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SUZETRIGINE, A NEW SELECTIVE NaV1.8 INHIBITOR, AS A BREAKTHROUGH IN THE TREATMENT OF PAIN – A REVIEW ARTICLE

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ABSTRACT

Introduction and purpose: Pain, especially chronic, remains a major public health burden, often refractory to existing treatments and associated with significant individual and social costs. Recent advances in our understanding of voltage-gated sodium channels, particularly NaV1.8, have highlighted their pivotal role in nociceptive signal transmission in peripheral sensory neurons. Suzetrigine, a novel and highly selective NaV1.8 inhibitor, has emerged as a promising therapeutic candidate in this context.
Aim: This review aims to evaluate the efficacy, safety, and therapeutic potential of suzetrigine, a novel and selective NaV1.8 channel inhibitor, in pain management and to assess its role as a non-opioid alternative in modern pain treatment.
Materials and Methods: A comprehensive review of literature available in the PubMed database was performed. This process involved a thorough search of articles written in English containing the following key terms: "suzetrigine", "selective voltage-gated sodium channels", "pain", "pain management", "NaV1.8". The gathered data was then scrupulously examined and analyzed.
Conclusion: Suzetrigine with its high NaV1.8 channel selectivity and robust acute pain efficacy may represent a breakthrough in analgesia and pain management strategies. By minimizing off-target effects commonly associated with non-selective sodium channel blockers, suzetrigine offers a compelling alternative to opioids in treatment of postoperative pain. Its role in chronic and neuropathic pain remains under active investigation, with promising but not yet definitive results.

KEYWORDS

Suzetrigine, Selective Voltage-Gated Sodium Channels, Pain, Pain Management, NaV1.8

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Introduction.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" and further categorizes pain into acute and chronic (Raja et al., 2020). Acute pain is pain that lasts from a few seconds to three months, and is usually associated with actual or threatened tissue injury (Raja et al., 2020). Chronic pain, on the other hand, is pain that lasts or recurs for more than three months, and can remain for several years. The International Association for the Study of Pain (IASP) and the World Health Organization (WHO) classify chronic pain into categories such as primary, cancerous, neuropathic, or musculoskeletal pain. Chronic pain affects significant proportion of the population worldwide. Epidemiological studies show that the percentage of people with chronic pain ranges from 8% to 55% depending on the country. In industrialized countries such as the United States, about 20% of adults experience chronic pain. Similar results were achieved in Europe, including Poland (Raffaeli et al., 2021). In a large survey study conducted across 15 European countries and Israel, which included 46,394 adult respondents, 19% reported pain lasting more than 6 months. Out of the 4,839 individuals interviewed in-depth, 66% rated its intensity as moderate and 34% as severe (Breivik et al., 2006). That being said, chronic pain is one of the most common reasons patients visit healthcare professionals looking for help and relief. In the United States, the annual costs associated with chronic pain are estimated at $560 billion to $635 billion, including both direct costs (treatment, hospitalizations) and indirect costs (loss of productivity, disability) (Gaskin & Richard, 2012). It imposes enormous costs on healthcare systems. Chronic pain has also significant impact on the quality patients' life. People with chronic pain often experience limitations in daily activities, sleep disorders, depression, and social isolation. The already mentioned survey study indicates that out of 4,839 individuals with chronic pain interviewed in-depth, 61% had difficulty to work, and 19% lost their jobs because of the pain (Breivik et al., 2006). Treating pain is crucial for several interconnected biological, psychological, social, economic as well as ethical reasons.

Although medical science has made significant progress, managing pain effectively continues to be a major challenge, as many patients either do not get sufficient relief or experience adverse side effects of current treatments.

Aim

This review aims to provide a comprehensive overview of the pharmacology of NaV1.8, its contribution to pain pathophysiology, and mechanism of targeting this channel selectively. We discuss the clinical evidence supporting suzetrigine's efficacy, selectivity, and favorable safety profile, comparing it to traditional analgesics.

