Finding Relief in the Big Easy: Advances in Non-Opioid Analgesia

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Disclosures

- No relevant financial conflicts of interest

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Learning Objectives

- Identify emerging targets for non-opioid analgesics
- Evaluate the efficacy and safety data, when available, for new and emerging non-opioid analgesics
- Describe opportunities for the re-purposing of existing medications for use as non-opioid analgesics, co-analgesics, or adjuvant analgesics
- Apply principles of mechanism-based analgesic selection to clinical scenarios involving acute and chronic pain

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Case

Jim is a 45 year old flooring contractor with a 10 year history of CLBP w/ radiculopathy who presents today for f/u of uncontrolled pain. L-spine MR significant for multi-level facet dz, L4/L5 and L5/S1 mild-mod foraminal narrowing and L5/S1 mild central canal stenosis 2/2 broad based disc bulge. Describes as pressure and stabbing locally, burning and electric in lower extremities extending to ankles. Radicular symptoms more bothersome than localized sx.

PMHx: CLBP, HTN, h/o polysub use

Meds: GBP 600mg q8, duloxetine 60mg QAM, losartan 50mg QAM

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Emerging / New (and repurposed) Analgesic Opportunities

- Cannabinoid modulators
- NSAID like-analgesics
- Glutamate modulators
- VGSC selective antagonists
- TRP channel modulators
- NGF antagonists
- TrkA modulators
- ATP-gated ion channel modulators
- ASIC inhibitors
- Glial cell modulators

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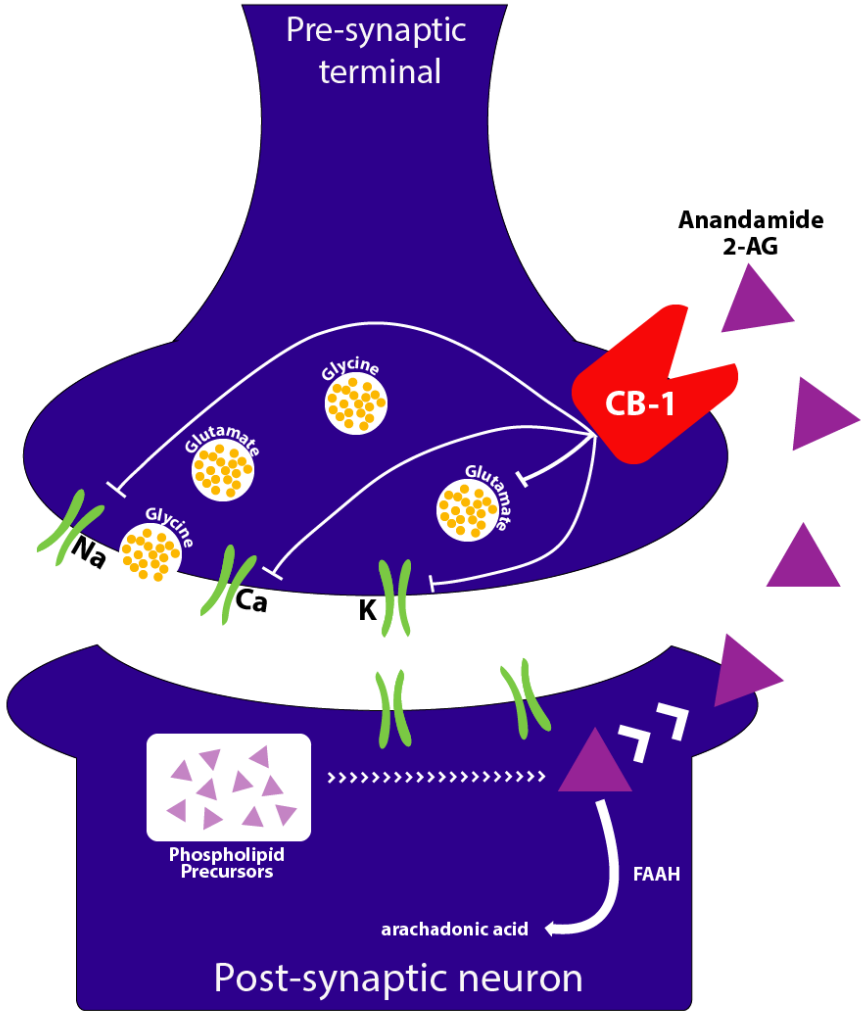
Cannabinoids & Endocannabinoid Modulators

