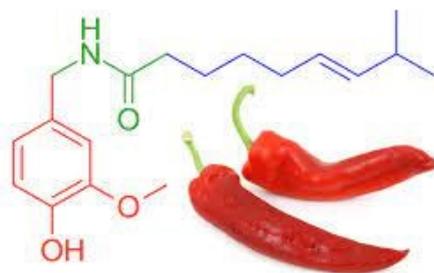


Vocacapsaicin for Postoperative Pain



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Disclosures

None



Limitations of Current Post-Operative Analgesics

- Opioids: respiratory depression, risk of dependence
 - **Long-term use often originates from acute use**
- Non-opioids: dependent on mechanisms
 - **Acetaminophen: hepatotoxic capability**
 - **NSAIDs: issues in patients with renal insufficiency, bleeding risk; concerns for healing in some surgeries**
 - **Gabapentinoids: significant neurologic side effects**
- Local anesthetics: can delay mobilization due to sensory/motor blockade, risk of toxicity



TRPV-1

- 2021 Nobel Prize awarded to David Julius and Ardem Patapoutian



- 1997 *Nature* paper from Julius lab: living beings transmit all stimuli from external world using ion channels, including temperature
- TRPV-1 discovered same year
 - **Nonselective cation channel permeable to calcium**
 - **Activated by capsaicin as well as noxious heat (>40 C) and low pH**





TRPV-1 Receptor

- Capsaicin used in original model by Julius lab to better understand pain signaling
- Capsaicin-insensitive cells transfected with cDNA clone for TRPV1
 - **Sensitized to cytotoxic effects of induced by capsaicin**
 - **These responses could be blocked by antagonist**
- TRPV1 was expressed in nociceptive DRG neurons





TRPV-1 Receptor

- TRPV-1 expression is increased in neuropathic pain from nerve lesions
- Transducer of noxious temperature and chemical stimuli
- Sensitized by inflammatory mediators and contributes to inflammatory pain arising from tissue injury
- Agonists can induce persistent depolarization of nerve terminals, decreasing generation and propagation of action potentials



Capsaicin



- Potent TRPV-1 agonist
- Selective desensitization of pain-conducting nerve fibers without causing numbness or weakness
- Most commonly used topically for neuropathic pain
- Currently available topically ranging from 0.1-8% patch for osteoarthritis, post-herpetic neuralgia, painful diabetic neuropathy



CNTX-4975 (Injectable High-Potency Capsaicin)

- Synthetic trans-capsaicin developed as intra-articular injection
- Phase 3 trials in OA knee pain, however did not demonstrate statistically significant improvement in pain relief over placebo



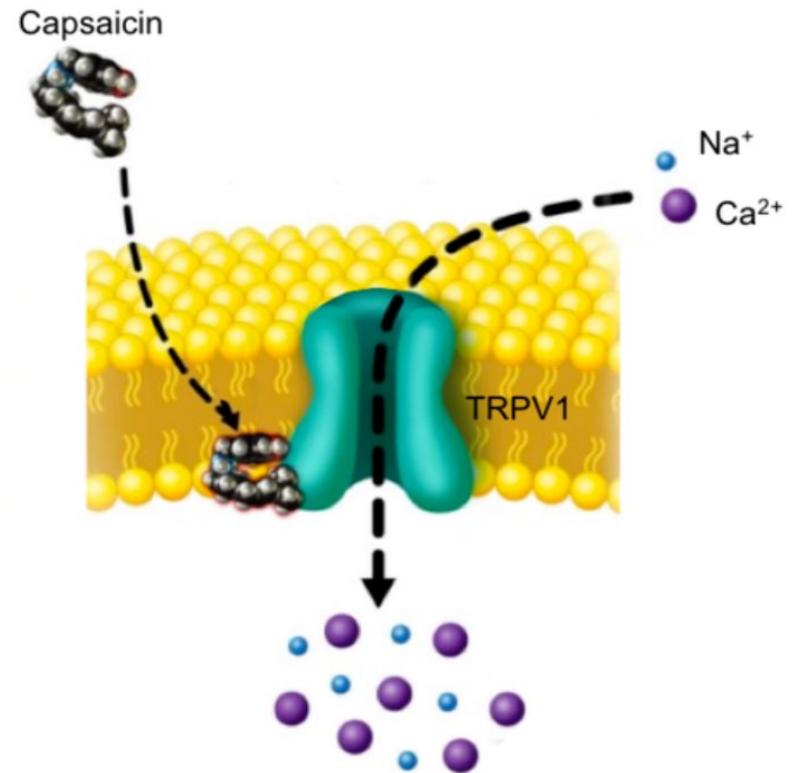
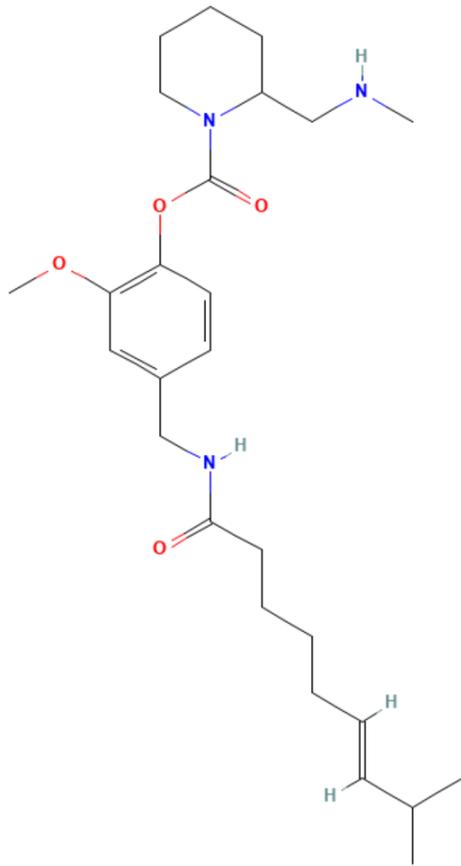