Materials and Methods

A comprehensive review of literature available in the PubMed database was performed. This process involved a thorough search of articles written in English containing the following key terms: "suzetrigine", "selective voltage-gated sodium channels", "pain", "pain management", "NaV1.8". The literature was critically reviewed and selected based on relevance to the aim of the paper. The gathered data was then scrupulously examined and analyzed in order to synthesize current scientific knowledge on suzetrigine and its efficacy, comparing it to traditional analgesics.

Analysis of literature

Traditional methods of chronic pain treatment

The traditional pharmaceuticals used to treat pain can be divided into four main groups: non-opioid analgesics, opioid analgesics, antidepressants and anticonvulsants (adjuvant analgesics). Moreover, some sources mention also a fifth group - the corticosteroids (Alorfi, 2023).

Opioids

Opioids, such as morphine and oxycodone, are generally used to treat moderate to severe pain. However, they are associated with a range of adverse effects. Their long-term use is associated with the risk of addiction, tolerance, and side effects such as respiratory depression and constipation. Additionally, in some cases they can lead to hyperalgesia, or increased sensitivity to pain (Alorfi, 2023; Rosenblum et al., 2008).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs, such as ibuprofen and naproxen, are often used to treat pain, especially of an inflammatory origin. They are commonly used for mild to moderate pain management. However, similarly to the previous group, they are not free of side effects. Their long-term use can lead to damage to the stomach lining, gastrointestinal bleeding, renal impairment or cardiovascular disorders (Alorfi, 2023; Ghlichloo & Gerriets, 2025).

Antiepileptics and antidepressants

Antiepileptics (e.g. gabapentin, pregabalin) and antidepressants (e.g. amitriptyline, fluoxetine) are commonly used as the adjuvant analgesics. They show great efficacy in the treatment of neuropathic pain. Moreover, they improve sleep quality and reduce anxiety and depression, all of which are common comorbidities in patients with chronic pain. Although they can be effective, their use is also associated with side effects such as sedation, dizziness, drowsiness, cognitive impairment, xerostomia and weight gain (Alorfi, 2023; Maizels & McCarberg, 2005a; Sullivan & Robinson, 2006).

Corticosteroids

Corticosteroids, such as prednisone and dexamethasone, reduce the production of pain-inducing substances and inflammatory mediators, such as prostaglandins, leukotrienes, and cytokines, therefore they can be used in the management of inflammatory pain. Additionally, this pharmacological group stands out for its immunosuppressive effects, which can be beneficial in the management of pain associated with autoimmune diseases, such as rheumatoid arthritis. However, long-term use may lead to weight gain, fluid retention, hypertension, gastrointestinal disturbances, osteoporosis, muscle weakness, and increased risk of infections (Alorfi, 2023; Benzon et al., 2025).

Current methods of treating pain often do not provide the expected relief to patients. Many of the available therapies are associated with high risk of adverse effects, and their effectiveness is limited. Furthermore, there are no therapies that are effective for all patients, which emphasizes the need to individualize treatment and search for new, more effective therapeutic methods.

NaV Sodium Channels as Therapeutic Targets in Pain Management

Voltage-Gated Sodium Channels (VGSCs) play a key role in the generation and conduction of action potentials in neurons. In the context of pain, the NaV1.7 and NaV1.8 subtypes are particularly relevant. They are mainly expressed in sensory neurons of the dorsal root ganglia (DRG) and are involved in the transmission of nociceptive signals (Bennett et al., 2019; Wang et al., 2024).

