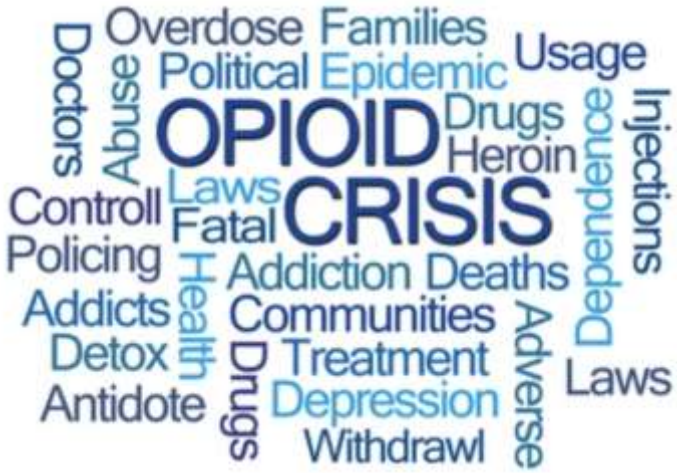
There has never been a greater need for safe and effective analgesics…

- Conventional opioids and nonsteroidal analgesics (NSAIDs) carry significant risks of addiction and adverse side effects
- Side effects lower quality of life and drive medical costs; thousands of patients are tragically dying from opioid overdose, stroke and heart attacks
- Our novel pH-sensitive compound (NFEPP) selectively acts at sites of inflammation where tissue is acidic but not elsewhere in the body (e.g., brain) and hence is devoid of addiction risk and other side effects
- The pain market is projected to increase by 50% in North America in 5 years



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NFEPP: First-in-Class Analgesic that Could Replace Opioids and NSAIDs

- Similar potency as opioids, NSAIDs and local anesthetics in inflammatory and cancer pain
- No addictive potential due to selective targeting of acidic pain sites outside of the brain; no side effects such as nausea, constipation, respiratory depression, cognitive and locomotor impairment
- Compelling pre-clinical data in multiple pain models and independent laboratories
- Potential anti-inflammatory and anti-cancer effects

Pharmacology & Therapeutics 2020;210:107519
Trends Pharmacol Sciences 2013;34:303

"the non-addictive pain killer that lacks side effects"

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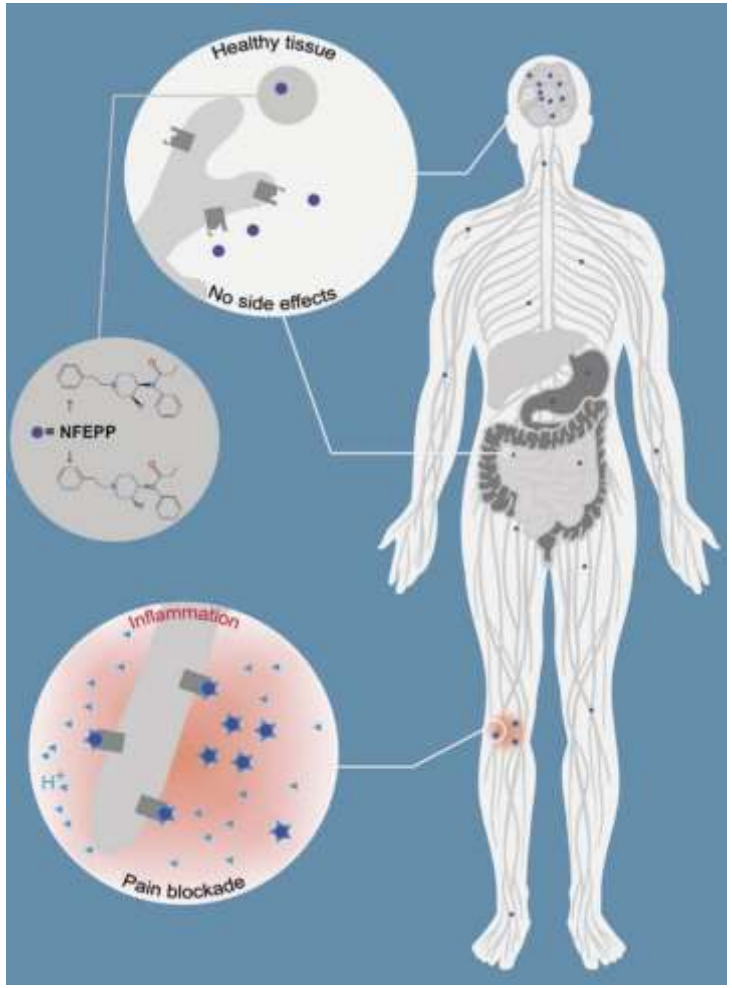
pHarm Therapeutics: First-in-Class Analgesic Selective for Site of Pain Origin

