Compound Medications:
What are they and why are they used?

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Agenda

- Compounding Basics
- Regulations
- Clinical Concerns
- Non–Clinical Controversies
- Evidence–Based Approach
- Practical Guidance for Workers’ Compensation
- Q & A
Compounding Basics
Records of apothecary or pharmacy practice date back to 2,600 BC
Close ties between medical/pharmacy/spiritual professions
Compounding pharmacies show up in the US in 1800s
  ◦ Prescription = “Recipe” in Latin meaning “take thou”
  ◦ Old fashioned soda fountains
Mass manufacturing and distribution leads to decline of compounding pharmacies
Rise of community or retail pharmacy
Today compounding pharmacies offers unique, specialized services
  ◦ Serve needs ignored or unaddressed by larger pharmacies
  ◦ Tailored medications
Compounding Basics

Definition of pharmacy compounding
  ◦ Licensed pharmacist
  ◦ Combination, mix, or alteration of ingredients of a drug
  ◦ With a valid prescription from a licensed medical practitioner
  ◦ To create a tailored product for an individual patient
Compounding Basics

- Nonsterile compounding processes and tools

https://upload.wikimedia.org/wikipedia/commons/thumb/8/8d/Pestle_and_Mortar_with_peppercorns.jpg/800px-Pestle_and_Mortar_with_peppercorns.jpg
Compounding Basics

Place in therapy or clinical use considerations

- Limited systemic exposure
  - Gastrointestinal tract
  - Cardiovascular events
  - Kidney exposure
  - Liver metabolism

- Alternative options for those with ingredient allergies
  - Fillers (lactose, etc.)
  - Dyes (titanium dioxide, quinolone yellow, talcum, red 40, etc.)
Compounding Basics

- Non-commercially available
  - Obscure doses
  - Alternate formulations/delivery methods
  - Titrating hormone doses (levothyroxine, estrogen, progesterone)

- Supplemental supply for drug shortages
  - Voltaren gel
  - Daraprim, Turing Pharmaceuticals & Martin Shkreli
Regulations
State boards license all pharmacies (compounding and other) the same way
- Day-to-day oversight
- Intervention and license revocation when necessary

The FDA's regulatory authority is more limited than its authority over other drug manufacturers
- Compounds are not FDA approved
- Compounding pharmacies not required to register with FDA

Current Compounding Regulations

- **Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act**
  - FDA defers to state boards of pharmacy regarding enforcement
  - Compounds must be made in compliance with USP chapters on pharmacy compounding
  - Compounds can not be a commercially available product
  - Compounds may not include any ingredients withdrawn from the market due to safety or efficacy issues (Vioxx)
  - Compounds are still subject to adulteration and misbranding regulations
  - Limited quantities of anticipatory compounding may be done

- **Drug Quality and Security Act created new category of compounding pharmacies called outsourcing facilities (503B)**
  - Facilities producing sterile compounds must register with the FDA and are subject to FDA inspection
Pending Regulations

In March 2017, the Pennsylvania State Board of Pharmacy proposed to add a new section within PA Code Chapter 27 directly relating to compounding

- Compounding must be done in accordance with the current version of USP 795 and 797
- Wholesale distribution of compounded drug products to other pharmacies, commercial entities, or prescribers is prohibited
- Production record must be prepared and kept for a minimum of 2 years for each compounded product

http://www.pabulletin.com/secure/data/vol47/47-10/427.html
Accreditation Groups

Pharmacy Compounding Accreditation Board (PCAB)

- "A voluntary accreditation program that recognizes adherence to established principles."
- Only 3 accredited pharmacies in PA in 2013
- Now there are 22 accredited pharmacies

http://www.pcab.org/accredited-locations.html
Accreditation Groups

DynaLabs: Continuous Quality Improvement (CQI) Partnership

- Pharmacy “Centers of Excellence” earn the CQI certificate by establishing and following quality metrics and processes
- Analytical tests certify the quality of the products dispensed from the pharmacy

http://www.dynalabs.us/products-services/cqi-program/
Clinical Concerns
Pharmacology of topical Compounds

- **Key importance for transdermal efficacy**
  - Dissolving the drug in the vehicle
  - Movement from vehicle into skin

