COMMENTARY article

First-in-class non-opioid analgesics: Molecular mechanisms and clinical impact of Suetrigine

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Abstract: Effective and safe pain management remains a challenge for clinicians and researchers, despite the fact that pain is one of the most common and important clinical challenges in medicine. Despite their well-established risks of addiction, tolerance, respiratory depression, and a host of other negative effects, opioid analgesics continued to be the standard treatment for moderate to severe pain for many years. Recent scientific discoveries and regulatory initiatives have encouraged the creation of non-opioid analgesics with unique modes of action. As the first in a new class of non-opioid, peripherally acting painkillers approved by the U.S. Food and Drug Administration in 2025, suzetrigine, marketed as Journavx™-represents a significant milestone. This article synthesizes current knowledge on the pharmacology, molecular mechanism, clinical efficacy, safety, and potential impact of suzetrigine in pain management.

Introduction

Millions of people worldwide suffer from acute and chronic pain, which is a major contributor to disability and medical usage [1]. Strong analgesics are often needed for acute pain, such as that which follows surgery, an injury, or an acute medical condition [2, 3]. When acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are insufficient to relieve pain, opioids such as morphine and hydrocodone have historically been prescribed [4-6]. Suzetrigine is an oral, non-opioid, selective inhibitor of the voltage-gated sodium channel Nav1.8 that was recently authorized for the treatment of moderate-to-severe acute pain in adults [7]. It was originally known as VX-548 and is currently marketed under the approved brand name Journavx™ [8]. Nav1.8 is preferentially expressed on peripheral nociceptive neurons and mediates pain sensation [9-11]. Suzetrigine has analgesic benefits without the central nervous system (CNS) adverse effects of conventional opioid analgesics by limiting its actions on peripheral nociceptive neurons [12]. Suzetrigine's effectiveness and safety in neuropathic and post-surgical pain models have been evaluated in several early and late-phase clinical studies. Suzetrigine showed comparable efficacy to hydrocodone/acetaminophen (HB/APAP) treatment and significantly greater pain relief over 48 hours when compared to an inactive oral capsule in phase II randomized, double-blind trials in patients undergoing abdominoplasty and bunionectomy [13, 14]. Interestingly, suzetrigine produced these results without producing opioid-related adverse effects such as drowsiness, constipation, respiratory depression, and overdose. Pharmacokinetic developments have examined suzetrigine tablet formulations, demonstrating that oral administration can be achieved in outpatient care settings [7].

Historical context of analgesic development: By binding to μ-opioid receptors in the central nervous system (CNS), opioids prevent pain signals. Despite its efficacy, this crucial mechanism has a variety of detrimental side effects that promote misuse, including euphoria, sedation, respiratory depression, and dependency [15]. NSAIDs reduce inflammation and prostaglandin synthesis by blocking cyclooxygenase (COX) enzymes. NSAIDs have the potential to cause gastrointestinal, renal, and cardiovascular toxicity, but they are safer in terms of addiction. Until the early 21st century, there was little clinical success with new targets such as transient receptor potential (TRP) channel inhibitors [16-18] and selective cannabinoid receptor modulators. Eventually, the focus of research shifted to gene-validated ion channels that are crucial for the transmission of pain, such as the voltage-gated sodium (NaV) channel subtypes expressed in nociceptors.

NaV1.8 sodium channels: Transmembrane proteins called voltage-gated sodium channels are essential for the start and spread of action potentials in excitable cells. The NaV1.8 subtype of the NaV family is primarily expressed in peripheral dorsal root ganglion (DRG) sensory neurons, which are the main afferent neurons that transmit nociceptive (pain) signals to the brain and spinal cord [19]. NaV1.8 has distinct biophysical characteristics. It sustains action potentials at lower temperatures and activates at greater depolarized potentials. This distinguishes it from other NaV subtypes involved in CNS or cardiac function. NaV1.8 was a desirable therapeutic target since it is primarily absent from the central nervous system. It has the ability to relieve pain without causing major adverse effects [20]. Suzetrigine - formerly known as VX-548 - was designed to exploit this target. Its high selectivity for NaV1.8 and unique interaction with the channel sets it apart from earlier, less specific sodium channel blockers [21].

