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Suzetrigine: The first Nav1.8 inhibitor approved for the treatment of moderate to severe acute pain

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SUMMARY: Opioids are commonly prescribed for the management of moderate to severe pain, but their use is associated with dependency and other adverse effects. For decades, the development of safe and effective non-addictive alternatives for treating moderate to severe pain has seen limited progress. On January 30, 2025, the U.S. Food and Drug Administration approved suzetrigine, the first Nav1.8 inhibitor, for the treatment of moderate to severe acute pain. Nav1.8 is a voltage-gated sodium channel that is selectively expressed in peripheral nociceptive neurons, which are responsible for transmitting pain signals. By highly selectively inhibiting the Nav1.8 channel, suzetrigine can effectively alleviate pain. Unlike opioids, this drug does not induce euphoria or excitement in the brain, thereby eliminating concerns about addiction. Suzetrigine offers a novel therapeutic option and a potential combination for multimodal analgesia, with the promise of transforming acute pain management and establishing new treatment standards.

Keywords: Opioids, Nav1.8, pain, postoperative, painful diabetic peripheral neuropathy (DPN), painful lumbosacral radiculopathy (LSR)

Acute pain refers to sharp, transient, and localized pain that occurs due to various physical, chemical, traumatic, or infectious factors. Research indicates that about 75% of patients experience moderate to severe pain postoperatively (*1*). Opioids, such as morphine, fentanyl, and pethidine, are widely used to manage moderate to severe acute pain. However, their use carries the risk of dependence and other adverse effects. It is reported that over 80 million Americans are prescribed medications for moderate to severe acute pain each year, with approximately 40 million of them being prescribed opioids (*2*). Among patients initially treated with opioids for acute pain, nearly 10% will continue using opioids long-term, and around 85,000 patients develop opioid use disorder annually (*2*). Poor management of acute pain can lead to reduced quality of life for patients, the development of chronic pain, and an increased burden on the healthcare system and society. Currently, there is a pressing clinical need for safe, effective, non-addictive alternatives to opioids for treating moderate to severe pain.

Suzetrigine (brand name: Journavx) is an oral, selective Nav1.8 sodium channel blocker developed by Vertex Pharmaceuticals (*2*). It was approved by the U.S. Food and Drug Administration on January 30, 2025, for the treatment of moderate to severe acute pain (*3*). Nav1.8 is a voltage-gated sodium channel that plays a key role in the transmission of pain signals in the peripheral nervous system (*4*). It is selectively expressed in dorsal root ganglia (DRG) and trigeminal ganglion (TG) neurons. When neurons are stimulated, the Nav1.8 channel opens, allowing a large influx of sodium ions, which causes depolarization of the cell membrane, generating an action potential and triggering the sensation of pain (*5*). Suzetrigine selectively acts on the Nav1.8 channels of peripheral nociceptive neurons, inhibiting the rapid influx of sodium ions and the generation of action potentials, thus blocking pain signal transmission (*5*). Since Nav1.8 channels are not expressed in the human central nervous system, suzetrigine does not produce excitatory effects or euphoria, and therefore does not have addictive properties (*5*).

Multiple clinical trials have demonstrated that suzetrigine is effective in relieving moderate to severe acute pain. Phase 2 and phase 3 randomized controlled trials tested suzetrigine's analgesic effects following abdominoplasty and bunionectomy (*5-7*). 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

Table 1. The Nav1.8 inhibitors that are currently undergoing clinical trials

Drug candidates	Indication	Clinical trial	Company
Suzetrigine (VX-548)	Painful diabetic peripheral neuropathy;	Phase 3;	Vertex Pharmaceuticals Incorporated
	Painful lumbosacral radiculopathy	Phase 2	
VX-993	Acute pain after a bunionectomy;	Phase 2;	Vertex Pharmaceuticals Incorporated
	Painful diabetic peripheral neuropathy	Phase 2	
LTG-001	Acute pain after third molar removal surgery in adults	Phase 2	Latigo Biotherapeutics
JMKX000623	Diabetic peripheral neuropathic pain	Phase 2	Jemincare
HRS-2129	Postoperative analgesia in orthopaedics	Phase 1	Shandong Suncadia Medicine
VX-973	—	Phase 1	Vertex Pharmaceuticals Incorporated
LTG-305	—	Phase 1	Latigo Biotherapeutics
HBW-004285	—	Phase 1	Hyperway Pharmaceutical
FZ008-145	—	Phase 1	Guangzhou Fermion Technology
STC-004	—	Phase 1	SiteOne Therapeutics

in statistically significant and clinically meaningful reductions in moderate to severe pain. In a subsequent phase 3 single-arm clinical trial, suzetrigine was administered for up to 14 days to patients with moderate to severe acute pain resulting from surgical and non-surgical causes, further confirming its analgesic efficacy (*5*). Regarding safety, the results from three phase 3 clinical trials, which included a total of 2,447 participants, indicated that suzetrigine does not carry a potential for addiction (*5*). The most common adverse reactions were itching, muscle spasms, elevated blood creatine phosphokinase levels, and rash (*2,7*).

The approval of suzetrigine highlights that targeting Nav1.8 could be an important strategy for treating moderate to severe acute pain. Currently, the number of Nav1.8 inhibitors that have entered clinical research is still limited (Table 1). The approval of suzetrigine is expected to encourage pharmaceutical companies to develop more Nav1.8 inhibitors for pain treatment. In addition to postoperative pain, candidate drugs in clinical research are expanding into new indications. Suzetrigine has already entered a phase 3 clinical trial for the treatment of painful diabetic peripheral neuropathy (DPN) (*8*), and a phase 2 trial for treating painful lumbosacral radiculopathy (LSR) have been completed, with the potential to move into phase 3 trials (*9*). 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.

Suzetrigine offers a novel non-opioid treatment option for patients with acute pain. However, whether suzetrigine can serve as a replacement for opioids and help reduce the public health issues caused by opioid abuse requires further clinical research. Regardless, suzetrigine provides a novel drug option and combination for multimodal analgesia, with the potential to transform the paradigm of acute pain management and establish new treatment standards. It is anticipated that analgesic drugs with novel mechanisms will bring advancements in the clinical treatment of both acute and chronic pain.

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