- **Partition coefficients**
  - Ketamine: 2.2
  - Gabapentin: −1.1
  - Lidocaine: 2.3
  - Baclofen: 1.3
  - Flurbiprofen: 4.2
  - Bupivacaine: 3.4
  - Cyclobenzaprine: 5.2
  - Diclofenac: 4.4

[pubchem.ncbi.nlm.nih.gov](http://drugdelivery.chbe.gatech.edu/Papers/2012/Prausnitz%20Derm%20Book%20Chapter%202012.pdf)
Therapy Duplication

- **NSAIDs**
  - Diclofenac
  - Flurbiprofen
  - Ketoprofen
  - Meloxicam

- **Muscle Relaxants**
  - Baclofen
  - Cyclobenzaprine
  - Tizanidine
Bioavailability Issues

- **Skin Characteristics**
  - Thickness, perfusion (blood flow), porous nature, temperature, composed or broken skin
Bioavailability Issues

- Drug Characteristics
  - Molecular size, lipophilicity, permeability, concentration, duration of contact, acidity of drug or vehicle
  - Stability of active ingredients in vehicle is unknown
From: Evaluation of the Percutaneous Absorption of Ketamine HCl, Gabapentin, Clonidine HCl, and Baclofen, in Compounded Transdermal Pain Formulations, Using the Franz Finite Dose Model


Figure Legend:

Distribution of ketamine in the skin 48 hours after transdermal application. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax and tested on skin from three donors with three replicate sections per donor. Forty-eight hours after application, the skin was tape-stripped and the amount of ketamine in each skin layer was determined using HPLC/MS. The results are expressed as mean ± SE.
From: Evaluation of the Percutaneous Absorption of Ketamine HCl, Gabapentin, Clonidine HCl, and Baclofen, in Compounded Transdermal Pain Formulations, Using the Franz Finite Dose Model


Figure Legend:

Percutaneous absorption of clonidine over time. Ketamine HCl 5% w/w, gabapentin 10% w/w, clonidine HCl 0.2% w/w, and baclofen 2% w/w were compounded into Lipoderm or Lipoderm ActiveMax. Each formulation was tested on skin from three different donors and three replicate skin sections per donor. Samples of receptor solution were taken over time and analyzed for clonidine content using HPLC/MS. The means from each donor were averaged and results are expressed as mean ± SE.
Bioavailability Issues

- Dose Ambiguity

![Image of pills](https://www.pexels.com/photo/applying-bodycare-bodylotion-care-275856/)

![Image of body lotion](https://upload.wikimedia.org/wikipedia/commons/thumb/5/58/Cream_Clapton_Bruce_Baker_1960s.jpg/230px-Cream_Clapton_Bruce_Baker_1960s.jpg)

![Image of pills](https://cdn.pixabay.com/photo/2016/07/05/12/35/pills-1498602_960_720.jpg)
Bioavailability Issues

- Stability of drug in vehicle is unknown
- Super- or sub-therapeutic concentrations

![Image of a beaker with concentrations: 75%, 105%, 50%, 100%, 115%](https://cdn.pixabay.com/photo/2014/04/02/11/04/jar-305387_960_720.png)
Bioavailability Issues

- Questionable conclusions from available evidence on bioavailability
  - Transdermal absorption using Franz Finite Dose Model
Franz Finite Dose Model

Fig. 1. Franz™ diffusion cell (static type).
Compound Conundrum

- **Benefits of topical vs systemic exposure advertised**
  - Maximum plasma concentration from topical dose (15 ng/mL +/- 7.33) was about 0.7% of the systemic dose (2,270 ng/mL +/- 778)

- Yet efficacy is touted for centrally-acting medications
Topical Analgesic Compound Rx
Non-Clinical Controversies
Non-Clinical Controversies:
“Letters of Medical Necessity”

PATIENT NAME: [Redacted]
MEMBER ID: [Redacted]
DATE OF BIRTH: [Redacted]
DATE OF INJURY: [Redacted]
MEDICATION: CNA-10 Neuropathic and Anti-Inflammatory Combination Compound Cream (Ketamine 10%, Flurbiprofen 10%, Gabapentin 10%, Cyclobenzaprine 3%, Bupivacaine 2%)

Dear Claim Handler:

I am the treating physician for [Redacted] and have prescribed the transdermal analgesic cream listed above. I believe this medication to be a reasonable and medically necessary component of the treatment I am providing this patient. My rationale is described below.

