Compounded Medications for Alternative Pain Management
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Objectives
- Define Prescription Compounding
- Explain Prescription Compounding’s Role in Pain Management
- Potential benefits
- How to begin therapy
- How to measure and adjust
- Where to apply
- Additional Compounded Preparations for Pain
  - Trans-dermal Cetyl Myristoleate
  - Oral Ketamine
  - Sublingual/Intra-Nasal Oxytocin + hCG
  - Oral Dextromethorphan
  - Oral Low Dose Naltrexone

What is prescription compounding?1
- USP <795> Definition:
  - “the preparation, mixing, assembling, altering, packaging, or labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner’s prescription, medication order, or initiative.”
- The art and science of preparing personalized medications for patients.
- Prepared based on a practitioner’s prescription.
- Prepared under the guidance of the USP, often through the combination of APIs utilized in FDA-approved drugs.
- Prepared by State Boards of Pharmacy with FDA oversight.
- Pharmacy Compounding Accreditation Board (PCAB)

Common side effects of oral pain medication.6,7,8,9,10,11,12

<table>
<thead>
<tr>
<th>Oral Pain Medication</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDS</td>
<td>GI toxicity and complications such as bleeding, perforation, and ulcers, nephrotoxicity, cardiovascular disease, and cartilage degeneration.</td>
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<tr>
<td>Acetaminophen</td>
<td>Toxic ingestion: renal insufficiency and acute liver failure</td>
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<tr>
<td>Narcotics (Opioids)</td>
<td>Nausea, constipation, CNS effects such as sedation and decreased cognition.</td>
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<tr>
<td>Muscle relaxants</td>
<td>CNS effects such as dizziness and drowsiness</td>
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<tr>
<td>Tricyclic antidepressants</td>
<td>CNS effects, constipation, dry mouth, and tachycardia</td>
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Potential Benefits of Transdermal Compounded Medication.\textsuperscript{13,14,15,16,17,18}

- Customizable dosages, formulations, and drug combinations
- Ability to combine multiple drugs with various mechanisms of action
- Application directly at the site of pain
- Potential for less systemic absorption and minimization of side effects
- More convenience and better adherence to treatment regimen
- Easy adjustment or titration to meet patient needs
- Minimization of abuse and addiction risk

Keys to Effectively Beginning Transdermal Pain Therapy

\begin{itemize}
  \item[1.]{Get a drug on board for each type of pain you can identify}
  \item[2.]{Each therapy should be adjusted to its maximum therapeutic dose and route.}
  \item[3.]{Don’t repeat what you know will fail}
  \item[4.]{Use the Algorithm for Chronic Pain as a guide to starting therapy.}
\end{itemize}

Algorithm for Trans-dermal Treatment of Chronic Pain\textsuperscript{19,20}

A Standard Starting Regimen: Ketamine 5% + Gabapentin 10% + Clonidine 0.2% + Baclofen 2%

Drugs Used in Transdermal Pain Management.

- Acyclovir
- Bretylium
- Colchicine
- Doxepin
- Indomethacin
- Menthol
- Piroxicam
- Acetaminophen
- Bupivacaine
- Cyclobenzaprine
- Flurbiprofen
- Ketamine
- Methocarbamol
- Prednisone
- Adderall
- Capsaicin
- Deoxy-D-Glucose
- Gabapentin
- Ketoprofen
- Morphine
- Sotalol
- Aminophylline
- Carisoprodol
- Dehydroepiandrosterone
- Dexamethasone
- Guaifenesin
- Lidoceine
- Hyoscyamine
- Diphenhydramine
- Magnesium
- Chloride
- Phenytoin
- Verapamil
- Arginine
- Cetyl
- Myristoleate
- Dextromethorphan
- Hydromorphone
- Lipoic Acid
- Orphenadrine
- Tramadol
- Baclofen
- Clobetasol
- Diclofenac
- Ibuprofen
- Loperamide
- Pentoxifylline
- Triamcinolone
- Benzocaine