- ABHD6 inhibitors
- FAAH inhibitors
- NAAA inhibitors
- CB2 selective agonists



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NSAID-like analgesics

- Otenaproxesul (ATB-352) and ATB-346 – H_2S releasing naproxen and ketoprofen derivatives
  - Statistically improved GI toxicity in clinical Phase 1
  - Abandoned by Antibe Therapeutics but purchased by Sun Pharma
- Imrexoxib – balanced COX-2 selective antagonist
- DFV890 – NLRP3 inflammasome (NLRP3 protein) inhibitor with downstream inhibition of IL1B and IL18
  - Results of Phase 2a Knee OA study (n=115) resulted Dec 2024
  - Statistically improved KOOO scores

Clinicaltrials.gov. Accessed Jan 11, 2026.
Gatlik E, et al. *Clin Transl Sci*. 2024;17(5):e13789.
Glowacka U, et al. *Antioxidants*. 2023;12(8):1545.

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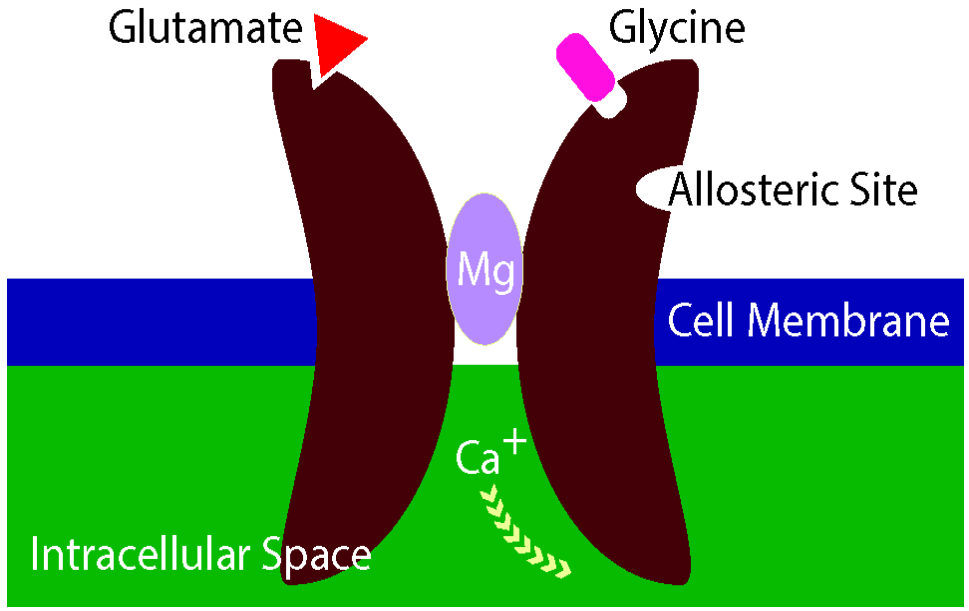
NMDA / glutamate modulators

- Amantadine
- Memantine
- Dextromethorphan
- Ketamine
- Esketamine
- Methadone
- Minocycline
- Levorphanol
- Orphenadrine



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Memantine (MEM)

Author, year	Population	Methods	Intervention	Outcome
Bigal, 2008	Refractory migraine, n = 28	Prospective, open-label, 3-month Primary outcome: HA frequency	MEM PO 10-20mg daily	2 & 3 month reduction in headache days (15.4, p<0.01 and 16.1, p<0.01)
Gustin, 2010	CRPS I & II, n = 20	DBPCR, 7 week study Primary outcome: VAS at rest	Morphine (M) PO 30mg + MEM PO 40mg or PBO	M + MEM separated from M + PBO (p< 0.001)
Maier, 2003	Phantom Limb, n = 36	DBPCR, 4 week study Primary outcome: NRS daily average	MEM PO 30mg daily Placebo	No treatment effect vs. PBO
Morel, 2016	Post-mastectomy, n = 40	Single blind, randomized, placebo-controlled 4 week study (-14 thru +14) Primary outcome: NRS and BPI	MEM PO 20mg daily Placebo	Month 3: p = 0.017 Month 6: p = 0.10
Nikolajsen, 2000	NpP (post-surg or PLP), n = 19	DBPCR, 2 period, 5 week, crossover Primary outcome: NRS Secondary outcome: McGill	MEM PO 20mg daily Placebo	No effect for primary or secondary outcomes
OB, 2014	Fibromyalgia, n = 63	DBPCR parallel 6 month study Primary outcome: VAS Secondary outcome: FIQ	MEM PO 20mg daily Placebo	VAS reduction at 1,3, & 6 months (p = 0.001)