- pH-sensitive NFEPP selectively acts at sites of inflammation/injury (low pH) but not elsewhere in the body (normal pH, e.g. brain)
- US patent 14/239,461
- Ready for IND-enabling studies
- Potential phase I/II clinical trial in orthopedic surgery in 3-5 years



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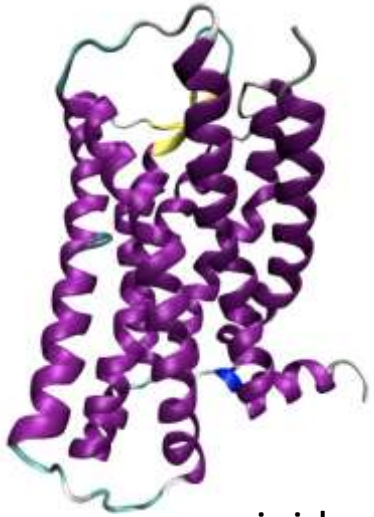
NFEPP Development

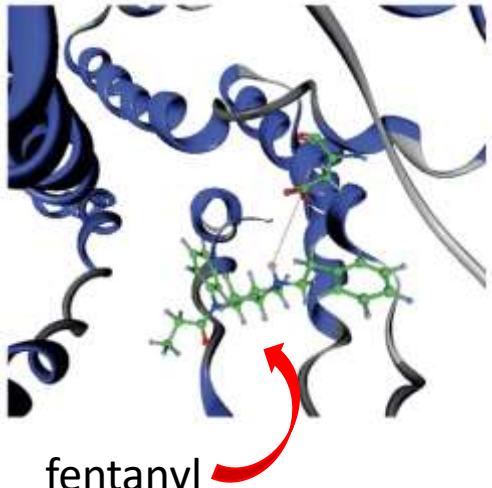
addiction + side effects



mu opioid receptor

Pathological opioid receptor

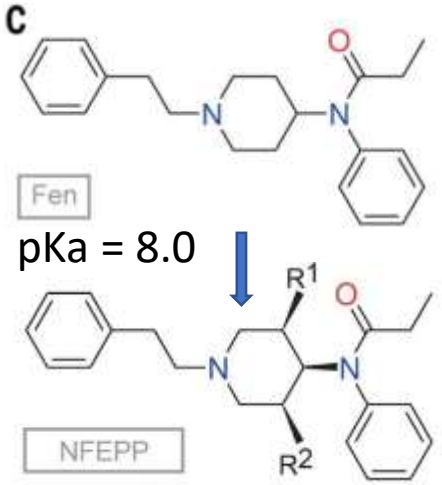
protonated fentanyl binds MOR



fentanyl

Computer modelling

NFEPP is only protonated in acidic tissues (inflamed)



pKa = 6.8 Fl^- at R1 or R2

Drug design

inflammation + cancer pain models

Pre-clinical validation

Spahn et al. Science 2017

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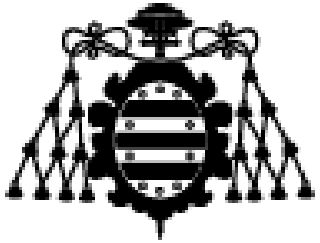
NFEPP: External and Cross-Species Validation



