COMPounded TRANsDERMAl PAIN THERAPy – A DRUG OVERVIEW

OMAR ALLIBHAI, PHARMD, RPH, FACA COMPOUNDING PHARMACY FELLOW
Objectives

- Compare the pros and cons of transdermal analgesia

- Explore the use of compounded agents:
  - Their mechanism of action
  - Evidence supporting their use

- Identify appropriate candidates for transderal pain therapy
Nociceptive Pain

- Nociceptors (pain detecting nerves) send signals from the painful site to the spinal cord and brain for interpretation and reaction.

1. Somatic
   - Arise from skin, bone, joint, muscle, or connective tissue
   - Easier to locate than visceral pain
   - More intense pain

2. Visceral
   - Arise from internal organs
   - Dull pain
   - Harder to pinpoint
Pathophysiology

- **Neuropathic Pain**
  - Result of *nerve damage*, abnormality of nerve pathway
  - Examples: Post-herpetic neuralgia, diabetic neuropathy

- **Functional Pain**
  - *Abnormal operation* of the nervous system
  - Examples: fibromyalgia, irritable bowel syndrome, tension-type headache, non-cardiac chest pain
Classifications of Pain$^{1,3}$

1. **Acute pain**
   - Results from disease, inflammation, or tissue injury that comes suddenly
   - Subsides quickly

2. **Chronic pain**
   - Persist over long period of time
     - Weeks, months to years
   - Maybe resulted from changes of receptors and nerve fibers
Transdermal: Advantages²

- Can minimize systemic absorption
  - Less side effects
- Avoidance of first pass metabolism
- Ease of administration
  - Convenient and painless administration
  - Improve patient compliance
  - Oral dosing is not feasible for patient (unconscious or nauseated patients)
- Alternative formulation in special populations
  - Elderly
  - Pediatrics
Transdermal: Disadvantages

- Topicals have appropriate molecular size and physiochemical properties in order to penetrate the skin
  - Size <500 Da
    - Example: Clonidine 230Da
- Aqueous and lipid solubility
- Skin permeability varies in different population
- Certain disease states alter penetration
  - Healthy vs. disease skin
- Localized skin irritation and erythema can occur (Contact Dermatitis)
### Molecular Size

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dalton (Da)</th>
<th>DRUG</th>
<th>Dalton (Da)</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>277</td>
<td>Gabapentin</td>
<td>171</td>
</tr>
<tr>
<td>Baclofen</td>
<td>213</td>
<td>Ibuprofen</td>
<td>206</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>165</td>
<td>Ketamine</td>
<td>237</td>
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<tr>
<td>Bupivacaine</td>
<td>288</td>
<td>Ketoprofen</td>
<td>254</td>
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<tr>
<td>Carbamazepine</td>
<td>236</td>
<td>Lidocaine</td>
<td>234</td>
</tr>
<tr>
<td>Clonidine</td>
<td>230</td>
<td>Naproxen</td>
<td>230</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>275</td>
<td>Tetracaine</td>
<td>264</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>296</td>
<td>Piroxicam</td>
<td>331</td>
</tr>
</tbody>
</table>
Why Compound?

- A natural fit to a complementary medical practice and the whole patient concept.
- The ability to customize therapy to fit the individual needs of a patient.
  - Instead of a one-size-fits-all approach of commercially available drugs, the possibilities with a compounded prescription are endless.
Pain Management

Chronic pain may have a myriad of causes and perpetuating factors, and therefore can be much more difficult to manage than acute pain, requiring a multidisciplinary approach and customized treatment protocols to meet the specific needs of each patient.