For a long time, NaV1.7 was regarded as a promising target for pain therapy due to the scientific evidence showing that mutations increasing its activity lead to heightened pain sensitivity, while loss-of-function mutations result in reduction of pain perception. This spurred significant interest of major pharmaceutical companies in developing the NaV1.7-selective drugs. Unfortunately, despite the extensive research and development efforts by both academic institutions and the pharmaceutical industry, no NaV1.7-targeting compound has yet received regulatory approval for pain management (Mulcahy et al., 2019; Wang et al., 2024). NaV1.8 is a tetrodotoxin (TTX)-resistant sodium channel encoded by the SCN10A gene. It is specifically expressed in DRG neurons and trigeminal ganglia (TG), particularly in small, unmyelinated C-fibers, which are responsible for pain transmission (Mulcahy et al., 2019; Theile & Cummins, 2011; Wang et al., 2024). NaV1.8 is characterized by slow inactivation and rapid recovery of activation, which allows generation and maintenance of action potentials even under depolarizing conditions that inactivate other sodium channels (Wang et al., 2024). Due to these properties, NaV1.8 plays a key role in pain transmission, especially in inflammatory and neuropathic conditions and has become an attractive target for new pain therapies. Both NaV1.7 and NaV1.8 play a significant role in pain transmission. However, it has been observed that NaV1.7 blockade can lead to undesirable effects, due to its broader expression in different types of neurons. At the same time, NaV1.8, due to its restricted expression to nociceptive neurons, offers a more selective therapeutic target, minimizing the risk of adverse effects (Bennett et al., 2019; Hameed, 2019; Kasimova et al., 2016; Li et al., 2024; Mulcahy et al., 2019; Wang et al., 2024).

Suzetrigine – an innovative compound for pain treatment

Suzetrigine (brand name: Journavx), also known by its code name VX-548, was developed by Vertex Pharmaceuticals as an innovative, non-opioid pain reliever (Bertoch et al., 2025; Hu et al., 2025). The company, known for its research into gene therapies and cystic fibrosis drugs, has focused its research on developing an effective alternative to opioids in the pain treatment. Suzetrigine belongs to the chemical class of selective sodium channel inhibitors NaV1.8. It is a small molecule that works by selectively blocking the NaV1.8 channel responsible for the transmission of pain signals in sensory neurons. Unlike opioids, suzetrigine does not interact with opioid receptors in the central nervous system, which minimizes the risk of addiction and other adverse effects associated with the opioids (Bertoch et al., 2025; Hu et al., 2025).

Mechanism of action of suzetrigine

Suzetrigine (VX-548), as mentioned before, is a highly selective inhibitor of the NaV1.8 sodium channel, which plays a key role in transmission of pain signals in the peripheral nervous system. Studies confirmed that suzetrigine exhibits >31,000-fold greater selectivity for NaV1.8 compared to other sodium channel subtypes and 180 other molecular targets, minimizing the risk of adverse effects associated with nonselective sodium channel blockade (Osteen et al., 2025). Suzetrigine acts via a unique allosteric mechanism by binding to the second voltage sensor domain (VSD2) of the NaV1.8 channel. This binding stabilizes the closed state of the channel, leading to tonic inhibition and reduced transmission of pain signals in sensory neurons of the dorsal root ganglia (DRG) (Hu et al., 2025; Osteen et al., 2025). This mechanism of action is distinct from traditional analgesics, which often act by nonselectively blocking sodium channels or modulating receptors in the central nervous system. The NaV1.8 channel is selectively expressed in peripheral nociceptive neurons and is not present in the brain or spinal cord. As a result, suzetrigine acts exclusively at the peripheral level, blocking the transmission of pain signals without affecting cognitive functions or the risk of addiction (Bertoch et al., 2025). Clinical assessments have not demonstrated any adverse effects of suzetrigine related to the central nervous, cardiovascular systems or behavioral function (Osteen et al., 2025).

