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Selective NaV1.8 Inhibition with Suzetrigine: A Mechanism-Based, Non-Opioid Strategy for Cancer-Related Pain

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INTRODUCTION

Pain affects an estimated 44.5% of patients with cancer; opioids remain the mainstay despite respiratory depression, dependence, and incomplete analgesia.[1]

Approved January 2025, suzetrigine is an oral non-opioid that relieves acute pain by inhibiting the NaV1.8 sodium channel, silencing nociceptive signaling in peripheral sensory neurons.[2] In NAVIGATE, efficacy was comparable to hydrocodone after surgery; its role in cancer pain remains undefined.[3]

Because NaV1.8 is expressed preferentially in DRG nociceptors, its inhibition may match opioid analgesia while sparing respiratory depression. We reviewed its role in cancer-related pain.

MATERIALS & METHODS

Design. Narrative scoping review of PubMed and ClinicalTrials.gov, examining NaV1.8 biology, cancer pain pathophysiology, and suzetrigine pharmacology, efficacy, and safety.

Ethics. UM HSRO determined the project was not human subjects research (45 CFR 46.102(e)). All applications remain investigational.

KEY PHARMACOLOGY

- **>31,000×** selectivity for NaV1.8 over other Na^+ subtypes[2]
- **No CV / CNS** adverse effects in trials[2]
- **Top AEs:** nausea (7.4%), paresthesia[3]
- **CYP3A** substrate + moderate inducer — interacts with CYP3A chemotherapeutics & hormonal agents[5]
- **Non-opioid:** no respiratory depression, tolerance, or dependence

MECHANISM (FIGURE 1)

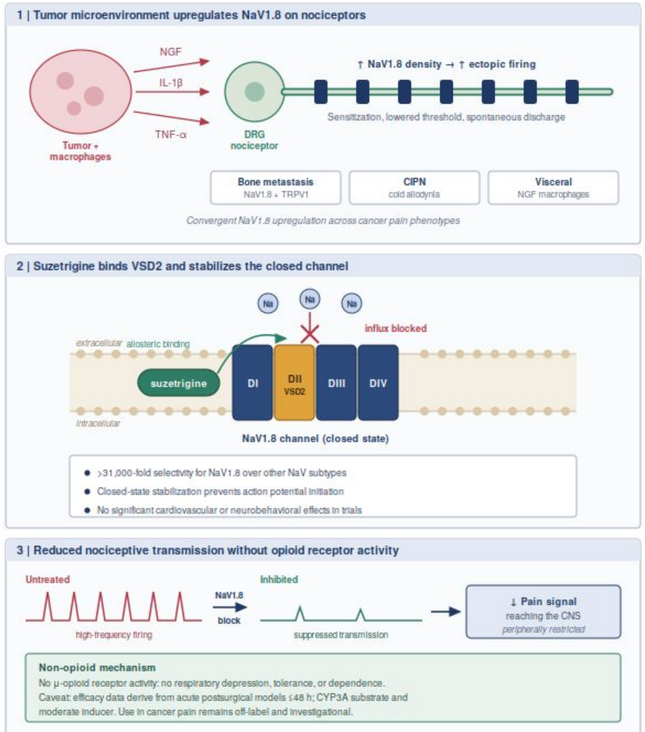


Figure 1. *Mechanistic basis for selective NaV1.8 inhibition in cancer-related pain (schematic; not to scale). CIPN, chemotherapy-induced peripheral neuropathy; CYP3A, cytochrome P450 3A; DRG, dorsal root ganglion; IL-1β, interleukin-1 beta; NGF, nerve growth factor; TNF-α, tumor necrosis factor alpha; VSD2, voltage-sensing domain 2.*

CONCLUSIONS

Suzetrigine offers a promising non-opioid alternative for patients vulnerable to opioid toxicity; prospective, controlled trials stratified by treatment modality are needed to establish safety, efficacy, and dosing before suzetrigine is incorporated into oncologic pain protocols.

RESULTS — CYP3A LIABILITY BY MODALITY

Table 1: Suitability of suzetrigine stratified by concurrent oncologic therapy[5]

Treatment Modality	CYP3A Risk	Rationale & Key Caveat
Active cytotoxic chemotherapy	**High**	Vincristine, docetaxel, imatinib, ibrutinib are CYP3A substrates/inhibitors; bidirectional exposure changes possible. Excluded from NAVIGATE - no PK dosing data.
Hormone therapy (enzalutamide, abiraterone)	**High**	Strong/moderate CYP3A interactors, high-risk despite not being cytotoxic. Other agents (fulvestrant, GnRH antagonists) lower-risk - class not uniform.
Immunotherapy (ICI monotherapy)	**Minimal**	Checkpoint inhibitors are mAbs cleared by proteolysis, not CYP. NaV1.8–tumor microenvironment and irAE pain biology incompletely understood.
Radiation therapy (standalone)	**None**	External beam, SRS/SBRT, brachytherapy are physical modalities - no systemic metabolism. Central/plexopathy pain may respond less to a peripheral agent.
Survivorship / CIPN (off treatment)	**Minimal**	No concurrent CYP3A therapy; strongest rationale for chronic, peripheral, NaV1.8-driven pain. No chronic-use efficacy data - off-label.

DISCUSSION

Acting on a channel implicated across nociceptive, neuropathic, and inflammatory cancer pain pathways,[4] suzetrigine offers a rational non-opioid alternative or adjunct for a population uniquely vulnerable to cumulative opioid toxicity. Yet evidence remains preliminary: every efficacy dataset derives from acute postsurgical models ≤48 hours;[3] no chronic-use or oncology-specific trial exists, and cancer-pain use remains off-label. CYP3A interactions demand careful stratification by concurrent therapy.[5]

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