How to reassess and adjust therapy

\begin{itemize}
  \item[1.]{There are only four potential outcomes of therapy}
  \item[2.]{(1) Fixed}
  \item[3.]{(2) Therapy produces a side effect}
  \item[4.]{(3) Partial improvement with no side effect}
  \item[5.]{(4) No improvement with no side effects.}
\end{itemize}

Where to apply transdermal therapy

\begin{itemize}
  \item[1.]{The location of the pain}
  \item[2.]{The site of the original injury}
  \item[3.]{The dermatome location.}
  \item[4.]{Any trigger point locations.}
\end{itemize}
Let’s Practice!
Case 1

PD is a 42-year-old Caucasian male presenting for the treatment of a disabling work-related lower back injury (an annulus propulsus tear). Upon examination it is noted PD is experiencing myofascial pain caused by his disc injury and characterized by muscle spasm and irritation of the dorsal spinal nerves. At presentation his pain is a 8 on a scale of 1 to 10.

Let’s Practice!
Case 1

What transdermal medication would you prescribe?
Neuroleptic/NT Modifier/Muscle Relaxant
Gabapentin/Amitriptyline/Cyclobenzprine

Let’s Practice!
Case 1

What do you do?
Increase dose(s)
Increase Frequency
Add a vasodilator (i.e. Nifedipine 2-15%, Clonidine 0.1-0.3%, Arginine 6-12.5%)

Let’s Practice!
Case 1

New prescription:
Gabapentin 10% + Amitriptyline 5% + Cyclobenzaprine 4% + Clonidine 0.2%
Encourage patient to apply Q2h until pain is controlled.

2-week telephone follow-up patient reports that preparation controls pain well (4 out of 10) when applied Q2h, but pain escalates to a 6+ if more than 2 hours goes between doses. He shares that he’d like to get by with QID application.
Let's Practice
Case 1

What do you do?
Increase dose(s)
Increase Frequency
*Add NMDA Receptor Antagonist*

New Prescription:
Gabapentin 10% + Amitriptyline 5% + Cyclobenzaprine 4% + Clonidine 0.2% + Ketamine 5%
Apply 1gm QID.

In 2 weeks patient reports pain has been well controlled (2-4 out of 10) with QID application.

Let's Practice
Case 2

35-year-old Caucasian female with temporomandibular joint point presents to you for the first time. Her pain is a 9 on a 10-point pain scale. Her discomfort increases when she eats or speaks, and pain profoundly and negatively affects her quality of life. She is currently being treated by another provider with oral duloxetine and high doses of oral oxycodone, which is providing effective pain control, but she can’t tolerate the side effects. A prior trial of gabapentin had proven ineffective.

What would you select for a trans-dermal preparation?

- Anti-inflammatory → Ketoprofen 5-20%
- Muscle Relaxant → Baclofen 2%
  - OR - an NMDA Ca channel blocker muscle relaxant → MgCl2 10-20%
- TCA/Sympatholytic/NE reuptake inhibitor → Amitriptyline 1-10%
- AMPA-Na Channel Blocker → Gabapentin 6-10%
  - OR - AMPA-Na Channel Blocker/Anesthetic → Tetracaine 4-5%
- NMDA Ca channel blocker → Ketamine 5-15%

Let's Practice!
Case 2

It was decided to start with:
Ketoprofen 10% + Amitriptyline 2% + Gabapentin 4%
Applied TID to affected area and around her jaw

2 weeks later she reports improvement and no side effects, but still continues to be uncomfortable.

What would you do?
Increase APIs to max.

Decided to increase Ketoprofen to 15%.
Pain was significantly relieved (3 on a 10 point pain scale) at her 8-week follow up allowing titration off of oxycodone. She continued on this preparation without systemic affects or the risk of addiction for 2 years.
Let's Practice!
Case 3

93-year-old Caucasian woman, who in otherwise good health, is referred to you for the treatment of moderate stiffness, compromised range of motion, and rheumatoid arthritis pain in her neck and shoulder.

Let's Practice!
Case 3

What would you select for a trans-dermal preparation?