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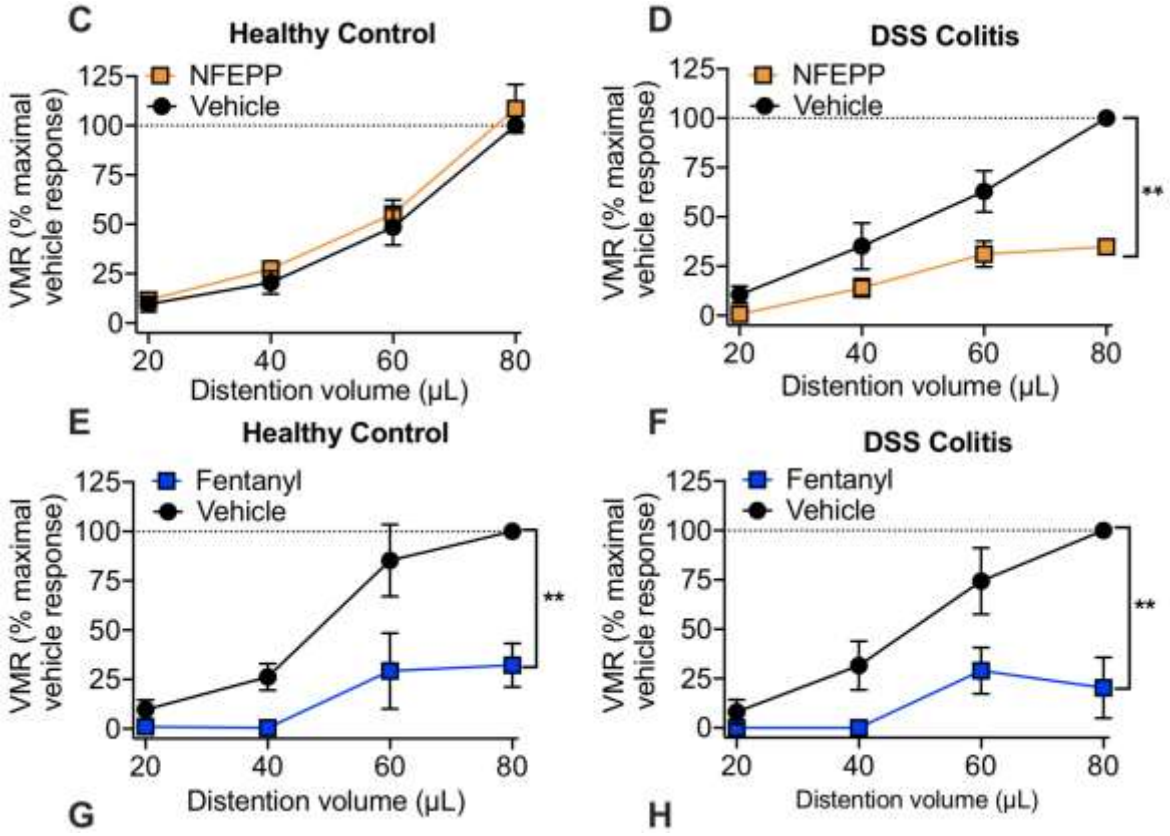
External Validation by Replication

Visceral inflammatory pain



Replicated in 3 other models

- **Arthritis inflammatory pain**
- **Cancer inflammatory pain**
- **Post-operative inflammatory pain**

NFEPP has similar potency to fentanyl for inflammatory and cancer pain

Spahn et al. Science 2017; Jimenez-Vargas et al. Gut 2021; Baamonde et al. Sci Rep 2020; Degro et al. PAIN 2023