- **Customize:**
  - **NSAID** Ketoprofen, Ibuprofen, Naproxen, Piroxicam, Diclofenac
  - **Local Anesthetic** Benzocaine, Bupivacaine, Lidocaine, Tetracaine
  - **Muscle Relaxant/Anti-Spasmodic** Baclofen, Cyclobenzaprine, Guaifenesin, Gabapentin, Clonidine
  - **Tri-Cyclic Anti-Depressant** Amitriptyline
  - **NMDA-antagonist** Ketamine, Magnesium
  - **Mu Agonists** Loperamide
## Medications Used in Transdermal Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>2-5%</td>
<td>NE Reuptake inhibitor</td>
</tr>
<tr>
<td>Baclofen</td>
<td>1-20%</td>
<td>GABA$_\beta$ Agonist</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>10-20%</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.5-5%</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1-0.2%</td>
<td>Alpha-2 Agonist</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>0.5-2%</td>
<td>Muscle Relaxant</td>
</tr>
<tr>
<td>Deoxy-D-Glucose-2</td>
<td>0.1-2%</td>
<td>Antiviral/Neuropathic Pain</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.2-2%</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>5-10%</td>
<td>NMDA Receptor Antagonist</td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>2-30%</td>
<td>NSAID</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>4-10%</td>
<td>Voltage Regulated Na(^+) &amp; Ca(^{++}) Blockade</td>
</tr>
<tr>
<td>DMSO</td>
<td>5-10%</td>
<td>NSAID + Penetration Enhancer</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>4-10%</td>
<td>Glutamate Antagonist</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>10%</td>
<td>Muscle Relaxant</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2-10%</td>
<td>NSAID</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>15-20%</td>
<td>NSAID</td>
</tr>
<tr>
<td>Ketamine</td>
<td>5-10%</td>
<td>NMDA Receptor Antagonist</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>10-30%</td>
<td>NSAID</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>5-10%</td>
<td>Local Anesthetic</td>
</tr>
</tbody>
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<tr>
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<tr>
<td>Lidocaine</td>
<td>2-10%</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Loperamide</td>
<td>5-10%</td>
<td>Mu agonist</td>
</tr>
<tr>
<td>Magnesium Chloride</td>
<td>2-25%</td>
<td>NMDA Antagonist</td>
</tr>
<tr>
<td>Mexelitine</td>
<td>2-10%</td>
<td>Na+ Channel Antagonist</td>
</tr>
<tr>
<td>Naproxen</td>
<td>5-10%</td>
<td>NSAID</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>1-16%</td>
<td>Non-NMDA Ca^{2+} Channel Antagonist</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>5-10%</td>
<td>TNF_{\alpha} Inhibitor, Peripheral Vasodilator</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.5-30%</td>
<td>NSAID</td>
</tr>
</tbody>
</table>
NSAIDS

- Peripheral MOA:
  - COX Inhibitors

- Topical Effects:
  - Anti-inflammatory
  - Analgesic

- Works Great to treat:
  - Arthritis related inflammation
  - Muscle Pain
  - Nerve Pain

- Diclofenac
- Ibuprofen
- Ketoprofen
- Piroxicam
- Indomethecan
- Flurbiprofen
Comparison of Ketoprofen, Piroxicam, and diclofenac gels in treatment of Acute Soft-Tissue Injury in General Practice

open-label, comparative, parallel-group, randomized, multicenter, general practice study comparing the efficacy, tolerability and acceptability of treatment of Ketoprofen, piroxicam, and diclofenac gel

1575 patients with moderate to severe injury

Treatment arm:

- Ketoprofen gel 2.5% (1048)
- Piroxicam gel 0.5% (263)
- Diclofenac gel 1% (264)

Direction:

- Ketoprofen gel 2.5%, Apply 4-5 g three times daily with or without measuring device 5 days
- Piroxicam gel 0.5%, Apply 1g three times daily 5 days
- Diclofenac Gel 1%, Apply 2g to 4g three times daily for 5 days
  - Patient’s were instructed to apply the gel by massaging it into the affected area, and to avoid covering the area with any occlusive dressing or protective bandage.
  - Treatment with paracetamol or coproxamol was permitted as rescue medication for symptomatic relief

Assessment

- Acceptability of treatment (4 point scale)
- Global assessment of any change in the injury at the end of treatment and determine the usefulness of the measuring device
- Physician evaluated the overall response to treatment using a four point scale
- Observe adverse events were noted
Physician Global assessment of treatment response showed that improvement in the effect of injury was better with Ketoprofen gel than with Piroxicam (74% vs. 65% p=0.0001), slightly better than with diclofenac (74% vs. 71).

Ketoprofen gel showed greater improvements in degree of stiffness (71% vs. 64% p=0.013), patient assessment of pain on pressure (81% vs. 78% p=0.02), and pain on movement (83% vs. 77% p=0.01) than piroxicam gel.

Global assessment of improvement of injury was significantly higher with Ketoprofen gel than with piroxicam gel (p=0.0002)

Improvement of mobility was significantly higher with ketoprofen gel (without the measuring device, 34% vs. 22% p=0.006)

Measuring device appeared to offer little benefit

Incidence of drug-related events was very low: ketoprofen gel (0.7%), Diclofenac gel (1.1%), piroxicam gel (2.3%). Local skin reaction at the site of application was the common drug-related event. (erythema, rash, itching)

Ketoprofen gel was preferred by most patients because it was easier to rub than piroxicam gel (89% vs. 81%p=0.001), apply(p<0.002) with less staining (p=<0.001) and rated by more patients as having a cooling effect than either comparator (79% vs. 49% piroxicam vs. 60% diclofenac p=<0.001)
Local Anesthetics

