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SUZETRIGINE: AN ANALGESIC OF THE FUTURE? – A CLINICAL REVIEW

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ABSTRACT

Suzetrigine is one of the revolutionary non-opioid analgesics developed with the specific intention of managing acute pain, mild to severe in intensity. As a blocker of voltage-gated sodium channels (Nav), which specifically target Nav1.7, Nav1.8, and Nav1.9, it effectively modulates the signalling pathways for pain while avoiding most of the adverse effects associated with the central nervous and the gastrointestinal systems seen in conventional analgesics and opioids. Suetrigine has a highly optimized pharmacological profile and provides advantages over existing pain management therapies, which often have risks of dependence, addiction, and adverse effects such as sedation and respiratory complications. In clinical trials involving more than 2,447 participants, suzetrigine proved to be safe and effective in reducing the intensity of pain without any risk of abuse or respiratory depression.

The approval of suzetrigine by the U.S. Food and Drug Administration is a significant development in pain management strategies. By addressing the shortcomings of current analgesics, including NSAIDs, acetaminophen, and opioids, suzetrigine offers a much-needed alternative for patients suffering from acute pain conditions. In addition, its novel mechanism of action avoids the gastrointestinal and renal risks of NSAIDs but has the potential for long-

term use in chronic pain management conditions such as diabetic neuropathy and postherpetic neuralgia. As healthcare systems continue to face the opioid crisis, suzetrigine represents a safer pain relief drug, addressing the critical need for effective analgesics that maintain patient safety without sacrificing efficacy. Thus, suzetrigine will play a critical role in redesigning the future of pain management.

Keywords: pain, analgesia, sodium channel, Suzetrigine

INTRODUCTION:

Pain is a complex phenomenon that is very much part of human biology and, at one level, provides a protective mechanism and a warning system for the potential injury to tissues. When pain becomes moderate or severe, it can be severely debilitating for a person, making proper management of pain necessary **[1]**. A number of therapeutic approaches are currently available for pain management, including various types of analgesics and medications that act on the central nervous system. These include acetaminophen, NSAIDs, local anesthetics, antidepressants, anticonvulsants, and opioids **[2, 3]**. Each treatment is valuable in its place, however, but has some inherent challenges, which point to the need for innovative and targeted therapies.

Opioids have been broadly used for the management of both acute and chronic pain. They act by binding to opioid receptors in the CNS, thus changing the perception of pain. However, the use of opioids is associated with significant problems, most notably the potential for dependence and addiction. The widespread misuse of prescription opioids has resulted in a public health crisis, marked by increasing rates of opioid overdose and a growing number of individuals struggling with opioid use disorder. Besides the risk of addiction, opioid therapy is associated with a variety of undesirable side effects, such as sedation, respiratory depression, constipation, and confusion **[4-6]**. These adverse effects not only decrease the quality of life but also complicate treatment regimens and prolong recovery times.

Similarly, NSAIDs and acetaminophen, though widely used for pain relief, have their own disadvantages. NSAIDs, such as ibuprofen and naproxen, are effective for inflammation-related pain but can pose risks of gastrointestinal bleeding, renal impairment, and cardiovascular complications with long-term use **[7, 8]**. Acetaminophen, on the other hand, is often considered a safer alternative for mild to moderate pain but has a narrow therapeutic window. Overdose can lead to severe hepatotoxicity, especially in patients with pre-existing liver conditions or in those who consume alcohol regularly **[9]**. With a failure in NSAIDs and acetaminophen to effectively treat severe pain coupled with

these safety concerns, what is required are new analgesics, with efficacy regarding pain relief that can have a better safety profile.

Mechanism of action of Suzetrigine

Suzetrigine is a 4-[(2R,3S,4S,5R)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-amido]pyridine-2-carboxamide **(Figure 1)**.