Prior to and during the time that I have been providing medical care to this patient they have been prescribed multiple analgesic medications with the goal of reduction in pain and improvement in function. As is often the case in complex acute and chronic pain conditions, analgesics from several classes of medications are utilized in an attempt to treat pain at different points along various pathways involved in the transmission of nociceptive and neuropathic pain. These medications include, but are not limited to, anti-inflammatory medications, muscle relaxant medications and anti-neuropathic pain medications. While these medication types are often effective in reducing pain perception, this can be at the cost of producing bothersome adverse effects that can contribute to significant morbidity and dissatisfaction on the part of the patient. These limitations have created the need for topical analgesic formulations.

This particular patient has experienced gastrointestinal upset with traditional oral NSAID medication trials across several subclasses of NSAIDs. Topical administration of the NSAID flurbiprofen results in significantly lower plasma concentration as compared to a comparable oral dose, minimizing systemic exposure to the medication without sacrificing efficacy.
Starting in 2012, there was a multi-state outbreak of fungal meningitis among patients who received contaminated preservative-free steroid injections, which was traced to the New England Compounding Center (NECC) in Framingham, Massachusetts:

- Affected 753 patients in 20 states, as far away as California
- Involved localized spinal or paraspinal infections (e.g. epidural abscess), as well as peripheral joint injections
- **64 DEATHS**
- $200 million settlement fund established for victims and families
- NECC president and former head pharmacist both on trial for second degree murder
- Other staffers pled or were found guilty of lesser charges
Non-Clinical Controversies: Potential for Fraud

defendants, and others known and unknown, with the intent to profit financially, were involved in a scheme targeting providers of health insurance (the “Victim Insurers”), by causing, and causing others to cause, corrupt doctors to issue unnecessary and excessive prescriptions for expensive compound cream (“Prescription Compound Cream”) that were then billed to the Victim Insurers. Had the Victim Insurers known the fraudulent nature of the scheme – that wrongful kickbacks were paid to doctors to write, and to patients to request and receive, unnecessary and excessive prescriptions for the Prescription Compound Cream – the Victim Insurers would not have issued reimbursements for the Prescription Compound Cream.

Non-Clinical Controversies: Potential for Fraud

U.S. Attorneys » Northern District of Texas » News

Department of Justice
U.S. Attorney's Office
Northern District of Texas

FOR IMMEDIATE RELEASE
Friday, October 14, 2016

Ten Additional Defendants Charged in $100 Million TRICARE Fraud Scheme

Two Defendants, Owners of CCMGRX, LLC, Were Indicted Earlier this Year in This Scheme That Involved Claims for Compounded Pain and Scar Creams

DALLAS — Special agents with the Federal Bureau of Investigation and the Defense Criminal Investigative Service (DCIS) arrested nine defendants this week in connection with their roles in a $100 million health care fraud conspiracy perpetrated against TRICARE, the health insurance program for members of the military and their families. A tenth defendant surrendered to the FBI. The defendants, including doctors, pharmacy owners, and marketers were charged in a 35-count superseding indictment returned last week in Dallas and unsealed this afternoon, announced U.S. Attorney John Parker of the Northern District of Texas.

"Exhaustive investigative work by FBI and DCIS special agents and investigators not only led to today's arrests, but to the identification and seizure of millions in assets that these defendants derived from their participation in this massive scheme that caused the TRICARE health insurance program—designed for our military personnel, veterans and their families—to suffer more than $100 million in actual losses," said U.S. Attorney Parker.

