benefits over placebo in pain relief during the first two days after surgery [10]. Moreover, these benefits were achieved without inducing opioid-like side effects such as sedation, respiratory depression, or dependence. Common side effects were mild, including headache and constipation, and no serious adverse events were attributed to the drug [10,14].

Despite these encouraging outcomes, controversy has arisen over the generalizability of the results. Critics argue that the choice of surgical models, which are abdominoplasty and bunionectomy, limits the relevance of the findings to more extensive, prolonged, or complex pain scenarios such as orthopedic or spinal surgeries [35]. Furthermore, the short 48-hour study window and unreported use of adjunctive NSAIDs complicate interpretation of the drug's true efficacy. Concerns have been raised regarding the comparator arms in the study. Specifically, the active control used was a relatively low dose of hydrocodone- acetaminophen, which unexpectedly did not perform better than placebo in certain metrics. This outcome has led to questions about the validity of the control setup used in the study [35].

Regardless of some setbacks, the underlying mechanism of NaV1.8 inhibition remains strong, and suzetrigine could still offer meaningful therapeutic benefits for a wider range of pain conditions. For instance, preliminary data in diabetic peripheral neuropathy suggest efficacy, and ongoing trials aim to clarify its role in chronic, inflammatory, and visceral pain syndromes [36]. Studies have also suggested that NaV1.8 upregulation contributes to pain in conditions like irritable bowel syndrome and post-surgical nerve sensitization, raising the possibility of extending suzetrigine’s use into gastrointestinal or pelvic pain contexts [37]. Furthermore, its pharmacological profile suggests compatibility with local anesthetics or multimodal analgesia protocols. In vitro studies show additive effects when combined with agents like bupivacaine or ropivacaine, suggesting that suzetrigine could provide extended analgesia as regional anesthesia subside, making it potentially valuable in sports medicine, perioperative care, or enhanced recovery protocols [15].

With FDA approval, suzetrigine becomes the first in a new class of non-opioid analgesics to reach the market in decades, offering a potentially safer alternative for treating moderate-to-

severe acute pain. Its approval marks a significant step forward in pain management, though its broader role, particularly in chronic pain, neuropathies, and complex regional pain syndromes, will depend on results from ongoing and future studies.
The cautious optimism surrounding suzetrigine underscores both the promise and the complexity of targeting NaV1.8, a path shaped by years of scientific persistence, clinical trials, and the urgent need for opioid alternatives.

5. A review of efficacy, challenges, and future directions in the development of NaV1.9 inhibitors for pain management

NaV1.9 is an atypical voltage-gated sodium channel distinguished by its slow activation and inactivation kinetics, setting it apart from other subtypes. This unique functional profile suggests its primary role lies in sustaining depolarization rather than initiating action potentials [17]. Its special properties position NaV1.9 as a key contributor to inflammatory and visceral pain signaling [26]. The ability of anti-inflammatory drugs like naproxen to alleviate symptoms in patients with familial episodic pain syndrome (FEPS3) suggests a direct role of NaV1.9 in mediating inflammation-related hyperexcitability [27].

From a therapeutic perspective, NaV1.9 is an especially attractive drug target due to its restricted expression in peripheral nociceptors and low sequence similarity with other NaV channel subtypes, offering the potential for high selectivity with reduced risk of off-target side effects [38]. In preclinical models, knockout or pharmacologic inhibition of NaV1.9 reduces inflammatory pain, mechanical hypersensitivity, and cold nociception, supporting its role in chronic and stimulus-evoked pain states [17,39]. Moreover, recent work has highlighted NaV1.9's involvement in gastrointestinal (GI) function. Its expression in the myenteric and submucosal plexuses and altered activity in conditions such as Hirschsprung's disease and irritable bowel syndrome (IBS) suggest future opportunities for targeting NaV1.9 in visceral hypersensitivity and motility disorders [26,27].

Despite its therapeutic potential, NaV1.9 drug discovery has faced significant challenges due to difficulties in expressing the functional protein in vitro. However, recent advances in co-expression with β-subunits and understanding how proteins move across cell membranes have allowed for the development of more reliable cell-based systems, which can now efficiently

screen large numbers of potential drug candidates [28]. These technical breakthroughs pave the way for identifying NaV1.9-selective modulators, which could be game-changing for conditions with few effective treatments, such as neuropathic pain, chronic visceral pain, and even functional GI disorders. Looking ahead, NaV1.9 inhibitors may complement or replace traditional analgesics in selected patient populations, especially those with genetic or inflammatory drivers of pain. Additionally, understanding NaV1.9's dual role in sensory and autonomic regulation could offer novel treatment avenues not only for pain syndromes but for disorders like IBS, functional dyspepsia, or even interstitial cystitis. As tools for molecular targeting and patient stratification evolve, the development of NaV1.9 inhibitors holds great potential for expanding the therapeutic landscape of precision pain medicine.

6. Conclusion:

The ongoing struggle to effectively manage pain, combined with the limitations and risks of opioid use, has driven a significant transformation in the development of analgesic drugs.Voltage-gated sodium channels like NaV1.7, NaV1.8, and NaV1.9, have emerged as promising targets in the search for non-opioid alternatives. Although early attempts to develop NaV1.7 inhibitors as clinical therapies encountered significant obstacles, these challenges have helped us better understand the molecular basis of pain and highlighted
the importance of more sophisticated treatment strategies. These strategies include using combination therapies and tailoring treatments to individual patients.

The recent FDA approval of suzetrigine, a selective NaV1.8 inhibitor, represents
a groundbreaking advancement in this evolution. Its ability to provide analgesia without central nervous system involvement or addictive potential represents a major breakthrough in pain pharmacology. Although there has been some discussion about trial design and generalizability, the clinical success of suzetrigine underscores the potential of targeting peripherally expressed sodium channels as a viable strategy for managing acute pain.Ongoing research may expand its indications to chronic, inflammatory, or visceral pain conditions.

Also, research on NaV1.9 continues to shed new light on potential treatments for chronic and visceral pain syndromes. Advances in protein expression systems and screening technologies are simplifying the discovery of selective NaV1.9 modulators, which could eventually complement or even replace existing therapies for neuropathic and gastrointestinal-related pain.

In conclusion, these advancements indicate a future in precision pain medicine, where ion channel modulation can be customized to address specific pain phenotypes, genetic profiles, and clinical circumstances. As our comprehension of sodium channel biology expands, so does the potential to transform our approach to pain management, providing safer and more effective relief for millions of patients around the globe.

Author's Contribution Statement

Conceptualization: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Data Curation: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Formal Analysis: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Investigation: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Methodology: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Project Administration: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Resources: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Software: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Supervision: [AK]
Validation: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Visualization: [AK] [JA] [KF] [EG] [PH] [NK] [AOg] [AOs] [JZ] [DZ]
Writing-original Draft: [AK] [JA] [KF] [EG] [PH] [NK]

Writing-Review and Editing: [AK] [AOg] [AOs] [JZ] [DZ]
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