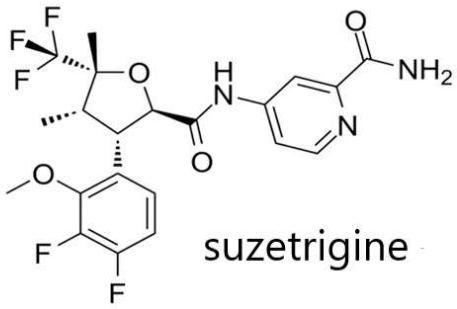

Figure 1: Chemical formula of suzetrigene

Newer analgesics include Suzetrigine (VX-548), which is an encouraging step towards better pain treatment. Suzetrigine is a selective voltage-gated sodium channel (Nav) blocker targeting Nav1.7, Nav1.8, and Nav1.9 channels, which are important in the transmission of nociceptive signals. Through specific action on these channels, Suzetrigine may be able to modulate the pain pathway more specifically than traditional pain medications, with the potential for effective pain relief with fewer side effects **(Figure 2)**.

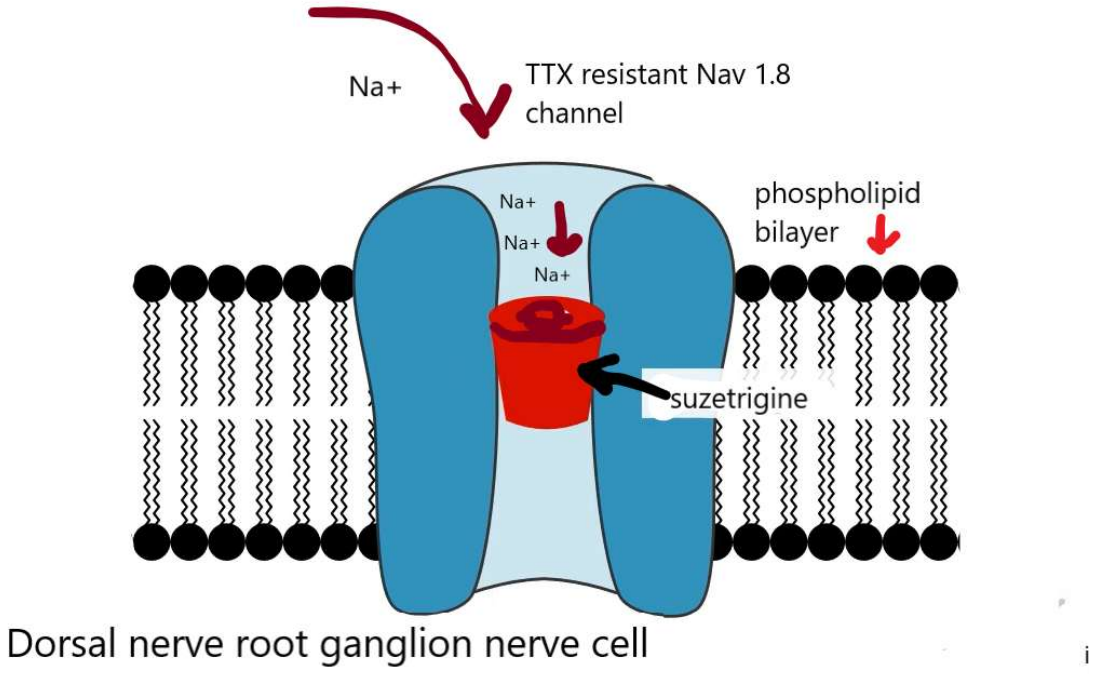

Figure 2: Mechanism of action of Suzetrigine

This targeted mechanism of action is particularly valuable in a clinical landscape that demands both efficacy and safety. Suzetrigine could reduce the risk of broad CNS side effects, which are common with opioids and other analgesics, as it selectively inhibits sodium channels involved in pain signaling but spares other physiological processes **[10]**. Additionally, its selective action might help avoid the gastrointestinal and renal risks associated with NSAIDs.