Bigal M, et al. *Headache* 2008;48:1337-1342; Gustin SM, et al. *Pain* 2010;151:69-76; Maier C, et al. *Pain* 2003;103:277-283; Morel V, et al. *PLoS ONE* 2016;11(4):e0152741; Nikolajsen L, et al. *Anesth Analg* 2000;91:960-966; Olivan-Blazquez B, et al. *Pain* 2014;155:2517-2525.

Minocycline (MIN)

Author, year	Population	Methods	Intervention	Outcome
Curtin, 2017	Carpal tunnel and trigger finger, n = 131	DBPCR, single dose Primary outcome: Time to pain resolution	MIN PO 200mg prior and 100mg Q12 X 5 days after OR Placebo	No reduction in primary or secondary outcomes
Gorsky, 2008	Aphthous stomatitis, n = 33	DBPCR 10 day cross-over study Primary outcome: self reported pain relief	MIN 2mg/ml (0.2%) mouthwash Placebo	MIN better than placebo beginning 24 hrs after initiation ($p < 0.05$)
Martinez, 2013	Lumbar discectomy, n = 100	DBPCR 8 day study Primary outcome: NRS pain intensity	MIN PO 100mg Q12 (-1 through +8 POD) Placebo	No difference in pain at rest, with movement
Syngle, 2014	Painful and autonomic diabetic neuropathy, n = 50	Randomized, placebo-control, open-label 6 week study Primary outcome: LANSS and PDI	MIN PO 100mg daily Placebo	LANSS and PDI better in MIN group ($p \leq 0.01$)
Vanelderen, 2015	Lumbar radiculopathy, n = 60	DBPCR, active comparator Primary outcome: 11 point NRS	MIN PO 100mg daily Amitriptyline 25mg daily Placebo	MIN and Amitriptyline both separated from placebo on day 14 ($p < 0.05$); no difference in responder analysis

Curtin CM, et al. *J Hand Surg Am* 2017;42:166-174.
Gorsky M, et al. *Spec Care Dentist* 2008;28(1):27-31.
Martinez, et al. *Pain* 2013;154:1197-1203.
Syngle A, et al. *Neurol Sci* 2014;35:1067-1073.
Vanelderen P, et al. *Anesthesiology* 2015;122:399-406.

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Ketamine

- Racemic mixture of S- and R- ketamine
  - S-ketamine (esketamine) 4x higher NMDA binding affinity than R-
  - R-ketamine 2 to 3x higher AMPA binding than S-
- Esketamine
  - Post-operative pain following video-assisted thoracoscopic surgery
  - Peri-operative pain during elective cesarean delivery
  - Post-operative pain following gastrointestinal surgeries in the elderly
  - Post-operative pain following thyroidectomy

Wang P, et al. *Br J Clin Pharmacol*. 2023;89(8):2542-2551; Liu J, et al. *BMC Anesthesiol*. 2024;24(1):46; Xu LL, et al. *JAMA Netw Open*. 2023;6(4):e239321; Yan H, et al. *Anesth Analg*. 2023;137(2):399-408.

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XW10508 (oral esketamine pro-drug)

- Phase 1 clinical studies
  - Major depressive disorder
  - Chronic pain
- Plans for once daily dosing
- Conjugate / hydrolysis with improved oral bioavailability

https://clinicaltrials.gov/study/NCT04966832. Accessed Jan 12, 2026.
Zanos P, et al. *Pharmacol Rev.* 2018;70(3):621-660.

