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Review Article

Suzetrigine and Targeted Nav1.8 Inhibition for Acute Pain Management

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Abstract

The lack of successful novel analgesics in recent decades means that opioids are still commonly prescribed to treat acute pain. However, suzetrigine (trade name: JOURNAX), developed by Vertex Pharmaceuticals, is a new oral Nav1.8 (voltage-gated sodium channel) inhibitor that is trying to flip the script. Suzetrigine was recently approved by the FDA in January 2025 to treat moderate-to-severe acute pain. Two Phase II studies showcased that suzetrigine significantly reduced pain scores compared to placebo in patients following their abdominoplasty or bunionectomy procedures. Data from Phase II and Phase III trials also suggested that suzetrigine is generally safe, with the most common adverse side effects being headaches and constipation. There is also no evidence to suggest that suzetrigine has addictive properties in animal models and from systemic analysis of clinical subjects so far. However, we have yet to test the effects of prolonged suzetrigine usage in patients with chronic pain. This review seeks to put into context the current literature on suzetrigine, scrutinize its testing, and ask questions about its future.

Keywords: Suzetrigine, VX-548, Nav1.8 inhibitor, Non-opioid analgesics, Acute pain management, Sodium channel, Postoperative pain

Introduction

One of the most difficult challenges in pain management continues to be balancing pain relief with the addiction and adverse effect of analgesics. Moderate-to-severe acute pain is especially tricky since there are limited medications that are both safe and potent. This shortfall leads doctors to continue to prescribe opioids in spite of its risk of addiction and misuse [1]. Long term opioid-related mortality in the United States showcases this trend as well. Based on the CDC data, age-adjusted drug overdose death rates rose from approximately 8.9 per 100,000 in 2003 to over 32 per 100,000 by 2023, almost tripling in the last twenty years [2]. All of this plus increasing public criticism and pressure over opioid prescriptions shows that there is a need for analgesics that do not cause addiction.

To come up with new innovative treatments for pain, researchers turned towards voltage-gated sodium channels that are critical for production and transmission of electrical signals in neurons [15]. The opening of these channels allows for the influx of sodium ions, causing depolarization and an action potential that returns to the CNS, translating to pain. So, many pharmaceutical companies are now focusing on inhibiting three important sodium channels (Nav1.7. Nav1.8, and Nav1.9) that can transmit peripheral pain signals [16]. The first sodium channel that caught their eyes was Nav1.7, and in July 2013, FDA approved of Vixotrigine as a Nav1.7 inhibitor that can be used for the treatment of trigeminal neuralgia. However, during its phase II clinical trials its efficacy was not significant enough to meets its primary or secondary endpoints causing it to be terminated [18]. Pfizer also tried its hand at developing a novel Nav1.7 inhibitor, called

PF-05089771, but it failed to significantly reduce pain in a randomized, double-blind clinical trial for diabetic neuropathic pain, leading to its termination [19]. Since Nav1.7 inhibitors failed to achieve clinical efficacy, a new target, Nav1.8, has now gained the spotlight as a promising target for pain management. Vortex Pharmaceuticals developed VX-150 as one of the first drugs to inhibit Nav1.8, and in a phase I, randomized, double-blind clinical trial involving healthy male subjects, it had promising results for the cold pressor and heat pain thresholds [20]. However, it was the associated adverse effects of VX-150 that held it back. Clinical application of VX-150 required a relatively high dosage of 1250 mg to have therapeutic effects, and it caused adverse effects, such as dizziness and headaches [20]. As a result, Vortex did not advance to late-stage clinical development for VX-150, instead shifting its efforts to produce a next-generation Nav1.8 inhibitor with improved potency and pharmacokinetics.

Learning from their past, a new non-opioid analgesic has recently been developed by Vortex Pharmaceuticals and marketed as Journavx, called suzetrigine (VX-548). On January 30, 2025, the FDA approved suzetrugine for the treatment of moderate-to-severe acute pain in adults in the United States. Suzetrigine's novelty comes from the fact that it is the first Nav1.8 inhibitor to be FDA, opening the way for other Nav1.8 non-opioid analgesics [3]. Nav1.8 is a type of voltage-gated sodium channel that is expressed in peripheral nociceptive neurons, including neurons of the dorsal-root ganglia [4]. There, it plays a key role in generating the action potential and propagating pain signals. Most importantly, Nav1.8 channels are not expressed in the central nervous system, and by targeting this peripheral pathway, VX-548 has shown no evidence of addictive potential while providing pain relief similar to that of opioids in the short term [4]. The objective of this article is to explore the mechanism of action, pharmacology, and research pertaining to suzetrigine as well as the drug's economic implications.

