

Evaluating the Therapeutic Potential of Emerging Precision Sodium Channel Modulators in Pain

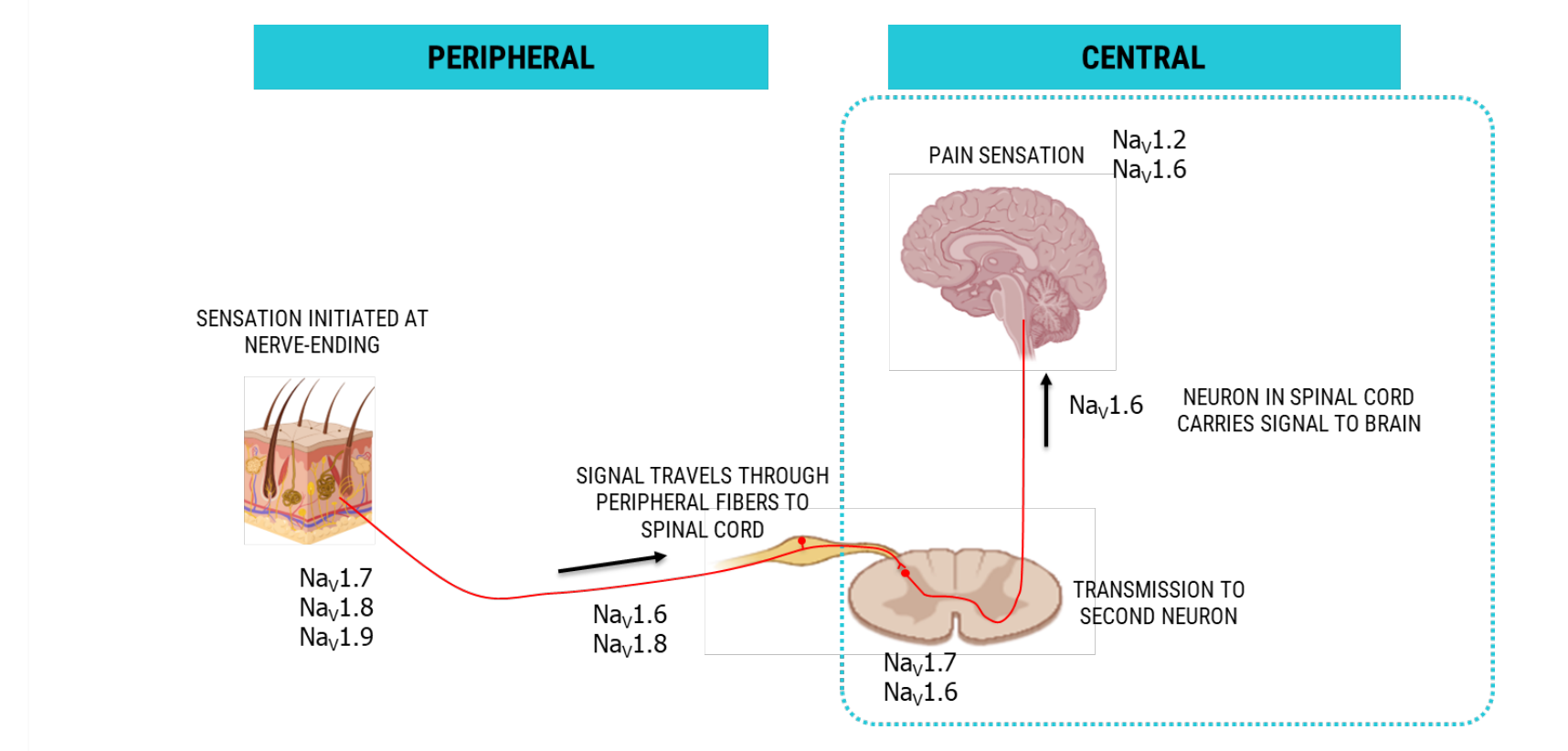
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BACKGROUND

- Despite multiple approved analgesics, effective and well-tolerated treatments for many acute and chronic pain conditions remain limited.
- Existing treatments fail to fully address the underlying peripheral and central mechanisms of pain signal transmission and sensitization.
- Voltage-gated sodium (Na_v) channels are key mediators of pain signaling.
- Conventional sodium channel blockers (SCBs) provide analgesia for several peripheral and central pain states but are limited by poor tolerability.
- Relutrigine, vortmatrigine and PRAX-1451 are next-generation Na_v channel modulators optimized to treat epilepsy with each demonstrating superior selectivity for pathologic states of brain Na_v isoforms.
- Emerging evidence from epilepsy trials points to improved efficacy and tolerability of these molecules over standard SCBs, supporting exploration of this differentiated Na_v modulation approach for potential therapeutic utility in pain.

