Utilization of Topical Pain Creams
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Learning Objectives
• Review the epidemiology of pain
• Discuss the pharmacology of pain with emphasis on peripheral nociception
• Evaluate the various pharmacological agents utilized for topical pain management
• Given a patient case decide which therapy is most appropriate
Is it a Problem?

Epidemiology

- It is estimated that over 50 million people are partially or totally disabled due to pain
- Severe, unrelenting pain interferes with patients’ quality of life, including their activities of daily living, their sleep, and their social interactions.
- Most elderly patients suffer from chronic pain.
- Most have pain in the last month of life
- Up to 50% of patients who are taking pain medication do not experience adequate relief

Epidemiology

- Health economists from Johns Hopkins University writing in The Journal of Pain reported the annual cost of chronic pain is as high as $635 billion a year [1]
- This is more than the yearly costs for cancer, heart disease and diabetes.

Epidemiology

- Percentage of US consumption of the world's opioid production in 2010:
  - Hydrocodone 90%
  - Oxycodone 80%
  - Methadone 58%
  - Hydromorphone 54%
  - Fentanyl 69%
  - Meperidine 43%

## Condition | Number of Sufferers | Source
--- | --- | ---
Chronic Pain | 100 million Americans | Institute of Medicine of The National Academies [2]
Diabetes | 25.8 million Americans | American Diabetes Association [3]
Coronary Heart Disease | 15.3 million Americans | American Heart Association [4]
Stroke | 7.0 million Americans | |
Epidemiology

What is Pain?

Medical Definition:
“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.”

*International Association for the Study of Pain, 1979*

“An unpleasant sensation induced by noxious stimuli and generally received by specialized nerve endings.”

*CancerWEB, 2011*
What is Pain?

Operative Definition:
“Pain is whatever the experiencing person says it is, existing whenever he/she says it does.”

Margo McCaffery, 1999

Presentation of Pain

Acute
- Often obvious distress
- Can be sharp, dull, shock-like, tingling, shooting, radiation, fluctuating in intensity, and varying in location (occur in timely relationship to noxious stimuli)
- Comorbid conditions not usually present
- May see HTN, increased HR, diaphoresis, pallor…

Chronic
- Can appear to have no noticeable suffering
- Can be sharp, dull, shock-like, tingling, shooting, radiation, fluctuating in intensity, and varying in location (do NOT occur in timely relationship to noxious stimuli)
- Symptoms may change over time
- Usually NO obvious signs

Emotions, Coping, and Pain

Chronic pain is associated with higher levels of anger, fear, sadness, anxiety and stress, but often fewer observable outward physical changes/signs.
Autonomic Response to Pain

- Grimacing
- Restlessness
- Guarding
- Increased respirations
- Increased heart rate
- Increased blood pressure
- Diaphoresis

Pharmacology of Nociception

1. Transduction
   - NSAIDs, Local Anesthetics & Anticonvulsants
2. Transmission
   - Opioids, NMDA Antagonists
3. Perception
   - Distraction, Relaxation, Imagery
4. Modulation
   - Tricyclic Antidepressants
   - Opioids
   - GABA-Agonists

Modified WHO Analgesic Ladder

Pain Severity

- Pain persisting or increasing
- 8 - 10
- Opioid for moderate to severe pain
- Non-opioid Adjunct

- Pain persisting or increasing
- 4 - 7
- Opioid for mild to moderate pain
- Non-opioid Adjunct

- Pain persisting or increasing
- 1 - 3
- Non-opioid Adjunct

Quality of Life

Proposed 4th Step

Invasive treatments

Opioid Delivery
Pharmacology of Nociception

Algorithm for Chronic Pain (by Mode of Action)
How They Work

• **Alpha II – Agonists**
  - Alpha II agonists have been in clinical use for decades, primarily in the treatment of hypertension.
  - In recent years, alpha II agonists have found wider application, particularly in the fields of anesthesia and pain management.
  - It has been noted that these agents can enhance analgesia provided by traditional analgesics, such as opiates, and may result in opiate-sparing effects. [6]
  - This has important implications for the management of acute postoperative pain and chronic pain states.
  - The alpha II agonists that are currently employed in compounding for pain management include clonidine and phenoxybenzamine.