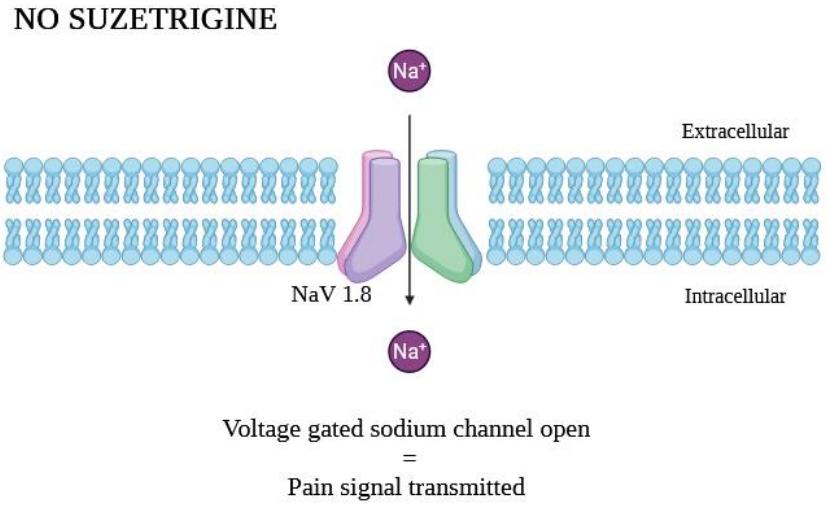

Fig. 1.

Figure 1 shows processes when suzetrigine is not present. The voltage gated sodium channels remain open, allowing pain signals to propagate, resulting in continued pain perception.

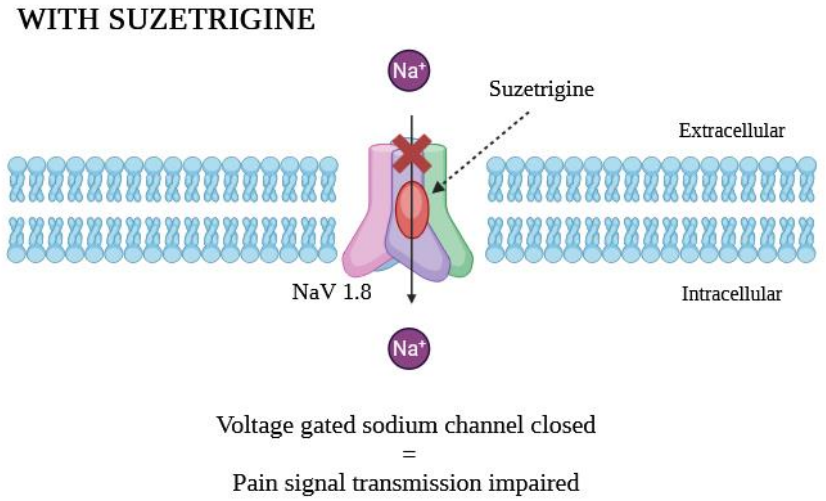

Fig. 2.

Figure 2 shows the mechanizm suzetrigine acts. Suzetrigine binds to the NaV1.8 sodium channel, particularly to its second voltage sensor domain (VSD2). By doing so, it stabilizes the channel in its closed state, preventing the influx of sodium ions into the cell. It reduces neuronal excitability and inhibits the transmission of pain signals.

Discovery and Development of Suzetrigine (VX-548)

In the early 1950s, research performed by Hodgkin and Huxley resulted in the identification of voltage-gated sodium (NaV) channels and marked the discovery of action potentials. The following decades led to identification of voltage-gated sodium (NaV) channels as a key component in the transmission of pain signals (Catterall, 2023). Particular attention has been paid to the NaV1.8 subtype, which is selectively expressed in nociceptive neurons of the dorsal root ganglia (DRG) and plays an important role in the transmission of pain signals in the peripheral nervous system (Bennett et al., 2019, p. 1; Catterall, 2023; Wang et al., 2024).

Vertex Pharmaceuticals began searching for selective NaV1.8 inhibitors with the goal to develop effective and safe analgesics. Several compounds, including VX-150, were developed through screening and