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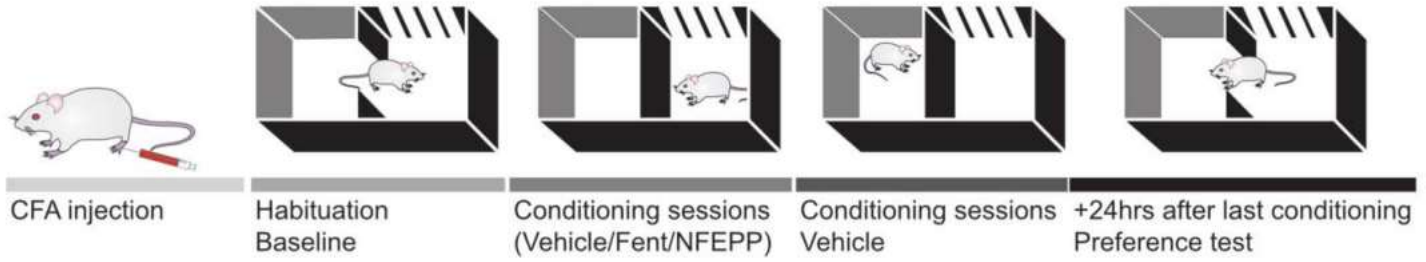
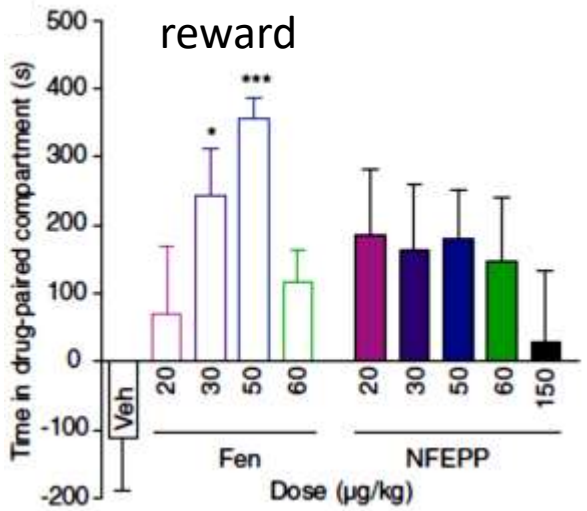
Safety Data: Addiction Studies Using Place Preference Model



Naïve animal

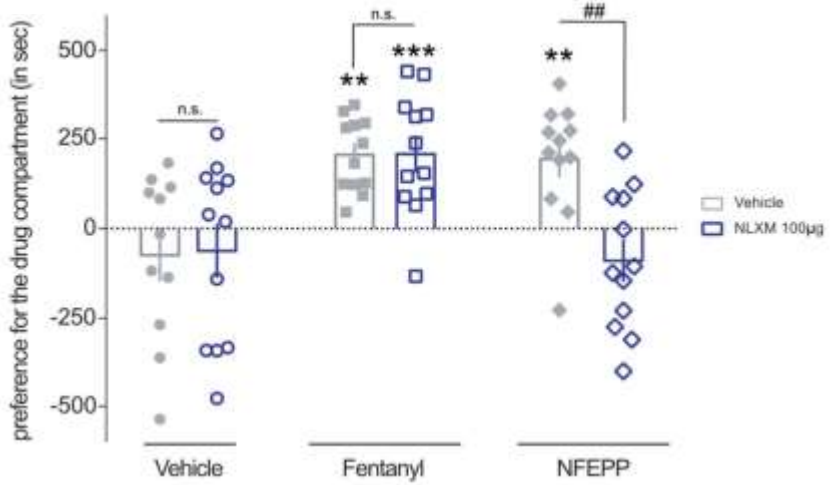
addiction reward



Spahn et al Science 2017

Inflamed Paw

analgesia reward



Massaly et al Pain 2020

Fentanyl directly produces addictive behaviour (addiction reward)

NFEPP induces no addictive behavior but pain relief (analgesia reward)