Here, we sought to evaluate the analgesic effect of precision sodium channel modulators across preclinical and human pain models.

Pain signals travel through both peripheral and central neurons. A CNS penetrant, pan-Na_v modulator can block pain signaling by interrupting multiple checkpoints in both peripheral and central compartments. Adapted from Yogi et al. *Life*. 2025; 15(4):640.



METHODS

Acute Pain

- Formalin:** Male CD-1 mice were used to assess the analgesic activity of relutrigine in the formalin-induced pain model. Mice were pre-treated with either vehicle, relutrigine or morphine prior to injection of dilute formalin into the right hind paw plantar surface. Pain response was measured as total lick time during the late phase.
- Incision Pain:** Male Sprague-Dawley rats received a surgical incision on the plantar surface of the left hind paw. Rats were pre-treated with vehicle, relutrigine or morphine and the 50% paw withdrawal threshold (PWT₅₀) was measured to assess mechanical allodynia.

Neuropathic Pain

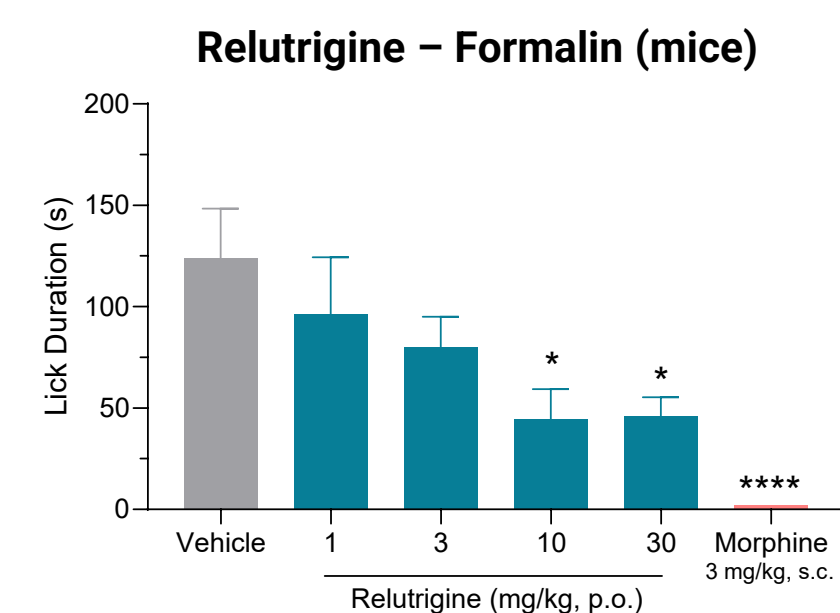
- Oxaliplatin-Induced Peripheral Neuropathy:** Male Sprague-Dawley rats and C57BL/6J mice were used to assess the activity of vortmatrigine and relutrigine in cold immersion or acetone tests, respectively. Repeated oxaliplatin injections were used to establish cold allodynia. Sham controls received no oxaliplatin injections.
- Chronic Constriction Injury:** Male Sprague-Dawley rats underwent surgical chronic constriction injury to induce mechanical allodynia. Rats were pre-treated with vehicle, vortmatrigine or gabapentin and the 50% paw withdrawal threshold (PWT₅₀) was measured to assess mechanical allodynia.