structural optimization, which showed promising pharmacological properties (Vaelli et al., 2024). VX-150 demonstrated significant relief of pain in patients examined during the clinical trials and proved its concept, however, it required high doses and frequent administrations to achieve the desired effect (Hijma et al., 2021). The failures of VX-961 and VX-128 highlighted challenges in successful transition of the NaV1.8-targeted therapies from preclinical models to effective treatments (Hijma et al., 2022). Further chemical modifications and biological testing led to the identification of VX-548 (suzetrigine) which presented high selectivity for NaV1.8 channels and a favorable pharmacokinetic profile (Vaelli et al., 2024). Vertex Pharmaceuticals continued with a series of clinical studies to assess the efficacy and safety of suzetrigine. During the phase 1, studies on healthy volunteers showed that suzetrigine was well tolerated and demonstrated favorable safety, dosing and pharmacocinetic profile, clearing the way for efficacy studies (Osteen et al., 2025). In phase 2, randomized, double-blind, placebo-controlled studies were performed, examining patients aged from 18 to 75 years undergoing surgery (e.g. abdominoplasty, bunionectomy). The results showed that, compared to a placebo, suzetrigine at a 100 mg loading dose followed by a 50 mg dose every 12 hours within 48 hours post-surgery resulted in statistically significant and clinically meaningful reductions in pain (Hu et al., 2025; Osteen et al., 2025). In the subsequent phase 3, two randomized, double-blind, placebo- and active-controlled (hydrocodone/acetaminophen) studies (NAVIGATE-1 and NAVIGATE-2) included a total of over 2000 post-surgical patients (e.g., abdominoplasty, bunionectomy) from 18 to 80 years old. Participants treated with VX-548 received an initial dose of 100 mg, followed by 50 mg every 12 hours for three doses. Comparative groups received either hydrocodone bitartrate/acetaminophen (5 mg/325 mg) given every six hours over 42 hour time period, or a placebo (Bertoch et al., 2025; Osteen et al., 2025). Suzetrigine significantly alleviated moderate-to-severe pain after abdominoplasty and bunionectomy procedures, demonstrating a clear advantage over placebo in reducing pain during the initial 48 hours post-surgery. Interestingly, VX-548 did not demonstrate superiority over hydrocodone/acetaminophen on $SPID_{48}$ (the time-weighted sum of the pain-intensity difference over the *48*-hour period) in either surgical trial. Another endpoint assessed, time to meaningful pain relief (defined as a ≥2-point reduction in the numeric pain rating scale), favored VX-548. The median time to pain relief was 2 hours in case of abdominoplasty and 4 hours in case of bunionectomy patients, compared to 8 hours for placebo in both trials (Bertoch et al., 2025; Osteen et al., 2025). Additionally, a separate safety and effectiveness, single-arm phase 3 study involving 256 patients with various surgical and non-surgical pain conditions evaluated suzetrigine over a 14-day time period. Participants received 100 mg for one dose followed by 50 mg every 12 hours and were evaluated for up to 14 days. Effectiveness was measured by a Patient Global Assessment. 83.2% of patients evaluated the treatment as good, very good or excellent for treating their pain (Bertoch et al., 2025; Hu et al., 2025; Osteen et al., 2025). The most common adverse effects were mostly mild to moderate, and included itching, muscle spasms, elevated blood creatine phosphokinase levels, and rash (Hu et al., 2025). Interestingly, the rate of adverse events was slightly lower in VX-548-treated patients than in those receiving placebo (abdominoplasty: 50% vs. 56.3%; bunionectomy: 31% vs. 35.2%) (*Vertex Announces Positive Results From the VX-548 Phase 3 Program for the Treatment of Moderate-to-Severe Acute Pain | Vertex Pharmaceuticals Newsroom*, n.d.). Overall, VX-548 delivered statistically and clinically meaningful pain relief in both post-surgical trials, with a favorable safety profile across a range of acute pain conditions (Osteen et al., 2025). Vertex continues to investigate the use of suzetrigine in treatment of neuropathic pain, including diabetic neuropathy and lumbosacral radiculopathy. Suzetrigine has already entered a phase 3 clinical trial for the treatment of painful diabetic peripheral neuropathy, and a phase 2 trial for treating painful lumbosacral radiculopathy have been already completed, with the potential to move into a phase 3 trials (*Vertex Announces Results From Phase 2 Study of Suzetrigine for the Treatment of Painful Lumbosacral Radiculopathy | Vertex Pharmaceuticals Newsroom*, n.d.; *Vertex to Present Phase 3 Data Highlighting Suzetrigine's Potential as a First-in-Class, Highly Selective Pain Signal Inhibitor at the American Society of Anesthesiologists Annual Meeting | Vertex Pharmaceuticals Newsroom*, n.d.). If clinical studies targeting these new indications are successful, the pain-relieving applications of NaV1.8 inhibitors will become more diverse, benefiting a broader range of patients.