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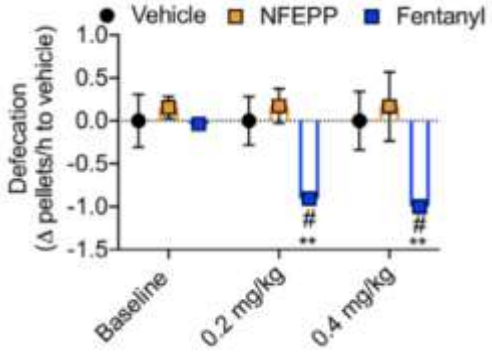
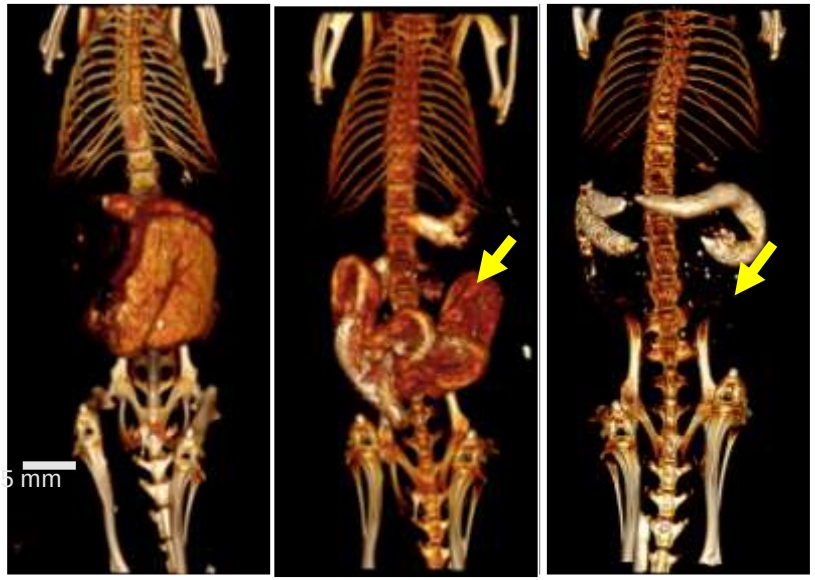
Safety Data: Monitoring Major Opioid Side Effects in GI tract and Lungs

A

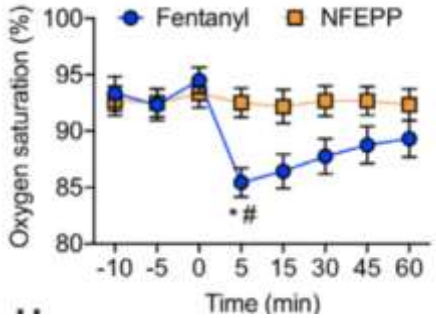


Oral gavaged contrast CT scans showing
Fentanyl but not NFEPP paralyzes GI motility