Translational Model

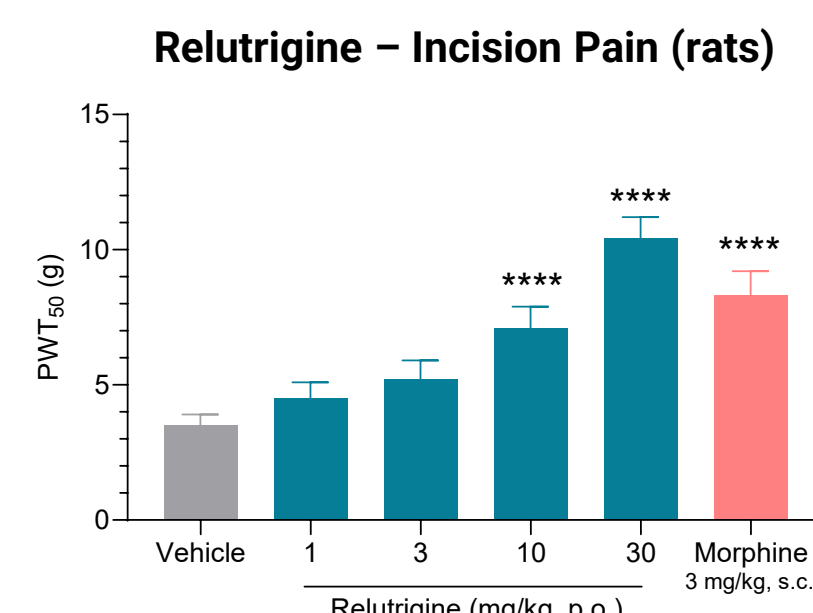
- PRAX-1451 effects were evaluated in healthy volunteers using Nerve Excitability Threshold Tracking (NETT) and the PainCart test battery as human biomarkers of Na_v-mediated analgesic mechanisms.

EFFICACY IN ACUTE PAIN

Relutrigine Demonstrates Dose-Dependent Efficacy in Acute Pain Models at Well-Tolerated Doses



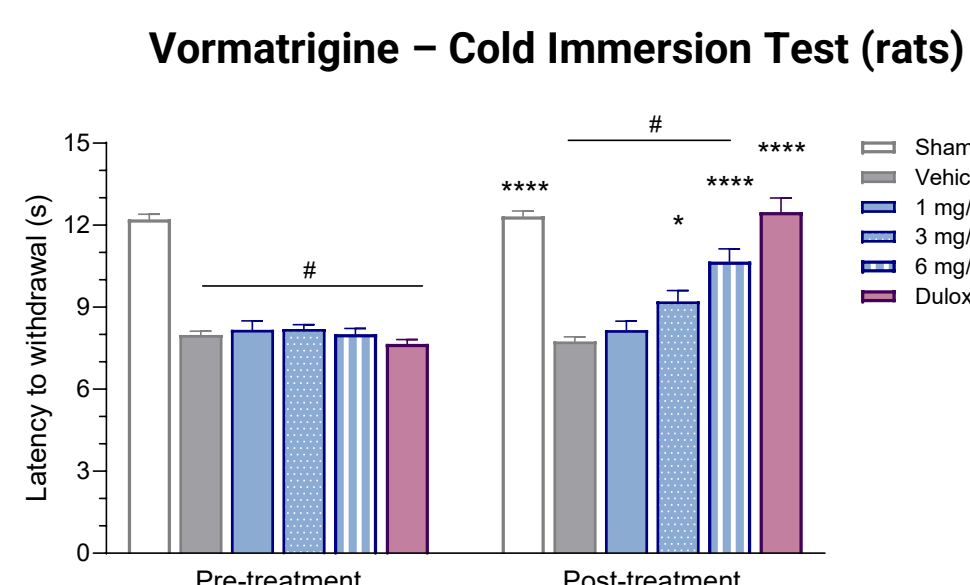
Relutrigine is Analgesic in the Mouse Formalin Model of Inflammatory Pain. Dose-dependent reduction in the formalin-induced pain response following treatment with relutrigine, p.o.=oral; s.c.=subcutaneous. *p<0.05, ****p<0.0001 vs. vehicle; one-way ANOVA followed by Dunnett's post-hoc.