Clinical trials have proven Suzetrigine safe and effective as an acute pain reliever, without the adverse effects of abuse or CNS action. According to Osteen *et al* . (2025), NaV1.8 sodium channel, for which Suzetrigine was primarily designed to target, has no expression in the brain and spinal cord; this greatly lowers the risk that is associated with opioid use when it comes to addiction. With its promising pharmacological profile, Suzetrigine may thus provide a superior alternative for managing moderate to severe pain and ease concerns related to traditional opioid therapies.

Suzetrigine works through a novel mechanism of allosteric inhibition, distinct from the mode of action of conventional sodium channel blockers, local anesthetics. Unlike these non-selective inhibitors that can act upon several subtypes of sodium channels and cause side effects systemically, Suzetrigine acts specifically on the VSD2 domain of NaV1.8, which stabilizes the channel in a closed state. This targeted effect effectively blocks peripheral pain signaling without affecting cardiac or neural sodium channel subtypes—an important advantage over traditional sodium channel blockers. Evidence shows that Suzetrigine is able to decrease pain by blocking action potentials in NaV1.8-expressing dorsal root ganglion (DRG) neurons, establishing it as the first-in-class, peripherally acting analgesic, with great clinical implications.

The efficacy of Suzetrigine has been proved in more than 2,447 participants involved in several Phase 3 clinical trials for its use in treating acute pain after surgery, specifically abdominoplasty and bunionectomy. These studies proved that the drug significantly reduces pain intensity without any CNS-related side effects, cardiovascular complications, or behavioral changes. Adverse event analyses revealed no signs of abuse potential; patients did not experience euphoria, cognitive impairment, or withdrawal symptoms. Moreover, long-term preclinical studies in rats and monkeys further confirmed that Suzetrigine is not addictive, since there were no signs of dependency effects. Compared to opioids, Suzetrigine has an equivalent analgesic efficacy but without the risk of addiction or respiratory depression, thus being a major breakthrough in the non-opioid management of pain.

To date, pain treatment involves a range of drug classes: NSAIDs, anticonvulsants, antidepressants, local anesthetics, and opioids. However, such widespread therapies have the side effect of being not desirable: NSAIDs induce gastrointestinal discomfort, opioids induce CNS depression, and local anesthetics are typically systemic inhibitors of sodium channels. On the other hand, Suzetrigine has been described as one of the most selective NaV1.8 blockers without interference with the receptors in the CNS or influence on other subtypes of sodium channels. Without inducing sedation, addiction, and cardiovascular complications, Suzetrigine presents a more desirable safety profile. The key specificity that Suzetrigine boasts over the general sodium channel blockers targeting NaV1.7, NaV1.8, and NaV1.9 is safety without a compromise in its analgesic profile. Its unprecedented pharmacological profile makes it capable of transforming pain management treatments.

Thanks to its mechanism of action being primarily peripheral, Suzetrigine is likely to be safer than gabapentinoids like gabapentin and pregabalin that modify calcium channels in the CNS and often cause side effects like drowsiness, lightheadedness, and impaired cognitive function. The challenge of chronic pain conditions, especially neuropathic and inflammatory pain syndromes, arises because of the ineffectiveness of current analgesics, combined with a high potential for opioid dependence. The evidence of research suggests that NaV1.8 is involved in transmitting chronic pain signals and, thus, represents an attractive target for long-term pain relief strategies **[11, 12]**. Although most of the research on Suzetrigine has been done within acute models of pain, its mechanism and possible efficacy make it a critical drug in treating chronic conditions such as diabetic neuropathy and postherpetic neuralgia.

USFDA approval:

The U.S. Food and Drug Administration has granted approval on 30thb January 2025 for suzetrigine, a 50 milligram oral tablet and the first non-opioid analgesic in its class, designed for treating moderate to severe acute pain in adults. This innovative medication alleviates pain by acting on a pain-signaling pathway that involves sodium channels within the peripheral nervous system, intervening before pain signals reach the brain **[13]**. Suzetrigine marks a groundbreaking advancement in pain management options.

