Compounding Prescriptions for Pain, Wound and Scar

Andy Ruiz, PharmD, MSc, FACA
COO/Partner
Stonegate Pharmacy

Learning Objectives
- Review the epidemiology of pain, wound and scar
- Discuss the pharmacology of pain with emphasis on peripheral nociception
- Discuss the pharmacology of wound and scars with respect to skin soft tissue
- Evaluate the various pharmacological agents utilized for topical pain, wound, and scar management
- Given a patient case decide which therapy is most appropriate

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 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 WORLDs opioid production in 2010:
  - Hydrocodone 90%
  - Oxycodone 80%
  - Methadone 58%
  - Hydromorphone 54%
  - Fentanyl 59%
  - Mepiridine 43%
Epidemiology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Sufferers</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>100 million Americans</td>
<td>Institute of Medicine of The National Academies [2]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.8 million Americans (diagnosed and estimated undiagnosed)</td>
<td>American Diabetes Association [3]</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>16.3 million Americans</td>
<td>American Heart Association [4]</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.0 million Americans</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>11.9 million Americans</td>
<td>American Cancer Society [5]</td>
</tr>
</tbody>
</table>

Epidemiology


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

- **Proposed 4th Step**
  - Opioid for severe pain
  - Non-opioid Adjunct
- **Quality of Life**
  - Severe Pain
  - Moderate Pain
  - Mild Pain
- **Pain Severity**
  - 8 - 10
  - 4 - 7
  - 1 - 3

The WHO Ladder

- **Step 1**
  - Non-opioid Adjunct
- **Step 2**
  - Opioid for mild to moderate pain
  - Non-opioid Adjunct
- **Step 3**
  - Opioid for moderate to severe pain
  - Non-opioid Adjunct
- **Step 4**
  - Opioid for moderate to severe pain
  - Non-opioid Adjunct

- **Pain**
  - Prevalence in the US
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 applications, 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 opioids, and may result in opioid-sparing effects. [8]
  - 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.

- **AMPA-Na Channel Blocker**
  - A number of lines of evidence suggest that AMPA 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 AMPA receptor antagonist MK-801. [7]

- **Laboratory Applications**
  - In recent years, alpha II agonists have found wider application, particularly in the fields of anesthesia and pain management.

[8] Department of Anesthesia, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, USA. hsmith3@caregroup.harvard.edu

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]


- **GABA-J 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
  - Other conditions that showed some improvement were benign essential/familial tremor, Restless Legs Syndrome, centrally mediated pain, and periodic nighttime leg movements [8]
  - Carlton: GP has a peripheral site of action & may offer a novel therapeutic agent for topical treatment of pain [10]


• Anti Inflamatory – 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.

• Anti Inflamatory – 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

• Calcium Channel Blocker
  - calcium channels have been recognized as key targets in controlling pain through modulation of the entry of calcium into neurons. [11]
  - 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 amino butyric 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 neurons ability of potentiating a signal and decreases pain [12].


• **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].


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

Pain Treatment: 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

Pain Treatment: 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

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

Wound and Scar

- The primary goals of the treatment of wounds are rapid wound closure and a functional and aesthetically satisfactory scar

The Problem

Arterial Disease  |  Diabetes
The Numbers

- Wound management market was valued approximately $11.7 billion in 2012.
- Mean cost to heal per wound was $3927 with jeopardized flaps and grafts the most expensive ($9358). In hospitalized patient with an average healing time of 15–33 weeks.
- Up to 11% of patients in this setting (LTC) are living with pressure ulcers, according to the National Nursing Home Survey.
- Pressure ulcers listed directly or indirectly in 80% of the most common deficiencies in LTC facilities.

Why Compound

- Shorter healing times
- Less nursing involvement
- Cost effective

Common Wound Ingredients

- Misoprostol
- Phenytion
- Pentoxifylline
- Nifedipine
- Other
- Antibiotics

Misoprostol

- **MOA**
  - Synthetic prostaglandin E1
  - Inhibits IL-1 and TNF
  - Enhances IL-6 production
  - Inhibits IL-10 expression
  - Decreases inflammatory process
  
- **Dose**
  - 0.0024%

References

**Phenytoin**

**MOA**
- Stimulation of fibroblast proliferation
- Facilitation of collagen disposition
- Glucocorticoid antagonism
- Antibacterial activity