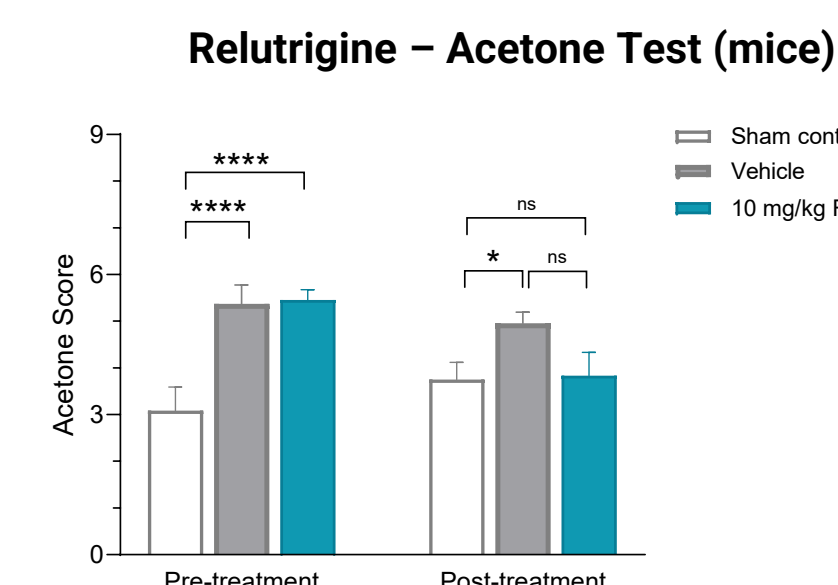
Relutrigine is Analgesic in the Rat Brennan Incision Model of Post-Operative Pain. Dose-dependent increase in the 50% paw withdrawal threshold (PWT) with relutrigine following hind paw incision, p.o.=oral; s.c.=subcutaneous. ****p<0.0001 vs. vehicle; one-way ANOVA followed by Dunnett's post-hoc.

EFFICACY IN NEUROPATHIC PAIN

Precision Sodium Channel Modulators Reduce Oxaliplatin-Induced Cold Allodynia

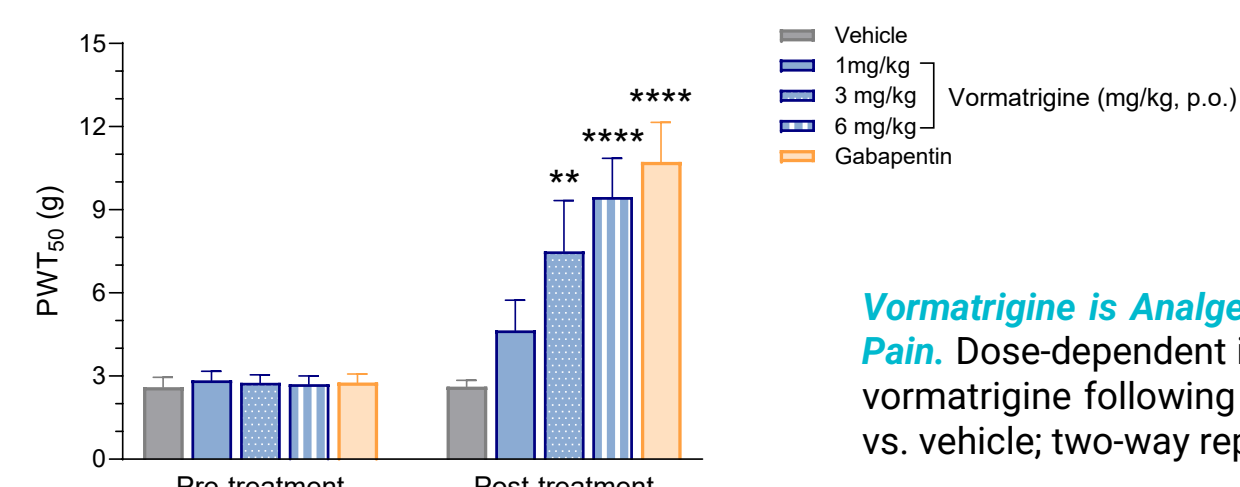


Vortmatrigine is Analgesic in the Rat Oxaliplatin Model of Chemotherapy-Induced Peripheral Neuropathy. Dose-dependent reversal of oxaliplatin-induced pain response following treatment with vortmatrigine, p.o.=oral; *p<0.05, ****p<0.0001 vs. vehicle; #p<0.05 vs. sham control; two-way repeated measures ANOVA followed by Tukey's post-hoc.



Relutrigine is Analgesic in the Mouse Oxaliplatin Model of Chemotherapy-Induced Peripheral Neuropathy. Relutrigine reverses oxaliplatin-induced pain response, p.o.=oral; *p<0.05, ****p<0.0001, n.s.=not significant; two-way repeated measures ANOVA followed by Tukey's post-hoc.