FDA Approval

Based on clinical trial results, suzetrigine was approved by the FDA in January 2025 for the treatment of moderate to severe acute pain in adults. It is the first new class of pain medication approved by the FDA in more than 20 years, offering an alternative to opioids without the risk of addiction (Keam, 2025).

Comparison of Suzetrigine with Other Pain Management Strategies

Opioids

Opioids such as morphine or oxycodone are effective in treating acute pain, but their use is associated with numerous adverse effects, among them the risk of addiction and respiratory depression (Wojtasik-Bakalarz et al., 2021). Suzetrigine, as a selective NaV1.8 channel inhibitor, offers an alternative without the risk of addiction, acting only on peripheral nociceptive neurons, minimizing the impact on the central nervous system (Bertoch et al., 2025).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs such as ibuprofen or naproxen are commonly used to treat inflammatory pain, but their long-term use can lead to adverse effects such as damage of the gastric mucosa, kidney dysfunction (Harirforoosh et al., 2013). Suzetrigine, acting selectively on the NaV1.8 channel, offers effective pain management without these risks (Osteen et al., 2025).

Antiepileptics and antidepressants

Antiepileptics (e.g. gabapentin) and antidepressants (e.g. amitriptyline) are used to treat neuropathic pain, but their efficacy is limited and side effects, such as drowsiness and dizziness, are common (Maizels & McCarberg, 2005b). Suzetrigine, by selectively acting on the NaV1.8 channel, may offer a more effective and better tolerated treatment for neuropathic pain.

Conclusions

Suzetrigine (VX-548), developed by the Vertex Pharmaceuticals, was approved by the FDA in January 2025 for the treatment of moderate to severe acute pain in adults. Thanks to its unique mechanism of action, suzetrigine offers effective pain management without the risk of addiction, which is crucial given the opioid crisis we are currently facing. Its selectivity for NaV1.8 and its action limited to the peripheral nervous system make it a promising alternative to traditional analgesics, especially in the treatment of acute and potentially chronic pain. However, further studies need to be performed to fully evaluate and asses its efficacy in different types of chronic pain.