**Dose**
- Topical 2% - 5%

---

**Pentoxifylline**

**MOA**
- Reduces blood viscosity
- Reduces vascular permeability
- Reverses the abnormal function of white and red blood cells and platelets
- Upregulates IL-10

**Dose**
- 5%

---

**Nifedipine**

**MOA**
- Calcium channel blocker
- Improves blood flow to the wound

**Dose**
- 0.25%

---

**Aloe Vera**

**MOA**
- Stimulates growth factor receptors on the fibroblasts
- Increases collagen synthesis and turnover
- Reduces Inflammation

**Dose**
- 0.2% - 0.5%

---

**Anesthetics**

- **Lidocaine**
  - Dose: 2 – 5%
  - Onset: 2-5 minutes
  - Duration: 3-60 minutes
  - Half-life: 1.5-2 hrs

- **Tetracaine**
  - Dose: 0.5 – 2%
  - Onset: 3-10 minutes
  - Duration: 3-60 minutes
  - Half-life: ???

- **Bupivacaine**
  - Dose: 0.25 – 0.5%
  - Onset: 1 – 10 minutes
  - Duration: 3 – 9 hrs
  - Half-life: 3.5 hrs

---

**Anti-Infectives**
Additional Ingredients

- **Hyaluronic acid (0.1 -2%)**
  - Regulatory role
  - Promotes cell proliferation and angiogenesis
  - Up regulates the production of pro-inflammatory cytokines and enhances chemotaxis of fibroblasts
  - Antioxidant/therapuetic/scavenger
- **Glucosamine (2%)**
  - Substrate for the synthesis of glycosaminoglycan polymers (i.e. hyaluronic acid)

Additional Ingredients

- **Nitric Oxide/L-Arginine (1%)**
  - Nitric oxide (NO) is a small radical, formed from the amino acid
  - L-arginine by three distinct isoforms of nitric oxide synthases
  - Stimulates the migration, proliferation and gene regulation in human dermal fibroblasts
- **Atorvastatin Topical (1-5%)**
  - Modulates the inflammatory response, possibly with inhibition of 
  - Statins altering the balance between vasodilation and vasoconstriction in favor of vasodilation
  - Increasing nitric oxide (NO) synthesis
  - Down regulating endothelin 1 synthesis
  - Reducing vascular response to angiotensin-2
- **Panthenol/dexpanthenol (0.5 – 5%)**
  - B complex vitamin (B5)
  - Stimulates the migration, proliferation and gene regulation in human dermal fibroblasts
- **Allantoin(0.5-2%)**
  - Modulates the inflammatory response, possibly with inhibition of 
  - inflammatory cells from infiltration into the wound and lowering the reactive oxidative species responsible for damage and stress
- **Tumeric/Curcumin(0.1–0.5%)**
  - Increases formation of granulation tissue, biosynthesis of extracellular matrix protein and TGF- B in wounds

Scar

- **C section: 1.4 million per year**
- **Out Patient Surgeries: 34.7 Million in 2006**
- **Knee replacements: >600,000 per year**
- **Hip replacements: 332,000 per year**
- **Hysterectomy: 498,000 per year**

Scar Morphology

- Mast cells stimulate fibroblast proliferation
- Fibroblasts produce collagen
- Wounds that penetrate into dermis are filled in by collagen forming a dense fibrous tissue
- Collagen is laid down in a disorganized fashion
- Results in different color and texture, and 70% as strong as normal skin

Additional Ingredients

- **Vitamin E**
  - Antioxidant
  - Regulates the synthesis of collagen and other extracellular matrix proteins
- **Collagen**
  - Important for wound healing
  - Provides hydration
- **Arginine (1%)**
  - Nitric oxide (NO) is a small radical, formed from the amino acid
  - Vascular smooth muscle relaxation and vasodilation
  - Promotes cell proliferation and angiogenesis
  - Reducing inflammatory cytokines and chemotaxis

Additional Ingredients

- **Topical antioxidants/anti-inflammatory**
  - Reduces the formation of scars
  - Increases collagen synthesis

Anesthetics

- **Scratches**
  - Do not reach below the papillary dermis
- **Normotrophic and Ablative scar**
  - Sagittal information, extracellular collagen synthesis
- **Hypertrophic scar and keloid**
  - High trauma inflammatory, extracellular collagen synthesis
The Cascade of Atrophic Scarring