Vehicle NFEPP Fentanyl



B



Fentanyl has major side effects but not NFEPP

Degro et al Pain 2023
Jimenez-Vargas et al Gut 2022

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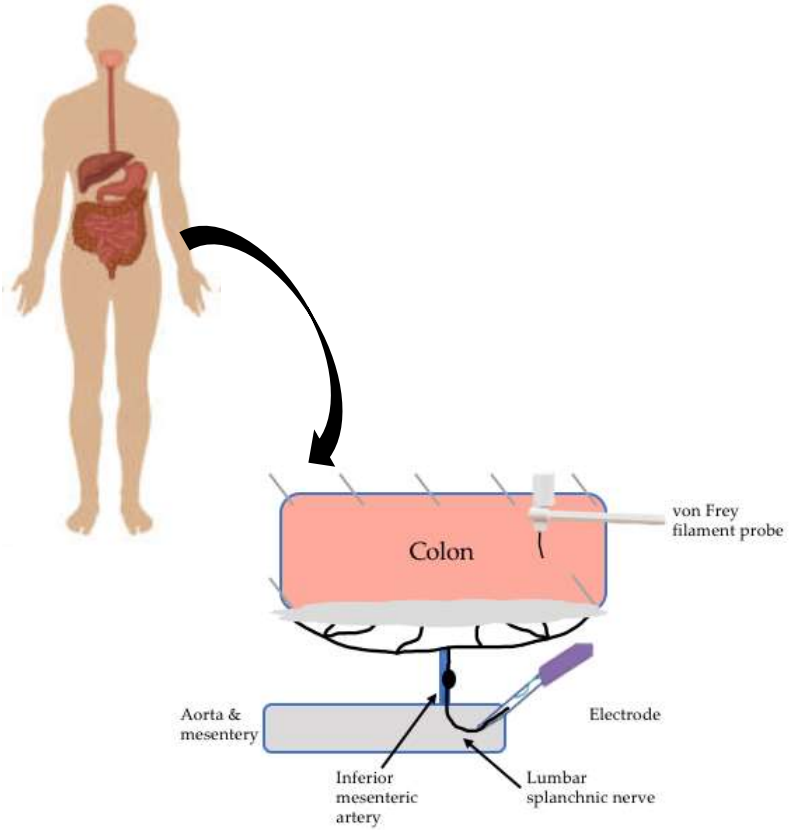
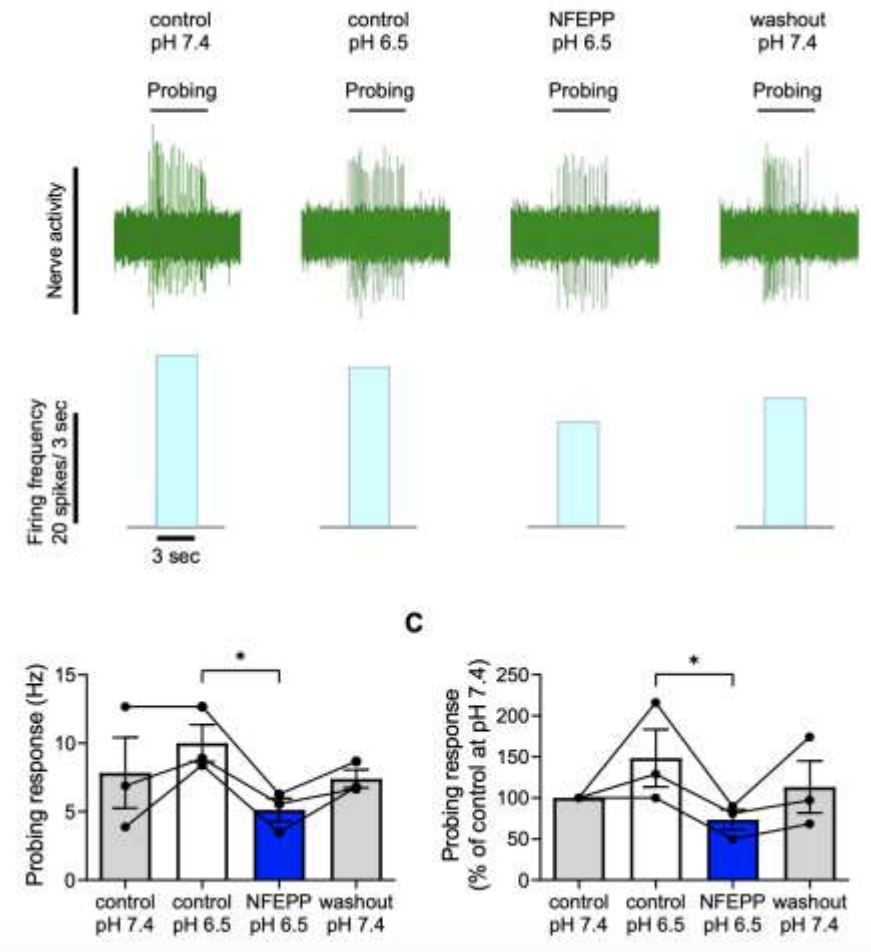
Validation of Mechanism of Action in Human Tissue