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REFERENCES

1. Alorfi, N. M. (2023). Pharmacological Methods of Pain Management: Narrative Review of Medication Used. *International Journal of General Medicine*, *16*, 3247–3256. https://doi.org/10.2147/IJGM.S419239
2. Bennett, D. L., Clark, A. J., Huang, J., Waxman, S. G., & Dib-Hajj, S. D. (2019). The Role of Voltage-Gated Sodium Channels in Pain Signaling. *Physiological Reviews*, *99*(2), 1079–1151. https://doi.org/10.1152/physrev.00052.2017
3. Benzon, H. T., Elmofty, D., Shankar, H., Rana, M., Chadwick, A. L., Shah, S., Souza, D., Nagpal, A. S., Abdi, S., Rafla, C., Abd-Elsayed, A., Doshi, T. L., Eckmann, M. S., Hoang, T. D., Hunt, C., Pino, C. A., Rivera, J., Schneider, B. J., Stout, A., … Shanthanna, H. (2025). Use of corticosteroids for adult chronic pain interventions: Sympathetic and peripheral nerve blocks, trigger point injections - guidelines from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, the American Society of Interventional Pain Physicians, and the International Pain and Spine Intervention Society. *Regional Anesthesia and Pain Medicine*, rapm-2024-105593. https://doi.org/10.1136/rapm-2024-105593
4. Bertoch, T., D'Aunno, D., McCoun, J., Solanki, D., Taber, L., Urban, J., Oswald, J., Swisher, M. W., Tian, S., Miao, X., Correll, D. J., Negulescu, P., Bozic, C., & Weiner, S. G. (2025). Suzetrigine, a Nonopioid Na V 1.8 Inhibitor for Treatment of Moderate-to-severe Acute Pain: Two Phase 3 Randomized Clinical Trials. *Anesthesiology*, *142*(6), 1085–1099. https://doi.org/10.1097/ALN.0000000000005460
5. Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain (London, England)*, *10*(4), 287–333. https://doi.org/10.1016/j.ejpain.2005.06.009
6. Catterall, W. A. (2023). Voltage gated sodium and calcium channels: Discovery, structure, function, and Pharmacology. *Channels*, *17*(1), 2281714. https://doi.org/10.1080/19336950.2023.2281714
7. Gaskin, D. J., & Richard, P. (2012). The economic costs of pain in the United States. *The Journal of Pain*, *13*(8), 715–724. https://doi.org/10.1016/j.jpain.2012.03.009
8. Ghlichloo, I., & Gerriets, V. (2025). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK547742/
9. Hameed, S. (2019). Nav1.7 and Nav1.8: Role in the pathophysiology of pain. *Molecular Pain*, *15*, 1744806919858801. https://doi.org/10.1177/1744806919858801
10. Harirforoosh, S., Asghar, W., & Jamali, F. (2013). Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. *Journal of Pharmacy & Pharmaceutical Sciences: A Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne Des Sciences Pharmaceutiques*, *16*(5), 821–847. https://doi.org/10.18433/j3vw2f
11. Hijma, H. J., Siebenga, P. S., de Kam, M. L., & Groeneveld, G. J. (2021). A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Pharmacodynamic Effects of VX-150, a Highly Selective NaV1.8 Inhibitor, in Healthy Male Adults. *Pain Medicine (Malden, Mass.)*, *22*(8), 1814–1826. https://doi.org/10.1093/pm/pnab032
12. Hijma, H. J., van Brummelen, E. M. J., Siebenga, P. S., & Groeneveld, G. J. (2022). A phase I, randomized, double-blind, placebo-controlled, single- and multiple dose escalation study evaluating the safety, pharmacokinetics and pharmacodynamics of VX-128, a highly selective Nav 1.8 inhibitor, in healthy adults. *Clinical and Translational Science*, *15*(4), 981–993. https://doi.org/10.1111/cts.13215
13. Hu, S., Lyu, D., & Gao, J. (2025). Suzetrigine: The first Nav1.8 inhibitor approved for the treatment of moderate to severe acute pain. *Drug Discoveries & Therapeutics*, *19*(1), 80–82. https://doi.org/10.5582/ddt.2025.01010
14. Kasimova, M. A., Granata, D., & Carnevale, V. (2016). Voltage-Gated Sodium Channels: Evolutionary History and Distinctive Sequence Features. *Current Topics in Membranes*, *78*, 261–286. https://doi.org/10.1016/bs.ctm.2016.05.002
15. Keam, S. J. (2025). Suzetrigine: First Approval. *Drugs*, *85*(6), 845–851. https://doi.org/10.1007/s40265-025-02178-w
16. Li, Z., Wu ,Qiurong, & and Yan, N. (2024). A structural atlas of druggable sites on Nav channels. *Channels*, *18*(1), 2287832. https://doi.org/10.1080/19336950.2023.2287832
17. Maizels, M., & McCarberg, B. (2005a). Antidepressants and antiepileptic drugs for chronic non-cancer pain. *American Family Physician*, *71*(3), 483–490.
18. Maizels, M., & McCarberg, B. (2005b). Antidepressants and antiepileptic drugs for chronic non-cancer pain. *American Family Physician*, *71*(3), 483–490.
19. Mulcahy, J. V., Pajouhesh, H., Beckley, J. T., Delwig, A., Bois, J. D., & Hunter, J. C. (2019). Challenges and Opportunities for Therapeutics Targeting the Voltage-Gated Sodium Channel Isoform NaV1.7. *Journal of Medicinal Chemistry*, *62*(19), 8695–8710. https://doi.org/10.1021/acs.jmedchem.8b01906
20. Osteen, J. D., Immani, S., Tapley, T. L., Indersmitten, T., Hurst, N. W., Healey, T., Aertgeerts, K., Negulescu, P. A., & Lechner, S. M. (2025). Pharmacology and Mechanism of Action of Suzetrigine, a Potent and Selective NaV1.8 Pain Signal Inhibitor for the Treatment of Moderate to Severe Pain. *Pain and Therapy*, *14*(2), 655–674. https://doi.org/10.1007/s40122-024-00697-0