Methods

For this narrative review, PubMed was used to search for relevant studies on suzetrigine and its Nav1.8 inhibition effect on acute pain relief, studies published up to January 2026 were included. Some search terms that were selected were "suzetrigine," "VX-548," "JOURNAVX", "Nav1.8 inhibitor," and "acute pain." Articles and databases from Vertex Pharmaceuticals and the FDA regarding suzetrigine were also used.

Mechanism of Action

We recognize pain inherently in its last stage, perception; however, the pain pathway is broken up by multiple preceding stages involving transduction, transmission, and modulation5. To begin, potentially damaging stimuli such as mechanical shearing, heat, cold, and inflammation are detected by specialized nociceptors and transduced into nerve impulses. These electrical signals are propagated by Aδ- and C-type fibers towards the dorsal root ganglion into the lateral horn of the spinal cord5. Next, the incoming signals engage second-order neurons through the release of excitatory neurotransmitters and ascend the spinothalamic tract until they reach the thalamus. At the thalamus, the signals are distributed to higher brain regions like the somatosensory cortex, which will interpret the physical features of the stimulus. On the other hand, brain regions such as the limbic and the prefrontal cortex will contribute to the emotional and cognitive aspect of pain perception [6]. During this process, the moving electric signals can be strengthened or reduced based on modulation that uses the autonomic nervous system, opioid receptors, and GABA and NMDA neurotransmitters [7]. Finally, during perception, there is a summation of electrical signals, and that is then translated to the conscious experience of pain. Since the start of this process, voltage-gated sodium channels have been integral to the continuation of these electrical impulses through a series of depolarization events, causing the initiation of the action potential. It is at this critical junction that suzetrigine comes into play.

Nav1.1-1.9 are the nine subtypes of voltage-gated sodium channels that we know of, and Nav1.8 and Nav1.9 are predominately found in the peripheral sensory neurons [8]. The SCN10A gene translates into Nav1.8 sodium channels and according to large-scale transcriptomic analyses, including RNA-seq data from more than 1000 postmortem samples and over 190 CNS tissues from the Human Protein Atlas and GTEx projects, they did not identify any significant expression of this gene in CNS tissues [4]. Suzetrigine inhibits Nav1.8 selectively with 31,000-fold sensitivity as compared to other Nav subtypes, and application of 10 nM suzetrigine is enough to nearly eliminate the peak and sustained phase of electric current in HEK cells [4]. The mechanism of action that suzetrigine employs to inhibit Nav1.8 involves binding to the voltage-sensing domain 2 (VSD2) of Nav1.8 and stabilizing the Closed state of the channel [4]. This interaction was showcased by Osteen et al. using chimeric Nav1.2/Nav1.8 constructs. Their work demonstrated that suzetrigine sensitivity is conferred to Nav1.2 when the VSD2 domain of Nav1.8 is inserted into Nav1.2, particularly the S3 and S4 transmembrane segments [4]. Voltage-gated sodium channels cycle through three stages, Figure 1: 1) closed activation gate with an open inactivation gate right before depolarization, 2) both gates are open during depolarization to allow influx of sodium, and 3) open activation gate but closed inactivation gate following depolarization [4]. Suzetrigine stabilizes the third inactivated, non-conducting state (Figure 1), which decreases the number of channels available to reopen. By reducing channel availability, suzetrigine limits the generation of additional action potentials, suppressing the propagation of pain signals.