Prescribed:
Ketamine 4% + Ketoprofen 6% + Lidocaine 2%

Instructions:
Every 4-6 hours moisten the skin over the painful areas and apply a pea-sized amount of the cream and rub it into the skin until dry, moisten fingers and again rub the cream into the skin for an additional minute.

Results:
Within 30-60 minutes after application she noted the onset of relief from pain and stiffness. After the 2nd week her arthritic symptoms had resolved to a manageable level.

1st year of treatment she applied 30gm each month; refilled monthly. In 2nd year used 1/3 the amount she originally required and fills Rx every 2-3 months. No adverse effects. Mainstay of treatment, augmented with acupuncture & occasional OTC IBU.

What's the perfect trans-dermal pain preparation?
The one that works!

Clinical Pearls – Trans-dermal Pain Preparations

- Seldom want to go above 20% API.
- Warming the area can help improve delivery.
  - Apply after a warm shower/warm compress
- Moisten area and rub cream in well.
- Re-moisten and rub again.
- May have to apply frequently at first especially with neuropathic pain.

Additional Compounded Medications for Pain Management

- Cetyl Myristoleate (CMO) trans-dermal for arthritis,23,24
  - 2004 study in the Journal of Rheumatology
    - Mixed cetylated fatty acids in a topical cream applied twice daily to patients with osteoarthritic knee joints.
    - After 30 days → improved knee range of motion, improved ability to climb stairs, rise from a chair and walk, improved balance, strength, & endurance.
All Practitioners should find a PACB Accredited Compounding Prescriber.

**Take Away Points**
- A compounding pharmacist can greatly augment the pain therapies you offer your patients - offering customized solutions to individualized pain.
- Many options exist for the trans-dermal treatment of pain - The Best Preparation is the one that works for the patient!
- Pick agents that make sense
- Maximize dose and frequency
- Give adequate time to work
- Compounded Prescription options for pain management extend beyond trans-dermal preparations.
- All Practitioners should find a PACB Accredited Compounding Pharmacist they know and trust to collaborate with.

**Additional Compounded Medications for Pain Management**
- **Oral Dextromethorphan**
  - **Dosing usually starts at 35mg TID**
  - Fewer & less severe adverse effects than parenteral
  - Smaller (peak) plasma levels
  - Higher plasma levels of nor-dextromethorphan via 1st-pass metabolism
  - Has a more favorable safety profile
  - Generally stops the upward progression of narcotic dosing
  - May reduce narcotic load
  - Retrospective study of 55 cases of oral ambulatory ketamine
  - 62% - opioid therapy could be reduced
  - 44% - refractory chronic pain was abolished
  - Only 22% - did not benefit

- **Low Dose Naltrexone**
  - A pure opioid antagonist with a high affinity for mu receptors.
  - At dose 10x lower effective for pain (4.5mg)
  - Possible MOA:
    - Opioids take the receptors off of other receptors, which are up-regulated in the CNS.
    - Responsible for the release of pro-inflammatory cytokines.
    - Transient opioid blockade leads to a compensatory long, lasting increase in endogenous opioid activity.
    - Effective in a variety of chronic pain.
  - Possible Side Effects:
    - Abomasal, diarrhea, nausea, vomiting.

- **Oral Ketamine**
  - Has an emetic effect and is an anticonvulsant.
  - Does not exhibit euphoric properties.
  - Lower required doses of opioids.
  - Improves emotional well-being.
  - Does not exhibit euphoric properties.

- **Low Dose Naltrexone**
  - Generally stops the upward progression of narcotic dosing.
  - Fewer & less severe adverse effects than parenteral.
  - Side Effects:
    - Nausea, vomiting, headaches.

- **Oxytocin + HCG**
  - Small study presented at the 2014 AAPM Annual Meeting
  - Doses
    - HCG: 150 – 500units SL QD
    - OT: 10units SL 2-4x/day
  - Out of 9 patients:
    - 30-40% reduction in opioid use.
    - Reduction in baseline pain, flare intensity, or an increase in time between flares.
  - Possible Side Effects:
    - 1 patient reported a heightened emotional state with excretion.

**Bibliography**

Bibliography


Questions?

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Thank you!