21. Raffaeli, W., Tenti, M., Corraro, A., Malafoglia, V., Ilari, S., Balzani, E., & Bonci, A. (2021). Chronic Pain: What Does It Mean? A Review on the Use of the Term Chronic Pain in Clinical Practice. *Journal of Pain Research*, *14*, 827–835. https://doi.org/10.2147/JPR.S303186
22. Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F. J., Mogil, J. S., Ringkamp, M., Sluka, K. A., Song, X.-J., Stevens, B., Sullivan, M. D., Tutelman, P. R., Ushida, T., & Vader, K. (2020). The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain*, *161*(9), 1976–1982. https://doi.org/10.1097/j.pain.0000000000001939
23. Rosenblum, A., Marsch, L. A., Joseph, H., & Portenoy, R. K. (2008). Opioids and the treatment of chronic pain: Controversies, current status, and future directions. *Experimental and Clinical Psychopharmacology*, *16*(5), 405–416. https://doi.org/10.1037/a0013628
24. Sullivan, M. D., & Robinson, J. P. (2006). Antidepressant and anticonvulsant medication for chronic pain. *Physical Medicine and Rehabilitation Clinics of North America*, *17*(2), 381–400, vi–vii. https://doi.org/10.1016/j.pmr.2005.12.006
25. Theile, J. W., & Cummins, T. R. (2011). Recent developments regarding voltage-gated sodium channel blockers for the treatment of inherited and acquired neuropathic pain syndromes. *Frontiers in Pharmacology*, *2*, 54. https://doi.org/10.3389/fphar.2011.00054
26. Vaelli, P., Fujita, A., Jo, S., Zhang, H.-X. B., Osorno, T., Ma, X., & Bean, B. P. (2024). State-Dependent Inhibition of Nav1.8 Sodium Channels by VX-150 and VX-548. *Molecular Pharmacology*, *106*(6), 298–308. https://doi.org/10.1124/molpharm.124.000944
27. *Vertex Announces Positive Results From the VX-548 Phase 3 Program for the Treatment of Moderate-to-Severe Acute Pain | Vertex Pharmaceuticals Newsroom*. (n.d.). Retrieved June 19, 2025, from https://news.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-vx-548-phase-3-program
28. *Vertex Announces Results From Phase 2 Study of Suzetrigine for the Treatment of Painful Lumbosacral Radiculopathy | Vertex Pharmaceuticals Newsroom*. (n.d.). Retrieved June 19, 2025, from https://news.vrtx.com/news-releases/news-release-details/vertex-announces-results-phase-2-study-suzetrigine-treatment
29. *Vertex to Present Phase 3 Data Highlighting Suzetrigine's Potential as a First-in-Class, Highly Selective Pain Signal Inhibitor at the American Society of Anesthesiologists Annual Meeting | Vertex Pharmaceuticals Newsroom*. (n.d.). Retrieved June 19, 2025, from https://news.vrtx.com/news-releases/news-release-details/vertex-present-phase-3-data-highlighting-suzetrigines-potential
30. Wang, H., Huang, J., Zang, J., Jin, X., & Yan, N. (2024). Drug discovery targeting Nav1.8: Structural insights and therapeutic potential. *Current Opinion in Chemical Biology*, *83*, 102538. https://doi.org/10.1016/j.cbpa.2024.102538
31. Wojtasik-Bakalarz, K., Woroń, J., & Siwek, M. (2021). Adverse effects of opioid analgesics from the central nervous system. *Palliative Medicine in Practice*, *15*(3), Article 3. https://doi.org/10.5603/PMPI.2021.0013