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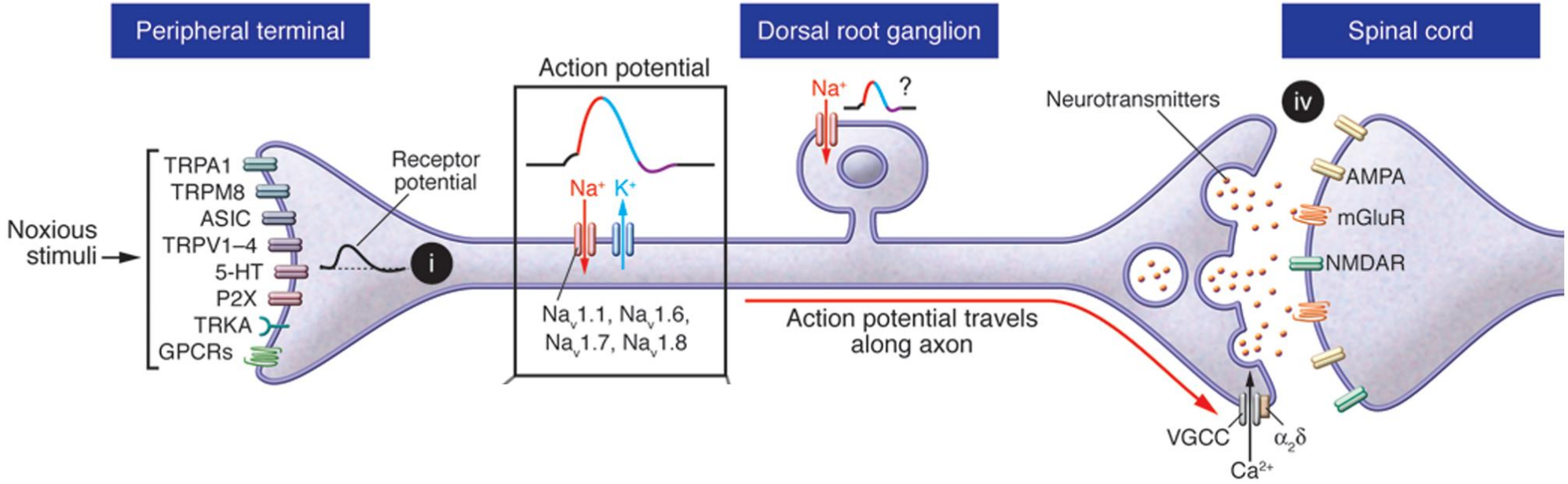
Sodium channel (NaV) role in nociception



Raouf R et al. *J Clin Invest*. 2010;120(11):3745-3752; Mears L et al. *Br J Nurs*. 2023;32(2):58-65.

