What is this thing called pain?

**Nociceptive pain**
- Noxious stimuli
  - Heat
  - Cold
  - Intense mechanical force
  - Chemical irritants

**Inflammatory pain**
- Inflammation
  - Macrophage
  - Mast cell
  - Neutrophil
  - Granulocyte
  - Tissue damage

**Pathological pain**
- Neuropathic pain
  - Neural lesion
  - Dysfunctional pain
    - No neural lesion
    - No inflammation

From Woolf C., JCI 2010


Functional MRI (fMRI)

Spino-parabrachial tract
Spinothalamic tract
Limbic system
Sensory, discriminative
Emotional, aversive

From Gilam G et al., Neuron 2020

Descartes 1644

Pain
Autonomic response
Withdrawal reflex

Spontaneous pain
Pain hypersensitivity

Peripheral nerve injury
Dorsal root ganglion
To periphery

Adapted from Woolf C., JCI 2010
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- Pain hypersensitivity

Brain recordings from deep brain stimulator (DBS)


Woolf C. JCI 2010
Heterotopic Ossification (HO)

- With pathological bone formation within muscle and connective tissues, HO is commonly acquired following orthopedic surgery and traumatic injuries.

Cholok D et al., *Bone* 2018
Debilitating pain, a hallmark of tissue injury and neuropathy, is an unmet clinical challenge in HO.

Little progress has been made in developing effective treatments for either HO or its associated pain.

Hereditary HO conditions such as Fibrodyplasia Ossificans Progressiva (FOP) provide important opportunities to elucidate mechanistic insights.
Chronic pain is an unmet clinical challenge in FOP

- Chronic pain was reported by 86% of patients in one cohort.
- 23-31% of patients reported hypersensitivity to touch or abnormal temperature sensation at baseline, suggesting that the ACVR1$^{R206H}$ may alter the somatosensory function.
Patients with FOP have mechanical and heat pain hypersensitivity

![Sad Emoticon]

ACVR1^{R206H} is sufficient and necessary for hyperexcitability of patient iPSC-derived sensory neurons, the hallmark of neuropathic pain.

Yu et al., 2022
Ether Day: October 16, 1846

Unfortunately, surgery and pain interventions may lead to catastrophic flare-ups in FOP patients.

Warren and Lucia Prosperi, 2001
Pharmacological therapy

- Antiinflammation (Corticosteroids and NSAIDs)
  - Acetaminophen/Tylenol
- Neuropathic Agents
  - Gabapentinoids
  - TCA
  - SNRIs
- Opioids
- Herbs

Multimodal pain management

- Non-selective
  - Naproxen
  - Ibuprofen
  - Advil
- COX-2 inhibitors
  - Celebrex
- Herbs
NSAIDs use in FOP

- Selective COX-2 inhibitors or oral/topical NSAIDS may have a role in the symptomatic management of flare-ups and chronic arthropathy when corticosteroids are not indicated.
  - NSAIDs lower inflammatory prostaglandin levels and potentially raise the threshold for HO, thus, making it more difficult for heterotopic bone to form.

- More than 100 million prescriptions were issued annually in the United States alone. Side effects include,
  - Kidney damage
  - Increasing bleeding by affecting platelet function.
  - GI bleeding: The COX-2 inhibitor has less GI side effects).
  - Cardiovascular risks:
    - In 2004, Merck pulled popular Vioxx (a COX-2 inhibitor) due to risks of heart attacks.
    - How is the cardiovascular safety of the sole remaining COX-2 inhibitor in the U.S. market, Celebrex (Celecoxib)?
The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen or ibuprofen;

At moderate doses, celecoxib (100 mg BID) was found to be noninferior to ibuprofen (600 mg TID) or naproxen (375 mg BID) with regard to cardiovascular safety.

(Precision trial, Nissen et al, 2016)
Topical NSAIDs

- To reduce the risk of systemic adverse effects, topical formulation of NSAIDs has been developed.
  - Voltaren (diclofenac) cream/patch
  - Ketoprofen cream/patch (not available in the U.S.)

- One early study concluded that ketoprofen gel (2.5%) was slightly better than diclofenac gel (1%) in the treatment of acute soft tissue injury (Patel et al., Clin Ther 1996).

- Several randomized, double-blind, placebo-controlled studies have shown the efficacy and safety of topical NSAID patch in comparison with placebo.

- Side effects:
  - Contact dermatitis, itching, paresthesia, photosensitivity reaction, rash.
  - Cases for lower gastrointestinal bleeding associated with diclofenac or ketoprofen topical patch were reported in elderly patients after chronic and overuses.
Other Topical Analgesics

- Topical local anesthetic (lidocaine): cream/patch
- Topical capsaicin: cream/patch
  - Side effects: unpleasant burning sensation
- Topical herbal medicines
- Over-the-Counter topical rubefacients (containing salicylates): Salonpas
  - Dilating the blood vessels of the skin to provide a soothing warmth.
Pharmacological therapy

- Antiinflammation (Corticosteroids and NSAIDs)
- Acetaminophen
- Neupathic Agents
  - Gabapentinoids: Gabapentin, Pregabalin
  - TCA: Amitriptyline, Nortriptyline
  - SNRIs: Duloxetine, Venlafaxine
- Opioids
- Herbs

Multimodal pain management

*First line treatment for neuropathic pain*
Side effects

Gabapentinoids: Gabapentin (Neurontin); Pregabalin (Lyrica)
- **Dose adjustment** in patients with renal dysfunction.
- Side effects: Sedation, GI upset; occasionally, ankle swelling can be noted.