Sluggish inflammation

↓

Low Concentration of Chemically Active Substances (TGF-β1 and TGF-β2)

↓

Low quantity of Active Fibroblasts

↓

Insufficient collagen synthesis

↓

Atrophic scar


The Cascade of Hypertrophic or Keloid Scar

High-intensity inflammation

↓

High concentration of chemically active substances (TGF-β1 and TGF-β2)

↓

Large amount of active fibroblasts

↓

Excessive collagen synthesis

↓

Hypertrophic or Keloidal Scar


Critical Excipients

Silicones

• Cyclopentasiloxane
  - Hydration, can modulate the effect of keratinocytes on skin fibroblasts by affecting the production of soluble factors
  - Acts on the epidermis to initiate signaling cascades that affect dermal fibroblasts and affect the activity and growth factor production

Permeation Agents

• Pentaclethra Macroloba Seed Oil
  - Enhances collagen restoration
  - May be used in new scars as well

Fatty Acids

• PEG-16 Macadamia Glycerides
  - Surfactant and water-soluble and oil dispersible emollient.
  - Phosphatidylcholine
  - Tocopheryl Acetate
  - Acts as skin protectant
  - May be used in new scars as well

Scar Prevention

Vitamin D

• Receptors (VDRs) in cultured keloid fibroblasts
  - Decrease fibrosis and may also be used in new scars

Zinc Sulfate

• Anti-inflammatory
  - Enhances collagen restoration
  - May be used in atrophic scars

Glycosaminoglycans

• Acts as also protease inhibitors

Aloe Vera

• Acts as also protease inhibitors

API – Keloid/Hypertrophic Scars

• Levocetirizine (0.5 – 2%)
  - Antihistamine that suppresses both stimulation-induced stromal and collagen synthesis of fibroblasts

• EDCg (0.1 – 0.5%)
  - Interferes with transforming growth factor (TGF) which is known to stimulate fibroblast proliferation, collagen production and the activation of fibroblasts

• Tranilast (0.5 – 2%)
  - Anti-allergic agent that blocks the release of chemical mediators, such as histamine and leukotrienes, from mast cells.

• Tamoxifen Citrate (0.1%)
  - Inhibits keloid fibroblasts, preventing larger, proliferative keloid scars by decreased levels of TGF-β1 produced by the fibroblasts
**API – Keloid/Hypertrophic Scars**

- **Calcium channel blockers: Verapamil 10%**
  - Blockers induce collagenase production and increase tissue degradation.
  - Induce changes in fibroblast gene expression resulting in decreased collagen synthesis and increased collagenase production.
- **Loratadine 0.5-1%**
  - Suppresses TGF-beta1-induced collagen deposition in keloid fibroblasts
- **Pentoxifylline 0.1-0.5%**
  - Decreases collagen production
  - Increases activity of collagenase in dermis and reduces fibroblast hyperactivity
- **Collegenase 250-300U/gm**
  - Digests collagen in collagen deposits
- **Hyaluronidase**
  - Breaks down hyaluronic acid in connective tissue

**API – Keloid/Hypertrophic Scars**

- **Betamethasone Valerate 0.1% - Sodium Phosphate 0.5%**
- **Fluocinolone**
- **Fluticasone Proprionate 0.05% - 1%**
  - Reduces bulk and tension in mature scars
  - Reduces fibroblast proliferation
  - Decreases collagen production in fibroblasts
- **Hyaluronic Acid 0.05-0.1%**
  - Regulated by TGF-ß in the epidermis
  - A four-fold reduction in HA was found in fibroblasts cultured from keloid tissue when compared to fibroblasts isolated from normal skin
- **Lipoic Acid (0.5%)**
  - Enhances synthesis of collagen in fibroblasts and of collagenase-processing enzyme

**API – Atrophic Scars**

- **Caffeine (0.1 – 1%)**
  - Induces differentiation and proliferation in epidermal keratinocytes
- **Tretinoin / Retinoic Acid (0.05-1%)**
  - Mediates cell differentiation and proliferation, apoptosis, and reproduction
- **Glycosaminoglycans (5%)**
  - Enhances collagen restoration

**Need More Information?**

Andres Ruiz, PharmD, MSc, FACA
COO/Partner
Stonegate Pharmacy
andyruiz@stonegaterx.com
www.stonegaterx.com