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How They Work

• **AMPA-Na Channel Blocker**
  - A number of lines of evidence suggest that NMDA receptor antagonists may have a role in attenuating features of neuropathic pain via the blockade of glutamate.
  - Davar and colleagues described the prevention of hyperalgesia development in the chronic constriction injury (CCI) model by continual pre- and post-injury i.p. administration of the NMDA receptor antagonist MK-801. [7]


How They Work

• **AMPA-Na Channel Blocker**
  - Gabapentin
    - Pts with central & peripherally mediated pain, migraine, and tremor were treated in an open-label study with GP, max. of 2,700 mg/day [8]
    - 39 pts (65%) had moderate-to-excellent results, the best response in pts with peripheral pain [8]

How They Work

- **AMPA-Na Channel Blocker**
  - Gabapentin
  - Other conditions that showed some improvement were benign essential/familial tremor, Restless Legs Syndrome, centrally mediated pain, and periodic nighttime leg movements [9]
  - Carlton: GP has a peripheral site of action & may offer a novel therapeutic agent for topical treatment of pain [10]


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How They Work

- **Anti Inflammatory**
  - NSAIDS
    - Blockade of Cox-1 and Cox-2 enzymes.
    - These enzymes play a key role in making prostaglandins.
    - decrease prostaglandin production = less swelling and less pain.

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How They Work

- **Anti Inflammatory**
  - Corticosteroids
    - Glucocorticoids reduce pain by inhibiting prostaglandin synthesis, which leads to inflammation, and reducing vascular permeability that results in tissue edema.
    - Ex. dexamethasone sodium phosphate
**How They Work**

- **Calcium Channel Blocker**
  - Calcium channels have been recognized as key targets in controlling pain through modulation of the entry of calcium into neurons. \(^{[1]}\)
  - When a pain signal is initiated, calcium channels open and the influx of calcium ions trigger the release of neurotransmitters, which thereby potentiates the signal to the brain where it is perceived as pain.
  - Ex. Nifedipine 2-16%


- **Gaba Agonist**
  - A lack of inhibition, particularly that mediated by gamma-aminobutyric acid (GABA) is responsible for many pain states.
  - The inhibition of pain transmission via GABA receptor activation is the mechanism by which pain is relieved
  - Ex. baclofen, clonazepam

- **MU Agonist**
  - The opioid system controls pain, reward and addictive behaviors. Opioids exert their pharmacological actions through three opioid receptors, mu, delta and kappa.
  - When an opioid binds to the mu-receptor it induces a change in shape which in turn induces a change in the ion channels of the associated cell membrane
  - Mu-receptor activation opens the ion channel allowing potassium ion outflow causing hyperpolarization.
  - This hyperpolarization causes difficulty for an action potential to be reached and decreases the firing of the neuron.
  - Ex. Morphine, oxycodone
How They Work

- **NMDA-Ca Channel Blocker**
  - The NMDA receptor is an ionotropic receptor that allows for the transfer of electrical signals via calcium influx
  - Blocking the NMDA receptor decreases the neuron's ability of potentiating a signal and decreases pain [12]

How They Work

- **NMDA-Ca Channel Blocker**
  - It is clear that NMDARs are critically involved in the induction and maintenance of neuronal hyperexcitability after noxious events.
  - Until recently, only central NMDARs were a primary focus of investigations. With the recognition of peripheral somatic and visceral NMDARs, it is now apparent that the role of NMDARs in pain is much greater than previously thought. [13]

How They Work

- **Tricyclic Antidepressants**
  - TCAs that inhibit the reuptake of norepinephrine or both norepinephrine and serotonin, such as amitriptyline and desipramine, have demonstrated efficacy in the treatment of chronic pain conditions such as diabetic neuropathy, fibromyalgia, chronic headaches, and post-herpetic neuralgia [14].

References:


[13] Petrenko, Andrei B. MD; Yamakura, Tomohiro MD, PhD; Baba, Hisashi MD, PhD; Mencaj, Kiki MD, PhD. The Role of N-Methyl-d-Aspartate (NMDA) Receptors in Pain: A Review. Anesthesiology & Analgesia: October 2003 - Volume 97 - Issue 4 - pp 1108-1116

How They Work

• **Tricyclic Antidepressants**
  - Their ability to relieve pain in these conditions appears to be independent of their antidepressant effect and may be directly related to their effect on neuronal reuptake of serotonin and norepinephrine and in part by the increased duration or concentration of serotonin and norepinephrine in synapses associated with central pain integration [15].