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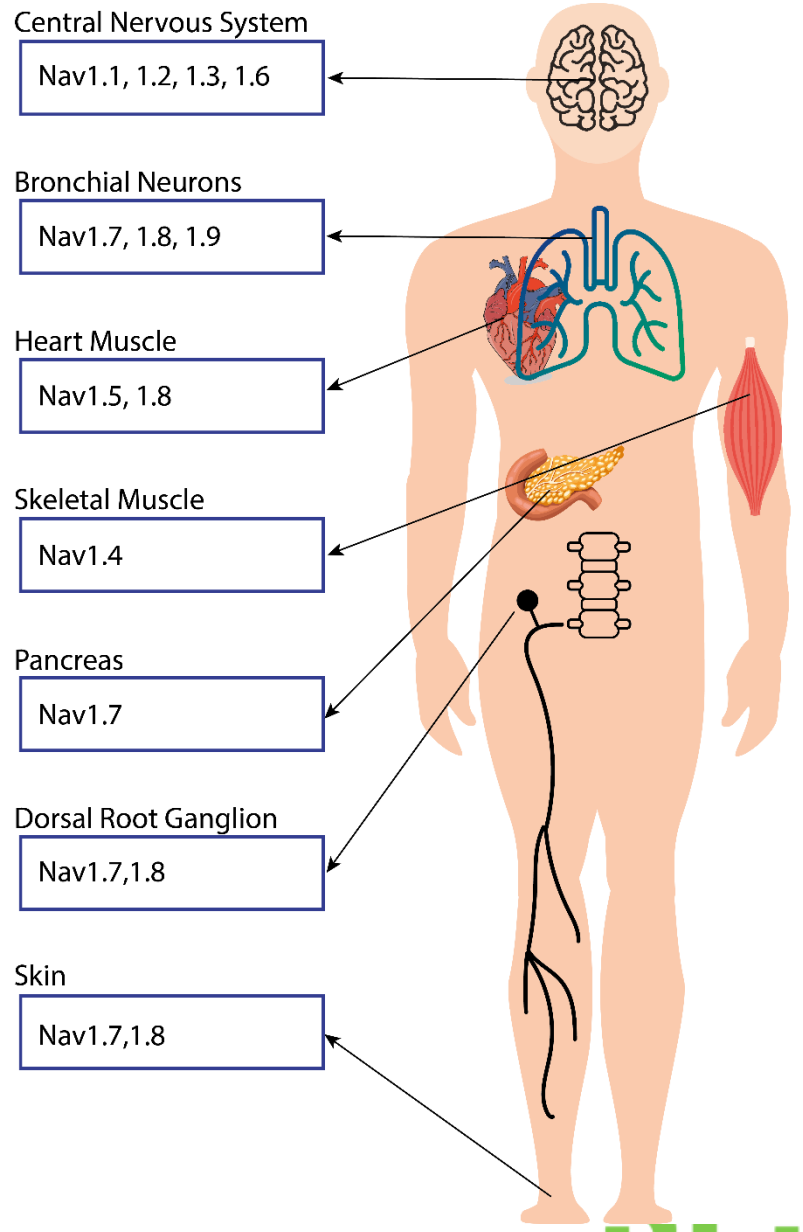
VGSC Distribution & Function

VGSC Subtype	Putative Action
Nav1.1	Inhibitory transmission/modulation
Nav1.2	CNS rapid firing
Nav1.3	Embryonic action potential
Nav1.4	Muscle contraction
Nav1.5	Cardiac conduction
Nav1.6	Repetitive firing in CNS/PNS
Nav1.7	Nociceptor action potential in PNS
Nav1.8	Nociceptor action potential in PNS, especially with inflammation or neuropathy
Nav1.9	Enhances excitability of nociceptive transmission in PNS



PNS, peripheral nervous system.

Waxman SG. *N Engl J Med*. 2023;389(5):466-469; Goodwin G et al. *Nat Rev Neurosci*. 2021;22(5):263-274; de Lera Ruiz M et al. *J Med Chem*. 2015;58(18):7093-118.

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VGSC selective antagonists

NaV 1.8

- Suzetrigine (VX-548)
- LTGO-33
- Dexpramipexole

NaV 1.7

- BIIB074
- Ralfinamide

NaV 1.7 / 1.8

- ABBV-318

Banh C, et al. *CNS Drugs*. 2025;Nov 3. doi: 10.1007/s40263-025-01244-x. Online ahead of print.