- Benzocaine
- Bupivacaine
- Lidocaine
- Tetracaine

- **Peripheral MOA:**
  - Blockade of voltage gated Sodium Channels

- **Topical Effects:**
  - Analgesic
  - Minimizes nerve response
  - Numbing effects

- **Works Great to treat:**
  - Diabetic Neuropathy
  - Neuralgias
  - Complex Regional Pain Syndrome
  - Post Herpatic Neuralgia
Gabapentin

- **Peripheral MOA:**
  - Blocks voltage gated Calcium Channel Blocker

- **Topical Effects:**
  - Minimize Nerve Response
  - Reduce Neuropathic Sprouting

- **Works Great to treat:**
  - Allodynia / Hyperalgesia
  - Diabetic Neuropathy
  - Post Herpatic Neuralgia
  - Migraine
  - Complex Regional Pain Syndrome
Topical Gabapentin in the treatment of localized and Generalized Vulvodynia

Studied the effects of 2%-6% Gabapentin in lipoderm base

A retrospective study

(50) Women diagnosed with generalized or localized vulvodynia from January 2001 to December 2006

- Hormonal therapies and anticonvulsants were more common prior treatment for women with generalized vulvodynia while topical lidocaine in women with localized vulvodynia

- **Treatment arm:**
  - (18) 2% Gabapentin  9=localized, 9=generalized
  - (10) 4% Gabapentin  7=localized 3=generalized
  - (22) 6% Gabapentin  16= localized, 6=generalized

- Direction: Apply 0.5 mL TID
  - Max daily dose: 30-90 mg for a minimum of 8 weeks duration of therapy
RESULTS:

- **Localized vulvodynia**
  - Mean pain score was significantly reduced from 7.92 to 2.71 (mean change -5.21, 95% CI -5.59 to -4.42, p<.001, 95% CI for % 6-37%)

- **Generalized vulvodynia**
  - Mean pain score was reduced from 5.82 to 2.00 (mean change -3.82, 95% CI -5.25 to -2.38, p<.001, 95% CI for % 28-79%)

- Use of topical Gabapentin for this disorder alleviate the pain, increase patient acceptability and tolerability, minimized ADR’s and increase patient compliance.

- **Common adverse effects of oral Gabapentin were not reported by any of the 50 patients studied in this trial**
Muscle Relaxants

- Baclofen
- Cyclobenzaprine
- Guaifenesin

- Peripheral MOA:
  - Decreases excitatory neurotransmitter release

- Topical Effects:
  - Relieves muscle spasticity

- Works Great to Treat:
  - Deep Muscle Pain
  - Myofacial Pain
Tri-Cyclic Antidepressants

- Amitriptyline
- Desimipramine
- Imipramine
- Nortriptyline

- **Peripheral MOA:**
  - Activation of Adenosine receptors
  - Inhibits sodium, potassium and Calcium Channels

- **Topical Effects:**
  - Minimizes nerve response
  - Provides Analgesia

- **Works Great to treat:**
  - Allodynia / Hyperalgesia
  - All types of Neuropathic Pain
NMDA Antagonists

- **Peripheral MOA:**
  - Inhibits NMDA excitatory pathways

- **Topical Effects:**
  - Minimizes Nerve Response
  - Analgesia
  - Numbing effects

- Works Great to treat:
  - All types of neuropathic pain
  - Pre-treat painful wounds / hyperalgesic areas
A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCTG trial N06CA

**Purpose:** evaluate a topical Baclofen, AmitriptylineHCl, and Ketamine (BAK) gel to alleviate neuropathic pain, numbness, and/or tingling of chemotherapy-induced peripheral neuropathy (CIPN)

- Secondary goals include the evaluation of function, general pain, and toxicity.

**Treatment arm:**
- Baclofen 10mg, 40mg Amitriptyline HCl, 20mg ketamine gel
- placebo gel (PLO)

**Direction:** Apply one level spoonful of gel topically to each area of pain, numbness, and or tingling, twice a day, in the morning and before bed for 4 weeks duration. (max of 4 spoonfuls of gel per application)

- **Primary endpoint:** changes in the sensory neuropathy subscale measured by the European Organization for research and Treatment of Cancer (EORTC) 20 item questionnaire assess sensory, motor and autonomic symptoms and functioning.
- Participants completed this questionnaire at baseline, before starting the study and at 4 weeks

**150 total patients→ 75 (BAK), 75 (placebo)**
BAK gel resulted more improvement in sensory neuropathy \((p=0.053)\); difference 95% CI 4.3(-0.6, 9.3)
- Mean change from baseline SD of 8.1(15.05) in BAK arm
- Mean change from baseline SD of 3.8 (15.52) in placebo arm