Vocacapsaicin

- Novel, non-opioid prodrug that rapidly converts to trans-capsaicin
- Localized injection as an aqueous solution intraoperatively
- Currently in Phase 3 trials
- Promising results in Phase 2 trials
 - **Randomized, double-blind, placebo-controlled studies**



Vocacapsaicin





Phase 2 Trial in Bunionectomy Patients (2018)

- 147 patients
- Bupivacaine Mayo block, IV ketorolac, IV acetaminophen for all
- Vocacapsaicin (4.2mg) vs. saline control, administered at surgical site
- 28 day observation period





Results

- 33% reduction in pain in first 96h post-op
- 26% patients opioid free in same period vs. 5% in control group
 - **Maintained through full 28-day observation period**
- 50% reduction in opioid consumption from 0-96h
- Through first week post-op: 32% reduction of pain at rest, 25% reduction of pain with ambulation





Phase 2 Trial in Total Knee Arthroplasty Patients (2021)

- 187 patients
- Spinal anesthesia, ketorolac, acetaminophen, ropivacaine (joint infiltration, femoral nerve and IPACK blocks) for all
- 2 arms for vocacapsaicin, 36mg and 60mg, placebo control
 - **Administered at surgical site**



Results

- 36mg group had best response
- 52% reduction in opioid consumption from 96h post-op through day 15 vs. control (36mg group)
- 15% reduction in pain at rest from immediate post-op through day 15
- 14% reduction in pain with ambulation through same time period





Pilot Study in Open Ventral Hernia Repair Patients (2022)

- 24 patients
- Bilateral bupivacaine rectus blocks, peri-incisional bupivacaine infiltration for all
- Vocacapsaicin (24mg) vs. saline control, administered at surgical site
- 28 day observation period





Results

- Clinically significant reduction of pain on coughing (by 46%) through first 96h post-op
- Trend toward significance in reduction of pain on ambulation (by 35%)



Safety/Adverse Effects

- No differences in safety profile of vocacapsaicin compared to control in any of the aforementioned studies
- No serious adverse events
- No differences in wound healing

Clinical Summary of Vocacapsaicin

- Promising findings in pain reduction and safety profile
 - Potential for reduction of opioid use in postsurgical and rehab periods
- Data from studies, including in **ventral hernia repairs, total knee arthroplasties and bunionectomies**, suggest vocacapsaicin may be efficacious in mitigating pain following **numerous surgery types**



Heading Forward

“The need for non-opioid pain medicine in the postsurgical setting cannot be overstated, and vocacapsaicin has the potential to fulfill that need.”

- Alparslan Turan, M.D., Vice Chair of the Department of Outcomes Research at the Cleveland Clinic





Next Steps

- Ongoing development of Phase 3 trials
 - **Seek to reproduce the same efficacy and safety results in upcoming Phase 3 studies**
- Primary TKA patient population promising
 - **Fairly high volume of surgeries**
 - **Relatively consistent perioperative anesthetic/analgesic management**
- Expansion to other orthopedic and soft tissue surgeries



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