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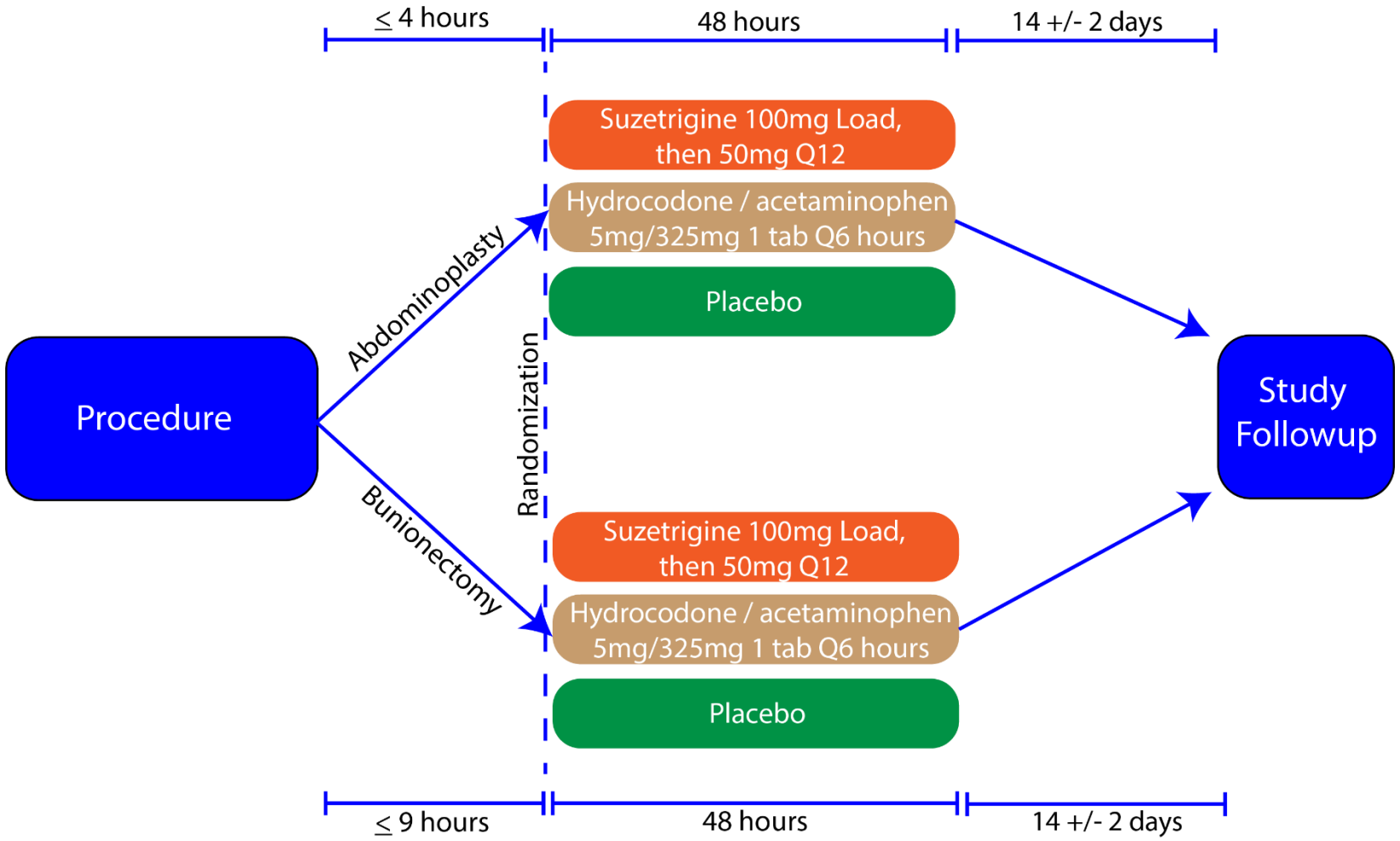
Suzetrigine Phase 3 Studies



Bertoch T, et al. *Anesthesiology*. 2025;142:1085-1099.

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Suzetrigine Phase 3 Results

Table 2. Primary Endpoint: SPID48 Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	**Placebo N = 223**	**Suzetrigine N = 426**	**Placebo N = 216**
Prespecified analysis with rescue imputation (imputed)				
LS mean ± SE	118.4 ± 4.3	70.1 ± 6.1	99.9 ± 4.5	70.6 ± 6.3
LS mean difference from placebo	48.4	—	29.3	—
95% CI	(33.6–63.1)	—	(14.0–44.6)	—
P value *vs.* placebo	<0.0001	—	0.0002	—
Post hoc analysis without rescue imputation (as treated)				
LS mean ± SE	153.0 ± 4.5	105.4 ± 6.4	128.8 ± 4.7	100.1 ± 6.6
LS mean difference from placebo	47.7	—	28.8	—
95% CI	(32.4–62.9)	—	(12.9–44.6)	—
Nominal *P* value *vs.* placebo*	< 0.0001	—	0.0004	—

Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

*Analyses for SPID48 compared to placebo without rescue imputation are *post hoc*; therefore, *P* values are nominal.

LS mean, least squares mean; N, number of participants in the analysis set; SE, standard error; SPID48, time-weighted sum of the pain intensity difference as recorded on the numeric pain rating scale from 0 to 48 h.

Bertoch T, et al. *Anesthesiology*. 2025;142:1085-1099.