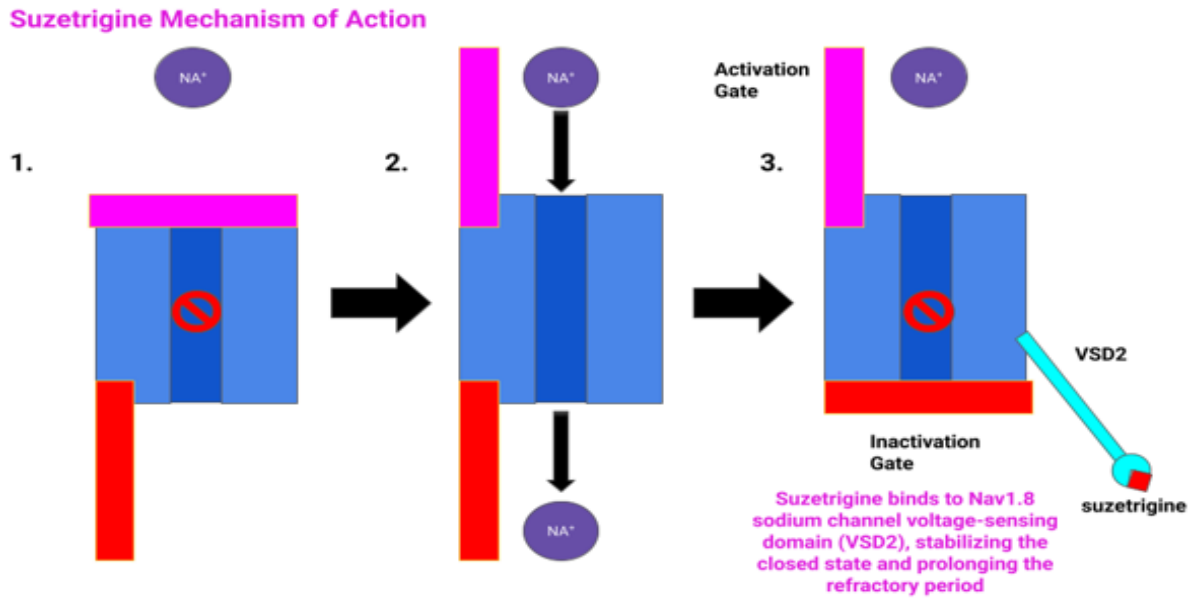

Figure 1: Mechanism of action of suzetrigine.

Some distinguishing characteristics of suzetrigine that are drawing interest are its apparent lack of off-target effects in cardiac muscles that have voltage-gated sodium channels (Nav1.5). In repeat-dose monkey studies lasting up to 9 months with suzetrigine administered at greater than or equal to the recommended human dose, no quantitative or qualitative changes were observed for respiratory function and on surface ECGs [4]. Although this suggests a favorable cardiac safety and respiratory profile, we must remain cautious because more research is necessary to understand long-term effects on human subjects. In addition, suzetrigine usage is also showing no evidence of addictive potential in animals. At pharmacologically relevant exposures of suzetrigine based on measured IC50s for Nav1.8 across species, monkeys did not show any observed neurobehavioral effects, including stimulant or sedative effects. While in rats, abrupt withdrawal of suzetrigine did not produce signs of dependency or significant changes to body temperature, weight, and motor activity [4]. Again, caution is needed as suzetrigine exhibits significant species-dependent potency at Nav1.8, as rodent Nav1.8 is shown to be 80-fold less sensitive to suzetrigine with an IC50 of 56 nM as compared to 0.68 nM in humans [9]. This showcases the importance of having human-specific data for suzetrigine.

Pharmacology

Suzetrigine has the molecular formula $C_{21}H_{20}F_5N_3O_4$ and a molecular weight of 473.4 g/mol [27]. It has been FDA approved for oral administration as a film-coated tablet starting at 100 mg loading dose administered as two 50 mg tablets taken either an hour before eating or two hours after eating [9]. Then, beginning 12 hours after the initial loading dose, take 50 mg of suzetrigine every 12 hours with or without food [9]. Since long-term safety data are limited, suzetrigine's drug course should be confined to the shortest duration consistent with pain control.

After oral administration, suzetrigine is well absorbed, with the volume of distribution being approximately 495L, suggesting there is substantial adipose tissue distribution [9]. When taken by mouth, suzetrigine reaches a median time to peak plasma concentration (Tmax) of around 3 hours when fasted, which is delayed to 5 hours with food [9]. It has an effective half-life of 23.6 hours, allowing it to taken twice per day [10]. Suzetrigine is metabolized primarily by CYP3A4 (cytochrome P450 3A4) through oxidative transformation into its active metabolite, M6-SUZ [9]. Additionally, M6-SUZ has about 3.7-fold weaker potency for Nav1.8 compared to suzetrigine, but both are excreted through feces (49.9%) and urine (44%) [9]. Given suzetrigine's interaction with CYP3A4, coadministration with strong CYP3A4 inhibitors is contraindicated. If used with CYP3A4 inhibitors such as diltiazem, it could cause a rise in suzetrigine level in the blood, leading to toxicity, so its dosage should be adjusted [9]. Suzetrigine increases the activity of CYP3A4, so if used together with sensitive CYP3A4 substrates, it may lead to faster metabolism and loss of efficacy, so dosage modification might be required [9]. The use of JOURNAVX in patients with severe hepatic impairment (Child-Pugh Class C) should be avoided, as they were not studied during clinical trials [11]. Similarly, there is a lack of data regarding suzetrigine's effect on patients with severe renal impairment (eGFR < 15 mL/min) [11]. The long-term effects of suzetrigine have not been well studied, with only a Phase II clinical trial consisting of 192 patients with painful diabetic peripheral neuropathy so far. Subjects were given varying dosages of suzetrigine for 12