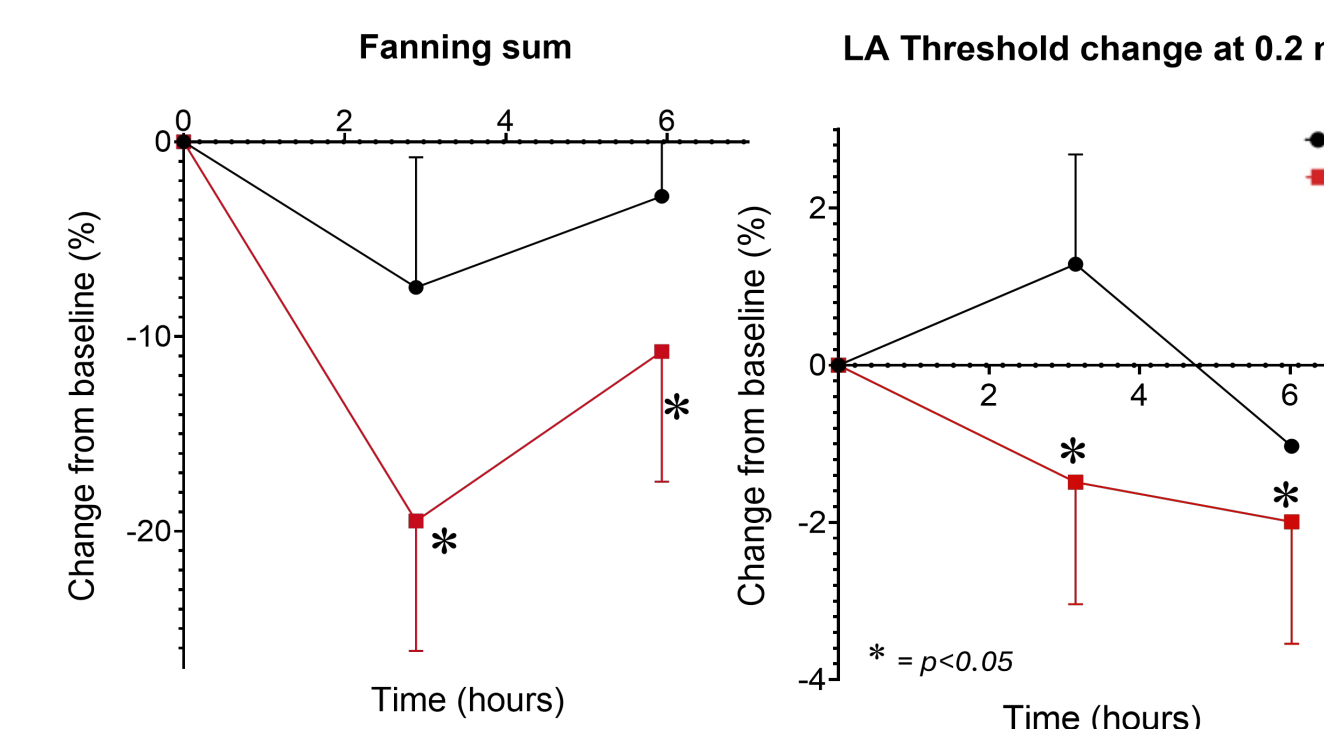
Vortmatrigine Dose-Dependently Reverses Mechanical Allodynia in Peripheral Nerve Injury Model



Vortmatrigine is Analgesic in the Rat Chronic Constriction Injury of Neuropathic Pain. Dose-dependent increase in the 50% paw withdrawal threshold (PWT) with vortmatrigine following peripheral nerve injury. p.o.=oral; **p<0.01, ****p<0.0001 vs. vehicle; two-way repeated measures ANOVA followed by Tukey's post-hoc.