Tricyclic antidepressant: Amitriptyline, Nortriptyline
- Dry mouth, weight gain, lowering of blood pressure when suddenly standing up, irregular heat beats.

Serotonin-noradrenaline reuptake inhibitor (SNRI): Duloxetine (Cymbalta), Venlafaxine (Effexor)
- **Duloxetine**: Nausea; liver dysfunction after chronic use.
Multimodal pain management

Pharmacological therapy

- Antiinflammation (Corticosteroids and NSAIDs)
- Acetaminophen
- Neuropathic Agents
  - Gabapentinoids
  - TCA
  - SNRIs
- Opioids
- Herbs

Non-selective
- COX-2 inhibitors
### Short-acting opioids

<table>
<thead>
<tr>
<th>Hydrocodone/APAP</th>
<th>Oxycodone</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norco</td>
<td>Roxicodone</td>
<td>MSIR</td>
</tr>
<tr>
<td>Lortab</td>
<td>Percocet</td>
<td>Roxanol (solution)</td>
</tr>
<tr>
<td>Vicodin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Long-acting opioids

<table>
<thead>
<tr>
<th>Oxycodone</th>
<th>Morphine</th>
<th>Fentanyl</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>MSContin</td>
<td>patch</td>
<td></td>
</tr>
</tbody>
</table>

Franklin, G.M., Neurology 2014; 83; 1277-1284
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Antiemetics, metoclopramide, anticholinergics, opioid rotation</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Antihistamines, opioid antagonists, propofol or 5-HT₃ antagonists, nonpharmacological treatments</td>
</tr>
<tr>
<td>Sedation</td>
<td>Discontinuation of other sedating medications; opioid rotation, psychostimulants, donepezil</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Opioid rotation, benzodiazepines, skeletal muscle relaxants</td>
</tr>
<tr>
<td>Delirium</td>
<td>Opioid rotation, haloperidol, benzodiazepines, anticholinesterase</td>
</tr>
<tr>
<td><strong>Respiratory depression</strong></td>
<td>Naloxone (emergency situations only)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Prophylactic treatment with a stool softener and bowel stimulant, nonabsorbable laxative (lactulose, polyethylene glycol), metoclopramide, opioid antagonists</td>
</tr>
<tr>
<td>Long-term side effects</td>
<td>Abnormal pain sensitivity: reduce opioid dose? Hypogonadism: testosterone or estrogen replacement</td>
</tr>
</tbody>
</table>
Global marijuana access

Acknowledgement: Hope Newport

https://disa.com/marijuana-legality-by-state (updated on 7/1/2023)
Medical cannabinoids

- Medical cannabinoids are a group of active compounds found in marijuana/cannabis.
- Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are the most well-known cannabinoids.
- Selective cannabinoids used clinically:
  - Dronabinol/Nabilone: synthetic form of THC.
  - Nabiximols contains a standardized extract of THC, the non-psychoactive CBD.
A historical timeline of key milestones in cannabis and cannabinoid research

Finn DP et al, Pain 2021
Cannabinoids, the endocannabinoid system, and pain
Distribution of the cannabinoid receptors and associated enzymes in pain pathways

Finn DP et al, Pain 2021
Cannabinoids, the endocannabinoid system, and pain

- In general, preclinical studies demonstrated antinociceptive efficacy of cannabinoids, as measured predominantly by attenuation of injury-/inflammation-associated hypersensitivity in evoked limb withdrawal (Finn DP et al, *Pain* 2021).

- However, translating this knowledge into clinically useful analgesic therapies continues to be a clinical challenge.

- A recent systematic review of randomized controlled trials concluded that the evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CBM in the management of pain. (Fisher E et al, *Pain* 2021).
Conclusion: The available evidence to support or discourage the use of cannabinoids for neuropathic pain remains weak.
Management of the perioperative patient on cannabis and cannabinoids

- Universal screening for cannabinoids should be performed prior to surgery: product type, amount and frequency, time and route of last consumption.

- We recommend that the frequent, heavy cannabis user be counseled on the potentially negative effects on postoperative pain control. Low-dose, medically supervised use likely has a lower risk of negative effects.

- We recommend postponing elective surgery in patients who have altered mental status or impairment of decision-making capacity due to acute cannabis intoxication.

- Pregnant patients should be educated about the risks of maternal cannabis use on the fetus/neonate.

Shah S, et al., RAPM 2023
How to reduce translational failures of preclinical research in novel analgesics?
Thank You!