Chemistry of suzetrigine: 4-[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-amido]pyridine2-carboxamide is the drug's chemical name. Its molecular formula is C21H20F5N3O4, and its molecular weight is 473.39 g/mol. Suzetrigine is essentially insoluble in water and is a white to off-white solid. Vertex Pharmaceuticals documented the drug's chemical production in a number of patents [22]. A different technique for making Suzetrigine was recently described as being environmentally friendly [23]. According to the patent, the method's benefits include fewer stages, a safer reaction, avoidance of the use and discharge of an ammonia methanol solution, and the potential racemization risk associated with preparing acid into acyl chloride.

Mechanism of action: The Nav1.8 sodium channel isoform, which is mostly expressed in peripheral nociceptors, is very selectively inhibited by suzetrigine through a new mechanism [19, 24]. In contrast to non-selective sodium channel blockers, suzetrigine selectively binds to the Nav1.8 sodium channel's voltage-sensing domain 2 (VSD2), maintaining the channel in its closed state via allosteric modulation. Several therapeutic benefits result from this special mechanism: Peripheral restriction: low CNS penetration, brain plasma ratio <0.1, prevents opioid-like central effects; Extraordinary selectivity: 31,000-fold higher affinity for Nav1.8 compared to other sodium channel subtypes (Nav1.1, Nav1.7, and Nav1.9); and Functional selectivity: Prevents pain transmission without totally blocking neurons [19, 25, 26]. Unprecedented insights into the structural pharmacology of Nav1.8 have also been revealed by recent structural investigations employing cryogenic electron microscopy (cryo-EM) and structure-based predictive modeling. However, the structure of Nav1.8 with VX-548 has not yet been established [27].

Clinical impact: When compared to a placebo, suzetrigine significantly reduced immediate pain after bunionectomy or abdominoplasty. Its effectiveness is similar to that of therapy with hydrocodone/acetaminophen (HB/APAP). The majority of adverse events (AEs) in phases II and III studies were categorized as mild to moderate in intensity, indicating that suzetrigine was generally well tolerated. It is noteworthy that three subjects had unrelated significant adverse events (SAEs) [13, 28]. Suzetrigine demonstrated good levels of patient satisfaction in individuals with a variety of surgical and non-surgical acute pain situations in the Phase III-Single-Arm: Mixed Acute Pain study. In particular, 83.2% of participants said they had a good, very good, or excellent experience [13]. All subgroups responded positively, with 82.0% of

surgical patients and 91.2% of non-surgical patients having good results. These outcomes demonstrate Suzetrigine's adaptability in a range of therapeutic contexts. Additionally, the majority of adverse events were categorized as mild to severe [14]. Randomized, double-blind, placebo- and active-controlled Phase III trials involving patients with acute postoperative pain, such as following abdominoplasty or bunionectomy, showed that suzetrigine was effective. When compared to a placebo, suzetrigine demonstrated statistically significant better pain relief in these trials. Although the drug's analgesic strength is typically described as modest in comparison to full-dose opioids, analgesic effects were comparable to established opioid combinations in certain measures [14, 29]. The Phase II-Lumbosacral Radiculopathy study assessed the impact of Suzetrigine on the treatment of persistent neuropathic pain [30]. At the 12-week evaluation, suzetrigine caused a mean decrease of 2.02 points on the numeric pain rating scale (NPRS) from baseline, whereas the placebo group had a decrease of 1.98 points. Suzetrigine was generally well tolerated, with AEs reported in 22.9% of patients taking suzetrigine compared to 32.4% in the placebo group, which is consistent with findings from other clinical studies. No SAEs were linked to the use of suzetrigine, and the majority of AEs were classified as mild or moderate.

Conclusion: The FDA's approval of suzetrigine, the first non-opioid analgesic class to be introduced in more than 20 years, is a significant development in pain management. Suzetrigine provides efficient relief from moderate to severe acute pain without the addiction and central nervous system risks associated with opioids by specifically targeting peripheral NaV1.8 sodium channels. Suzetrigine is an essential addition to the analgesic toolbox, despite ongoing difficulties such as a small analgesic effect size, a lack of long-term data, and financial concerns. Suzetrigine has the potential to revolutionize acute pain management and usher in a new era of non-opioid pain treatments as more research is conducted.

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