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Suzetrigine Prescribing Info

- **Indication:** for moderate to severe acute pain in adults
- **Dosing**: 100 mg orally (initially on an empty stomach), followed by 50 mg orally every 12 weeks with or without food
  - Avoid use in patients with severe hepatic impairment; moderate impairment requires reduction in frequency to 50 mg daily following 4 doses
  - Does not require renal dosing; avoid use in creatinine clearance (CrCL) rate <15 mL/min
  - Has not been studied beyond 14 days
- **Pharmacokinetics**: half-life of 23.6 hours; metabolized via CYP3A to M6-SUZ (active); 99% protein bound; elimination via feces (49.9%) and urine (44.0%)
- **Drug interactions**: STG is both a substrate and inducer of CYP3A; certain hormonal contraceptives
- **Contraindications**: concomitant use with strong CYP3A inhibitors

Journavx. Vertex Pharmaceuticals Incorporated; 2025. Accessed February 26, 2025. https://pi.vrtx.com/files/uspi_suzetrigine.pdf

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TRP Channel Modulators

- TRPV1 agonists
  - Capsaicin
  - Resiniferatoxin (ultrapotent analogue for injection)
- TRPA1 antagonists
  - Only clinical data for chronic cough
- TRPM8
  - Animal models only

Dangi A, et al. *Eur J Pharmacol*. 2024;980:176845.

NGF- inhibitors

- Tanezumab
  - Effective in Phase 3 studies
  - Development halted due to RPOA
- Fasinumab
  - Effective in Phase 3 studies
  - Development halted due to RPOA and osteonecrosis
- FDA clinical hold on further compound development

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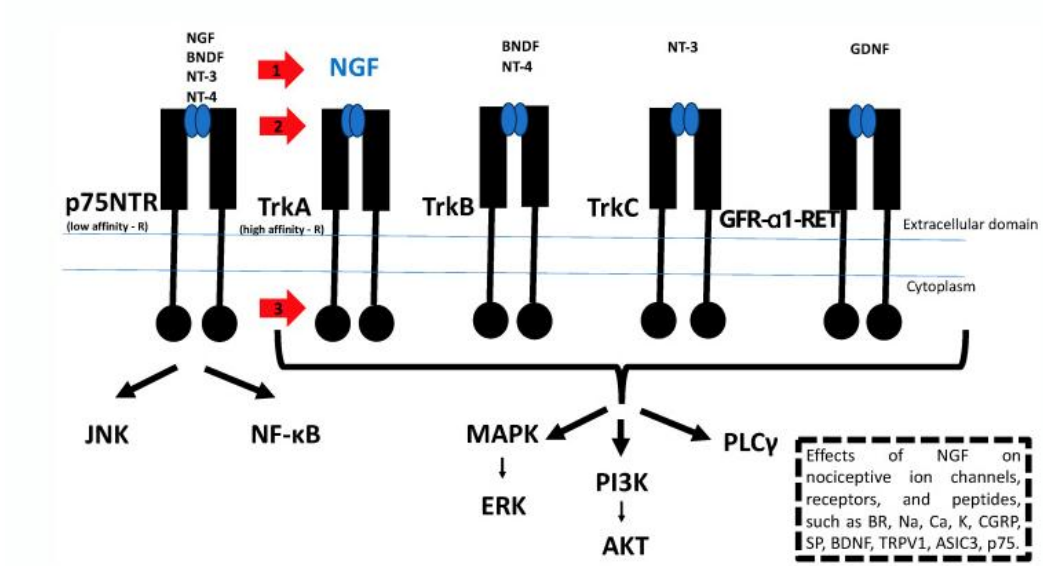
TrkA Modulators