NFEPP inhibits human pain nerves only in acidic inflamed tissues

Degro et al. PAIN 2023

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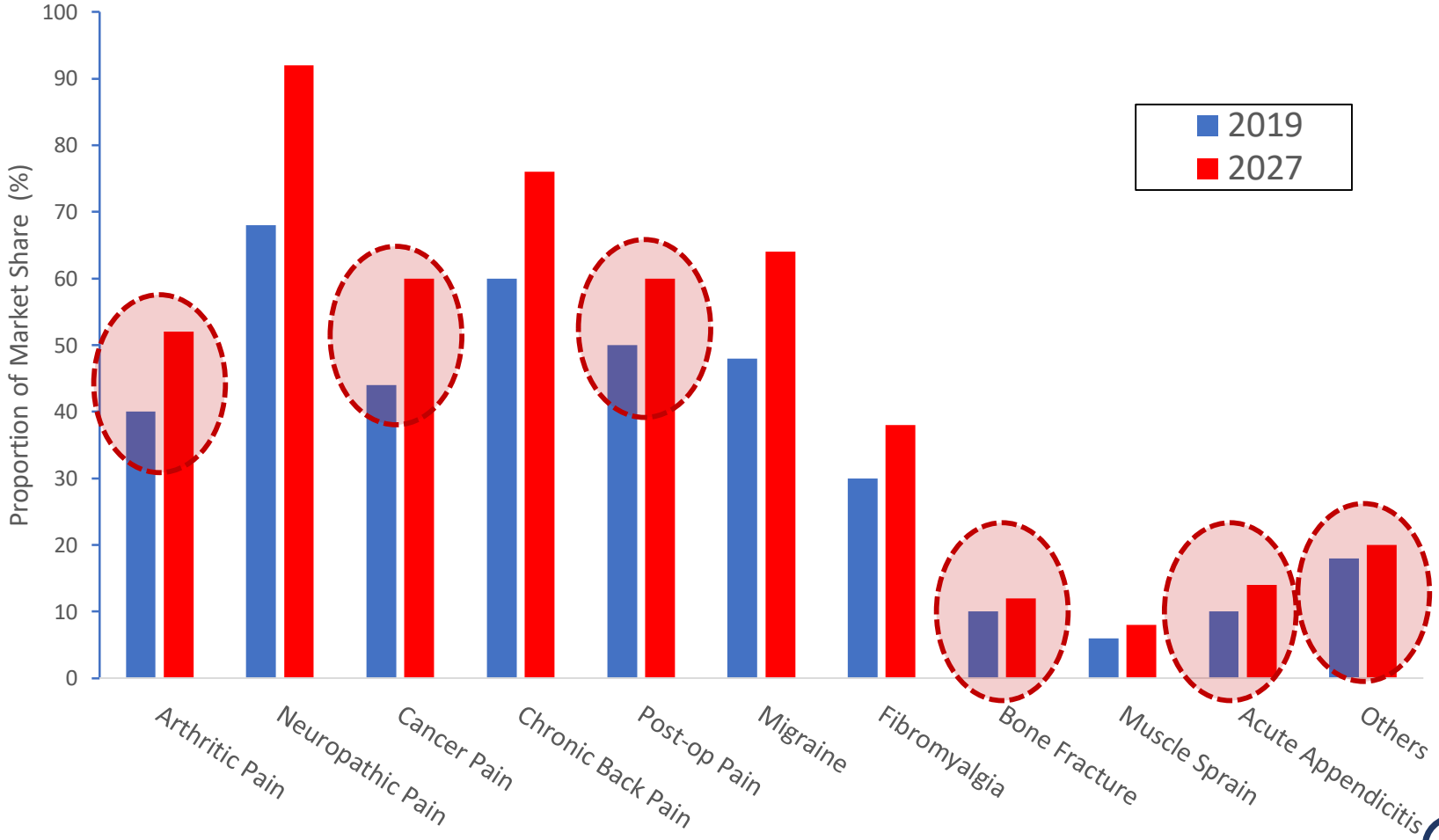
Projected Pain Management Drug Market



NFEPP has multiple indications in the growth pain market (red circles)

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