Creating a Plan

• Route
  - Oral
  - Rectal
  - Sublingual
  - Topical / Transdermal

• Medications
  - Class
  - Quantity
  - Timing

Creating a Plan

• Route
  - Oral
    • Tablets / Capsules
      - Sustained release
      - Immediate release
      - Special patient considerations
Creating a Plan

• Route
  – Rectal
    • suppositories
      – BASE TYPE
      – Immediate release
      – Special patient considerations

Creating a Plan

• Route
  – Sub Lingual
    • Liquid drops
    • Rapid Dissolve Tablets
      – Avoid 1st pass metabolism
      – Immediate release
      – Special patient considerations

Creating a Plan

Topical Route: Advantages
• Avoids the GI tract and hepatic first-pass metabolism
• Reduces systemic side effects
• Improves compliance
• Allows ↑ concentration of Rx at site of application
• Plasma concentrations of <10% compared to oral route

Creating a Plan

Topical Route: Drawbacks
• Variations in the stratum corneum barrier
  – Delivery dosing may require adjustment
  – Rate of absorption may vary
• Rash is most common SE
• May be difficult when treating larger areas

Electronic and Electro Mortar & Pestles
The electronic mortar & pestle provides pharmacists with the modern way to compound creams, gels, ointments and suspensions.

Ointment Mill
The ointment mill mixes powders, crystals and creams into a smooth, finished product
Examples of MOA

• Norepinephrine / serotonin inhibitors
  – TCAs, Amitriptyline
• Na channel
  – Anti-arrhythmics, Anticonvulsants
• Ca Channel
  – Nifedipine
• NMDA antagonists (the Ca channel)
  – Ketamine, DM, Amantadine, Orphenadrine
• COX-II inhibitors - NSAID’s
  – Ketoprofen, piroxicam

Examples of MOA

• Substance P inhibitors
  – Capsaicin, Opioids
• Alpha-2 Agonists
  – Clonidine
• Alpha-1 Antagonists
  – Prazosin, Phentolamine

Modalities of Topical Pain Treatment

• NSAID’s
  – ketoprofen, piroxicam, meloxicam
  – Treat pain and inflammation
  – Higher drug levels at site of application
  – Eliminate GI distress and complications
• Neuropathic agents
  – Gabapentin
  – Treats neuropathic pain as a AMPA-Na Channel Blocker
Examples
Anesthetics Before Needle Sticks / Laser treatments

- Benzocaine 20%/Lidocaine 6%/Tetracaine 4%
  Phenylephrine HCl 0.01% Topical PLO

- Why phenylephrine?

Examples
Neuropathic Pain

- Amitriptyline HCl 2%/Baclofen 5%/Ketamine HCl 5%/Ketoprofen 10% in PLO Transdermal Gel
- Ketoprofen 2%/Baclofen 2%/Lidocaine 5%/Clonidine 0.2%
- Amitriptyline HCl 2%/Gabapentin 2% Topical Lipoderm®
- Baclofen 5%/Ketoprofen 10%/Lidocaine 5%/Gabapentin 5% Topical Lipoderm®
- Ketamine 10%/Gabapentin 6%/Clonidine 0.2%/Nifedipine 2% Topical Lipoderm®
- Gabapentin 10%/Clonidine HCl 0.2%/Baclofen 1% Topical Anhydrous Lipoderm®

Examples
Rheumatoid Arthritis / Joint Pain

- Ketoprofen 10% in PLO Transdermal Gel

Soft Tissue Inflammation

- Ibuprofen 20% PLO Transdermal Gel
- Didofenac Sodium 10% PLO Transdermal Gel
- Ibuprofen 20%/Piroxicam 1% PLO Transdermal Gel
Multiple Modalities of Treatment

Ketoprofen 20%/Ibuprofen 2%/Ketamine 2%/Clonidine 0.2%/Amitriptyline 2%

• Ketoprofen – NSAID
• Ibuprofen – NSAID
• Ketamine - NMDA Receptor Antagonist
• Clonidine - Alpha -2 Agonist
• Amitriptyline - NE Reuptake inhibitor

Need More Information?

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