- GZ389988A only TrkA modulator with clinical data
- Unclear development pathway



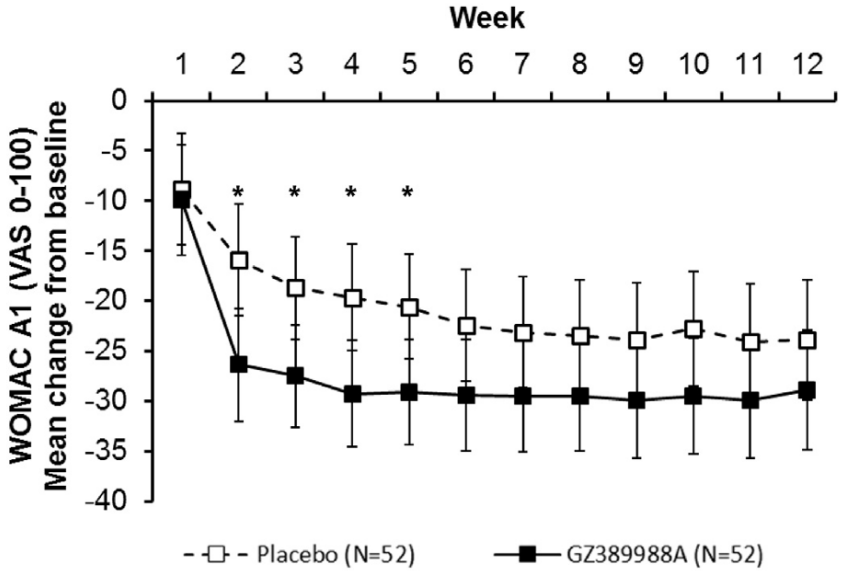


Fig. 2. WOMAC A1 (from eDiary) mean change from baseline. Data are presented as weekly least squares means ± 90% confidence intervals, *one-sided $P < 0.05$ vs placebo.

Krupka E, et al. *Osteoarthritis Cartilage*. 2019;27(11):1599-1607.

https://clinicaltrials.gov/study/NCT02845271. Accessed Jan 11, 2026.

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Imidazoline-2 (I2) receptor ligand (CR4056)

- Multicenter DBPCR 14 day study in Knee OA
- N = 213
- Primary outcome: change in WOMAC pain score
- Results:

Table II
Change in WOMAC pain and Q1 after 14-day treatment in ITT patients

	Placebo (N = 69)	CR4056 women (N = 92)	CR4056 men (N = 52)	CR4056 pooled (N = 144)
WOMAC pain				
Mean (SD)	−15.0 (19.0)	−17.3 (19.4)	−21.0 (19.4)	−18.6 (19.4)
Median (range)	−10 (−64; 14)	−14 (−64; 22)	−20 (−80; 4)	−16 (−80; 22)
P-value*		0.184	0.030	0.070
WOMAC pain Q1				
Mean (SD)	−11.4 (19.3)	−17.1 (22.6)	−17.3 (22.5)	−17.2 (22.5)
Median (range)	0 (−80; 20)	−10 (−80; 30)	−15 (−80; 30)	−10 (−80; 30)
P-value*		0.064	0.059	0.039

* Comparison vs placebo by Wilcoxon rank-sum test.

Rovati LC, et al. *Osteoarthritis Cartilage.* 2020;28:22-30.

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P2X3 / P2X2-3 receptor antagonists

- Gefapixant
  - Approved in EU, Switzerland, Japan for chronic cough
- Camlipixant
  - Phase 3 studies underway for chronic cough
- Eliapixant
  - Positive Phase 2b for chronic cough but suspended due to hepatotoxicity

- All 3 have positive pre-clinical data for visceral & neuropathic pain as well as mechanical hypersensitivity

Huerta MA, et al. *Eur J Pharmacol*. 2024;984:177052.

ASIC inhibitors

- Peptide toxins from animal venom and small molecules
- All data pre-clinical
- No listed trials underway on clinicaltrials.gov for candidate compounds

Belozerova OA, et al. *Pharmaceuticals*. 2020;13(8):163.

Glial modulators

- Minocycline
- Pentoxifylline
  - Radicular
  - Acute post-operative
- Ibudilast
- Azithromycin
- Glycine transport inhibitors

Gilron I, et al. *Pain*. 2025;166(5):1030-1049.

Tarabay B, et al. *Clin Neurol Neurosurg*. 2022;219:107309.

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Case Revisited

- Which newer or repurposed analgesics / adjuvant analgesics might be reasonable for Jim?

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Conclusions

- Numerous new agents are being investigated as non-opioid analgesics
- Re-purposing of currently marketed medications represents an opportunity to alleviate pain

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