weeks, and the data showed that 10.9% (N=6 out of N=55) of the high dose group (69 mg QID) had decreased creatinine clearance [12].

Clinical Efficacy

So far, the efficacy and safety of suzetrigine have been evaluated in two Phase II clinical trials and two Phase III clinical trials. Although the randomized phase III trials have been completed, the results have not been published and only a Phase III single-arm study for surgical or non-surgical acute pain has been peer-reviewed.

The Phase II clinical trials that have been published are randomized, double blinded, placebo-controlled experiments. There are 577 subjects that participated and they are between the ages of 18 to 75 [13]. The subjects are then separated into two groups: 303 subjects who completed bunionectomy and 274 subjects who completed abdominoplasty [13]. The subjects were selected based on a few criterias to ensure that they are as similar as possible in terms of their pain level. On the Numeric Pain Rating Scale, subjects must have rated their pain at least 4 [13]. In the abdominoplasty group, they also must rate their pain as either moderate or severe on the Verbal Categorical Rating Scale (VCR) within 4 hours of the surgery [13]. In the bunionectomy trial, the subject must also describe moderate or severe pain in the VCR within 9 hours of removing the popliteal sciatic nerve block on postoperative day one [13]. In the 48-hour abdominoplasty trial group, participants were randomized to receive high-dose suzetrigine (100-mg loading dose followed by 50 mg every 12 hours), middle-dose suzetrigine (60-mg loading dose followed by 30 mg every 12 hours), hydrocodone bitartrate/acetaminophen (5 mg/325 mg every 6 hours), or placebo every 6 hours [13]. In the 48-hour bunionectomy trial group, participants were randomized in a 2:2:1:2:2 ratio to receive high-dose, middle-dose, or low-dose suzetrigine (20-mg loading dose followed by 10 mg every 12 hours), hydrocodone bitartrate/acetaminophen (5 mg/325 mg every 6 hours), or placebo every 6 hours [13]. In both trials, NPRS was recorded throughout (19 measurements), and the primary efficacy endpoint was the time-weighted sum of the pain intensity difference (SPID) over a period of 48 hours (SPID48). The SPID48 value is calculated by multiplying a weight factor by each NPRS score before summing the values so that a higher value represents a greater reduction in pain [13]. A secondary efficacy endpoint was also calculated at the 24-hour period (SPID 24). The results illustrated that there is a significant difference of 36.8 in the SPID48 least-squares mean difference (LSM) between the high dose group and the placebo group (95% CI, 9.2 to 66.4) in the abdominoplasty trial and 36.8 (95% CI, 6.5 to 32.7) in the bunionectomy trial. The LSM between the high dose group and the placebo group for SPID24 of the abdominoplasty trial versus the bunionectomy trial was 19.6 (95% CI, 6.5 to 32.7) and 13.7 (95% CI, -1.8 to 29.1), respectively [13]. The conclusion of these two trials showed that participants who received high-dose suzetrigine had reduced acute pain over the 48 hours after abdominoplasty and bunionectomy. However, the middle and lower doses of suzetrigine did not have a significant effect on acute pain as compared to the placebo [13]. A significant outcome of these trials is that the side effects were quite mild. In fact, the most common adverse event occurring in at least 10% of the participants was nausea, headache, constipation, and vomiting in the abdominoplasty trial and nausea and headache in the bunionectomy trial [13]. In the abdominoplasty trial, the incidence of adverse events is either similar or lower than the placebo except for headache (14% vs. 6%) and constipation (9% vs. 5%) [13]. The study also reports no increase in respiratory depression or altered mental status compared to placebo [13]. A limitation of this study was that all adverse events were assessed by the site investigator, who was unaware of trial-group assignment, but these events were not adjudicated by an independent data monitoring committee [13].