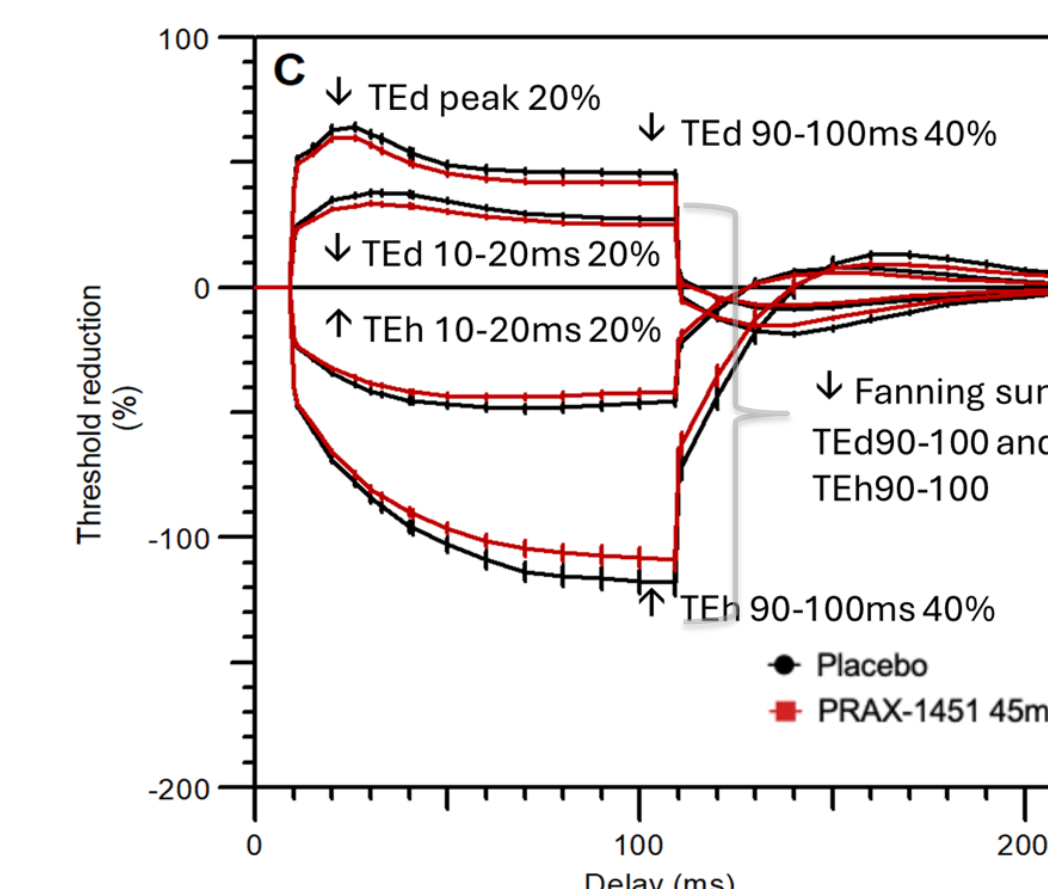
TRANSLATIONAL FINDINGS IN HEALTHY VOLUNTEERS

PRAX-1451 Significantly Decreases Sensory Axonal Excitability in Healthy Volunteers, with Distinct Effects on Latent Addition Protocols (LA) Confirming its MoA and Superior Functional Selectivity



Change from Baseline (Including 95% Confidence Interval Error Bars) for Sensory Axon Excitability Parameters. (Left) Threshold Electrotonus (TE) Fanning sum and (right) Latent Addition (LA) Threshold Change at 0.2 ms. The fanning sum is a sum of the depolarizing and hyperpolarizing conditioning pulse (CP) at 90-100 ms. The LA consists of a 90% hyperpolarizing CP pulse where the neuronal recovery is specific for persistent sodium channel function.

- 20 participants received treatments.
- Nerve Excitability Threshold Tracking (NETT) was performed using the TROND and LA protocols.
- Sensory Nerve Action Potential (SNAP) Main results:
 - ↓ Depolarizing TE (TEd, p<0.05)
 - ↑ Hyperpolarizing TE (TEh, p<0.05)
 - ↓ Fanning sum (p<0.05)
 - ↓ LA Threshold change at 0.2 ms (p<0.05)
- Additional significant results, *not shown*
 - ↓ Current-Threshold (I/V) sensory parameters
 - ↓ Recovery Cycle (RC) sensory parameters
- PRAX-1451 did not exhibit motor effects



TROND Graph for Sensory TE Parameters The TE paradigm consists of a 40% and 20% depolarizing or hyperpolarizing conditioning pulse during which a test pulse is given (10-100 ms after) to measure the neuron's compensatory ability. Baseline is in black. The 2hr and 5hr post-dose data are combined and plotted in red. Data are mean ± SE.

CONCLUSIONS

- Functionally selective Na_v modulators optimized to treat epilepsy also display analgesic potential in preclinical and human models.
- These data support advancing this differentiated mechanism of action to identify next-generation pain therapeutics.

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Ethical Statement All in vivo studies were performed in accordance with local and institutional animal care and use guidelines.

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Disclosures KK, LA, MS and SP are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders. KR, MC, IK, KdC and GJG performed clinical trial management and data analysis of PRAX-1451 translational findings, with financial assistance provided by Praxis Precision Medicines.