Clinical trials:

Rind *et al* in his report reviews suzetrigine as a therapeutic agent for the treatment of acute pain. This drug is being studied as an adjunct to treating chronic pain; however, currently, it is being considered for approval by the FDA strictly to treat acute pain.

Evidence used in this review comes from two Phase III randomized trials in which suzetrigine was compared with placebo and the opioid hydrocodone 5 mg combined with acetaminophen 325 mg (HB5/APAP325). Trials comprised patients post-bunionectomy and others post-abdominoplasty. The treatments were suzetrigine to 873, HB5/APAP325 to 879, and placebo to 439 patients. The results indicated that patients who were on suzetrigine had faster relief and marked pain with much higher intensity than those on placebo. For abdominoplasty, suzetrigine is equally effective to HB5/APAP325, but for bunionectomy, the onset of relief is delayed. Suzetrigine adverse effects were similar to those of placebo; nausea was less common than for HB5/APAP325 **[11, 14]**. A network meta-analysis did not allow confident comparison of efficacy to higher-dose opioids and NSAIDs.

Dosage schedules:

Indication for Acute Pain

Indication:

Suzetrigine is used in the management of moderate to severe acute pain.[14]

*Starting Dose***:**

Give an initial dose of 100 mg orally.

For maximum absorption, take on an empty stomach, at least one hour before or two hours after eating.

During this fasting period, clear liquids such as water, apple juice, vegetable broth, tea, or black coffee can be tolerated.

Follow-up Doses:

Administer the next dose 12 hours after the first dose.

The recommended dosage is 50 mg orally every 12 hours.

These additional doses may be administered with or without food.

Use suzetrigine for the shortest duration consistent with the individual treatment goals, since its use has not been evaluated beyond 14 days.

Dosage Adjustments

Renal Impairment:

No dose adjustment is recommended for patients with an estimated glomerular filtration rate (eGFR) of 15 mL/min or greater.

Avoid use in patients with eGFR less than 15 mL/min.

Hepatic Impairment:

For mild impairment (Child-Pugh A), no dose adjustment is required.

For moderate impairment (Child-Pugh B):

Dose 1: 100 mg orally once.

Doses 2, 3, and 4: 50 mg orally every 12 hours starting 12 hours after the first dose.

Doses 5 and all subsequent doses: 50 mg orally every 24 hours initiated 12 hours following the fourth dose.

Severe hepatic impairment (Child-Pugh C) : Contraindicated. It has not been studied.

Strong CYP3A Inhibitors:

Concomitant administration with strong CYP3A inhibitors is contraindicated with suzetrigine.

Moderate CYP3A Inhibitors:

Dose 1: 100 mg orally one time.

Doses 2, 3, and 4: Dosing regimen as for moderate hepatic impairment.

Dose 5 and onwards will follow the same principles as described above.

Clinical problems

The most common side effects from suzetrigine were itching, muscle spasms nausea, constipation, and headache. But most of these side effects were more common with placebo than suzetrigine. The cost is around 16 US dollars per 50 mg tablet, which comes to around Rs 1300. This is not acceptable in the middle-income countries like India

CONCLUSION:

In summary, suzetrigine represents the next level of therapeutic advancement in analgesia for acute pain that is moderate to severe. It is a new, non-opioid drug with a targeted mechanism of action. The selective inhibition it achieves on sodium channels that are utilized in pain signaling prevents the central nervous system side effects and potential for addiction associated with opioids and other traditional analgesics. This agent has been shown to be efficacious and safe in clinical trials, making it a promising new alternative in the management of pain. With increased demand for safer pain relief drugs, suzetrigine can be pivotal in addressing the challenge of opioid abuse in public health.

Conflict of interest – NIL

No external financial aid

No ethical issues

Both the authors have contributed significantly in the preparation of the manuscript.

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