In the single-arm Phase III clinical trial, 256 participants with a mean age of 43.9 (14.1 SD) received at least one dose of suzetrigine (100 mg first dose, then 50 mg every 12 hours for 14 days or until pain resolved [14]. The data showed that the subjects had a mean NPRS score of 6.7 and complained of moderate to severe pain [14]. Most of the participants had pain from surgical procedures (222 subjects) and the remaining 34 subjects had non-surgical pain [14]. One caveat was that subjects were allowed to take either acetaminophen (650 mg) and/or ibuprofen (400 mg) every 6 hours as needed as rescue medication. The findings from this study demonstrated that subjects had little to no issue taking suzetrigine, with the most common side effects (>= 2% of participants) being headache, constipation, nausea, falls, and rash. Only headache occurred in at least 5% of the participants [14]. Moreover, at the end of the treatment, 83.2% (213 of 256 participants) reported good, very good, or excellent pain relief from suzetrigine [14]. The proportion of participants reporting good, very good, or excellent on the assessment scale was similar between those who took rescue medication (82.4%, 154 of 187) and those who did not (85.5%, 59 of 69) [14]. Some limitations of this study were that the effectiveness of suzetrigine was not compared to a placebo, and that the number of participants who did not take rescue medication was significantly lower than those who did (69 vs.187 participants).

Benefits and Limitations

Currently, suzetrigine has been shown to effectively reduce pain and can be considered for the treatment of postoperative pain that is acute and at the moderate-to-severe pain scale. JOURNAX can be considered for pain resulting from soft tissue and orthopedic procedures, as well as musculoskeletal pain. It can be used as an alternative to NSAIDs and

opioids in high-risk patients and those with opioid use disorder. In a systematic analysis of abuse-related adverse effect terminology from phase II and open-label phase III trials of suzetrigine involving 2447 participants, it showed that the incidence of the abuse-related AEs was low and similar compared to the placebo [4]. Moreover, the FDA's assessment of the suzetrigine new drug application concluded that there is no abuse liability and that it does not require scheduling under the Controlled Substances Act [9]. Although there is no evidence of an addictive profile so far, the effects of long-term use must be explored.

From what we know so far, suzetrigine seems very promising, but there are still questions surrounding its use. For instance, suzetrigine should only be used for a maximum of 14 days since long-term safety and effectiveness beyond this period have not been established [9]. Studies are underway for the treatment of conditions like diabetic peripheral neuropathy, but evidence for chronic pain effectiveness is still emerging [21]. Furthermore, Vortex has initiated a phase II study of suzetrigine in lumbosacral radiculopathy, which is another form of peripheral neuropathic pain with data yet to be published [22]. Additionally, other upcoming next-generation Nav1.8 inhibitors could have better efficacy than suzetrigine. For example, Latigo Biotherapeutics was granted FDA fast-track designation for LTG-001 and is another Nav1.8 inhibitor that potentially treats acute pain [23]. Suzetrigine's high price tag could also be a problem because the wholesale price is around $15.50 per 50 mg tablet in the United States, which is much greater than NSAIDs or generic opioids [24]. The increased cost could mean decreased insurance coverage, so the out-of-pocket cost may stop some patients from being able to afford it.

When giving suzetrigine to patients, clinicians should keep in mind that common adverse reactions (occurring in ≥2% of patients) include headache, constipation, nausea, pruritus, rash, and muscle spasms [11]. Moreover, some suzetrigine drug-drug interactions are noted as "major" and should be avoided in combination. "Major" drugs such as ciprofloxacin, fluconazole, dexamethasone, and grapefruit are CYP3A4 inhibitors, which can decrease the breakdown of suzetrigine, causing a higher bioavailability and potential toxicity [25]. At this moment, there is no available data on the use of suzetrigine during human pregnancy. In rat studies, suzetrigine was given during organogenesis and gestation phases of the reproductive cycle at a dosage 2.2 times the maximum recommended human dose. The data from this study showed an association with increased post-implantation loss, decreased numbers of live fetuses, reduced fetal body weight, and increased postnatal mortality [9]. Furthermore, we should be cautious since suzetrigine could temporarily reduce the chances of pregnancy and may interfere with some progestin-containing contraceptives [9]. So before starting suzetrigine, patients should discuss pregnancy plans with their physician. Also, patients with reproductive capacity should continue using alternative contraceptives (oral contraceptives containing ethinyl estradiol or condoms) and for at least 28 days after stopping the medication [9].