BAK gel resulted statistically improvement in motor neuropathy \((p=0.021)\); difference 95% CI 5.3( 0.9, 9.7)
- Mean change from baseline and SD were 7.1 (13.72) for BAK arm
- Mean change from baseline and SD were 1.8 (14.05) for placebo arm

No significant differences in toxicities were observed between the BAK arm and the placebo through the 4 weeks of the study

Blood was drawn during the double-blind phase on a small subset of participants \((N=8)\) to evaluate systemic absorption
- 4 (BAK), 4(Placebo, no detectable levels)
- For BAK group:
  - 2 undetectable levels of all 3 drugs
  - 1 barely detectable amitriptyline, no detectable ketamine and baclofen
  - 1 low therapeutic levels of baclofen but undetectable levels of amitriptyline and ketamine
Mu Agonists

- **Peripheral MOA:**
  - Mu receptor (opioid) agonist

- **Topical Effects:**
  - Analgesia

- **Works Great to treat**
  - Arthritis
  - Hyperalgesia
LD Naltrexone for Fibromyalgia Trial

- **Low-Dose Naltrexone for the Treatment of Fibromyalgia**
- Randomized, double-blind, placebo-controlled crossover study assessing the efficacy, and tolerability of low-dose naltrexone in the treatment of fibromyalgia
- 31 women with fibromyalgia

**Treatment arm:**
- Naltrexone 4.5 mg PO at bedtime (16)
- Placebo (15)

**Study duration:** 20 weeks
- Placebo (4 weeks) → naltrexone (12 weeks) → follow-up (4 weeks)
  - OR
- Naltrexone (12 weeks) → placebo (4 weeks) → follow-up (4 weeks)

**Direction:**
- Naltrexone 4.5 mg PO at bedtime

**Assessment:**
- Reduction of baseline pain using scale 0-100
  - Pain measured in final 3 days in each condition
- Satisfaction using single-item visual analog scale
- Mood using single-item visual analog scale
- Sleep quality using single-item visual analog scale
LD Naltrexone for Fibromyalgia Trial

Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>4.5 mg naltrexone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in baseline pain</td>
<td>28.8%</td>
<td>18%</td>
<td>0.016</td>
</tr>
<tr>
<td>Increase in satisfaction</td>
<td>11.1%</td>
<td>3.2%</td>
<td>0.045</td>
</tr>
<tr>
<td>Mood improvement</td>
<td>10.7%</td>
<td>2.1%</td>
<td>0.039</td>
</tr>
<tr>
<td>Sleep quality improvement</td>
<td>10.4%</td>
<td>9.2%</td>
<td>0.575</td>
</tr>
</tbody>
</table>

Conclusion

Low-dose naltrexone significantly reduces pain, increases life satisfaction, and improves mood in patients with fibromyalgia.
Sample Transdermal Pain Formulations

Topical combinations can produce anti-inflammatory effects by acting on Peripheral NMDA receptors, blocking cox 1,2 and other various inflammatory mediators.

- **Formula 1**
  - Ketamine 5%, Ketoprofen 10%, Pentoxifylline 5%, Piroxicam 2% in Lipoderm +/- Gabapentin 6%

- **Formula 2**
  - Gabapentin 5%, Ketamine 5%, Ketoprofen 4%

- **Formula 3**
  - Baclofen 10%, Ketoprofen 10%, Lidocaine 10%
Multiple drugs in one formulation target many mechanisms and could also provide an additive effect to treat conditions such as neuropathic pain.

- **Formula 4**
  - Dextromethorphan 10%, Ketamine 10%, Ketoprofen 10%, Pentoxifylline 10%

- **Formula 5**
  - Amitriptyline 2%, Clonidine 0.2%, Gabapentin 5%, Ketamine 5%, Ketoprofen 5%

- **Formula 6**
  - Amitriptyline 2%, Bupivacaine 2%, Gabapentin 5%, Ketamine 5%, Ketoprofen 5%, Lidocaine 2%
Deoxy-D-Glucose can be a very effective topical antiviral medications, and has been seen used with Shingles and Herpetic Sores.

**Formula 7**
- Bupivacaine 1%, Clonidine 0.2%, Deoxy-D-Glucose 0.9%, Gabapentin 6%, Ketamine 10% in Lipoderm

**Formula 8**
- Amitriptyline 2%, Bupivacaine 3%, Clonidine 0.2%, Gabapentin 6%, Ketamine 10% in Lipoderm
REFERENCES