Discussion

Currently, suzetrigine is a promising alternative to opioids for the treatment of acute moderate-to-severe pain, but more rigorous testing must be completed to assess the extent of its pain-relieving effect. Karri et al offer some criticism regarding suzetrigine's two Phase 2 clinical trials. He mentions that although the trials demonstrated statistically significant reductions in pain scores compared to placebo, its clinical meaningfulness remains ambiguous. This is because the study relies on SPID measurement endpoints, which lack thresholds for clinically relevant effect sizes [26].

Moreover, there appears to be a lack of trials that compare suzetrigine's effectiveness versus full-dose opioids in treating acute pain. In the Phase 2 clinical trial, oral 5 mg hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours was given as a comparison, but this is a relatively low opioid dose for treating postoperative pain. This dosage of acetaminophen-hydrocodone also failed to outperform the placebo during the study, which could cast doubts on it as an active comparator for suzetrigiine's clinical relevance [26]. Another point of contention involves the use of abdominoplasty and bunionectomy as surgical modalities; while they are established pain models, they limit generalizability to more common surgeries, such as spine surgeries with prolonged postoperative pain and more complicated management [26]. The use of NSAIDs as "rescue" analgesia in the single-arm Phase III clinical trial may also be a confounding factor. During the duration of the study, there was a larger percentage of subjects who took the "rescue" medication compared to those who did not (69 vs 187). This could potentially muddy the results so that it is difficult to assess if the observed effect is due to the NSAIDs, suzetrigine, or a combination of the two.

Although the research around suzetrigine has grounds for improvement and further investigation, what we are seeing so far should garner our attention. Suzetrigine appears to be generally safe with minimal central nervous system effects and no evidence to date suggesting addictive indications. It reduces pain intensity with statistical significance compared to placebo, especially in controlled surgical settings with postoperative pain. This drug profile could be favored amongst ambulatory surgical centers and outpatient recovery to reduce opioid exposure and its associated risks, including misuse, respiratory depression, and sedation. Lastly, suzetrigine could have the potential to be utilized as a leading non-opioid medication that is integrated into multimodal pain regimens with NSAIDs, acetaminophen, muscle relaxants, topical analgesics, and gabapentinoids to treat severe acute pain without the need for opioids.

Conclusion

The current literature points to suzetrigine as a non-opioid painkiller that can provide significant pain relief to patients with acute moderate-to-severe pain. The drug binds to Nav1.8 voltage-gated sodium channels that are mainly expressed in peripheral neurons and not expressed in the CNS. Its mechanism of action consists of inhibiting Nav1.8 by binding to the VSD2 domain and stabilizing the inactivation phase, causing less action potential firings and less pain signals. Clinical trials demonstrated that suzetrigine is well-tolerated with the most common side effects being headaches, constipation, and nausea. As of now, suzetrigine does not show an addiction profile in humans, and in animal models with rats and monkeys, they showed no dependence or behavior changes after taking suzetrigine. These results pushed suzetrigine to be FDA-approved in January 2025 for the treatment of acute moderate-to-severe pain, however, we must still be cautious of its long-term effects. For instance, we should confirm its effects on pregnant women and reproductive potential. Furthermore, more studies must be done on the addictive potential of suzetrigine in humans who use the drug long term for chronic conditions. It seems that the healthcare systems, the FDA, and the general public are pushing for non-opioid options for treating pain and suzetrigine is coming out at the right time. However, current and future studies are important to check its performance in chronic neuropathic conditions, perioperative situations, and clinical settings. For now, JOURNAVX is an impressive development in acute pain management, and we are eagerly awaiting the publication of the results from the Phase III clinical trials for the treatment of diabetic peripheral neuropathy and lumbosacral radiculopathy.

Declarations

Ethics approval and consent to participate
Not applicable

Conflicts of Interest
The authors declare no conflicts of interest.

Consent for Publication
Not applicable

Availability of data and materials
Not applicable

Competing interests
The authors declare that they have no competing interests

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Author's Contributions
WC drafted the manuscript and conducted the literature review. SS critically revised and supervised the manuscript. All authors read and approved the final manuscript.

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