DOJ release: https://www.justice.gov/usao-ndtx/pr/ten-additional-defendants-charged-100-million-tricare-fraud-scheme
Evidence-Based Approach
Evidence of efficacy most robust for commercially available preparations (e.g. diclofenac, lidocaine, capsaicin)

Beyond that, literature is limited:
- Few randomized control trials
- Quality is questionable (small N, cases series, short term outcomes, focus on pain relief and not on functional improvement)
- Virtually no literature on multi-agent topical medications
- Example:
Evidence-Based Approach to Compounds: Literature Support for Topicals

Novel Treatment of Radicular Pain With a Multi-Mechanistic Combination Topical Agent: A Case Series and Literature Review

Pegah Safaeian, Ryan Mattie, Matthew Hahn, Christopher T. Plastaras, and Zachary L. McCormick

Abstract

Introduction

Pharmacologic treatment of radicular pain with oral medications is limited by adverse effects and concern for dependence. While topical formulations have been explored in pain research, there is no published literature evaluating the efficacy in radicular pain. We present the first three cases of radicular pain successfully treated with a topical formulation of diclofenac, ibuprofen, baclofen, cyclobenzaprine, bupivacaine, gabapentin, and pentoxifylline (T7).
Evidence-Based Approach to Compounds: National WC Guidelines—ACOEM

Chronic Pain Chapter:

- Capsaicin creams “Moderately recommended for short-term treatment of acute exacerbations of localized musculoskeletal chronic persistent pain.”

- Lidocaine patches “Sometimes Recommended…when there is a localized pain amenable to topical treatment…after other treatment strategies (e.g., NSAIDs, exercise/conditioning program) with documented efficacy have been tried first.”

- Topical NSAID’s “Sometimes Recommended…where the target tissue is located superficially” and oral NSAID’s are not tolerated or contraindicated.
Evidence-Based Approach to Compounds: National WC Guidelines – ACOEM (continued)

CRPS Chapter:
- Dimethyl sulfoxide (DMSO) “Recommended…as an adjunct to an active exercise program with an informed warning about its potential risks.”
Evidence-Based Approach to Compounds: National WC Guidelines—ODG (1)

Chronic Pain Chapter

- **Topical NSAID’s**
  - Recommended for short term use in acute pain
  - Emphasizes that only topical diclofenac is FDA-approved
  - Not recommended for OA of joints/back, wide-spread musculoskeletal pain, or neuropathic pain

- **Lidocaine patches**
  - Recommended on a trial basis as second line tx for neuropathic pain
  - Not recommended for OA, axial back pain, or myofascial pain
Capsaicin: “Recommended only as an option in patients who have not responded or are intolerant to other treatments”

Other topicals not recommended, specifically baclofen, other muscle relaxants, gabapentin, other anti–epilepsy drugs, and ketamine
Evidence-Based Approach to Compounds: National WC Guidelines—ODG

Compounded medications are not recommended as a first-line therapy:

“Any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended. The use of compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required.”
Evidence-Based Approach to Compounds: State WC Guidelines (1)

- CA MTUS: refer to ODG

- CT Medical Protocols: Hand OA, Knee Subacute allow for topical NSAID’s

- CO MTG’s: Topical NSAID’s for OA and acute MS injury; lidocaine, capsaicin for neuropathic pain; ketamine, tricyclics allowed for CRPS on trial basis, continuation is based on documentation of functional improvement or decreased use of other meds (e.g. opioid weaning)
Evidence-Based Approach to Compounds: State WC Guidelines

- LA Medical Guidelines: Chronic Pain chapter, non-specific on meds; CRPS, allows ketamine or capsaicin (but concedes no evidence)

- NY MTG: Non-Acute Pain chapter—“Topical, oral and/or systemic compound medications are not recommended.”

- WA Outpatient Drug Formulary: All compound preparations require prior authorization
Practical Guidance for WC
Lessons from Connecticut

- Scope: CT state health plan
- Magnitude of problem: Compounds went from $800K in FY 2012 to $24 million annualized for FY 2015
- In May 2015, State Comptroller Keith Lembo instituted a prior authorization program for all compound Rx requests, administered through CVS/Caremark
- Results: Total spending on compound Rx’s dropped from a high of $3.1 million in April 2015 to $36,229 in July 2015
Will we learn from these lessons?

THE GENERAL ASSEMBLY OF PENNSYLVANIA

HOUSE BILL
No. 18   Session of 2017

INTRODUCED BY MACKENZIE, A. HARRIS, HEFFLEY, MILLARD, SIMMONS
AND TOPPER, FEBRUARY 13, 2017

REFERRED TO COMMITTEE ON LABOR AND INDUSTRY, FEBRUARY 13, 2017

(J) The department shall select a nationally recognized, evidence-based prescription drug formulary appropriate for resolving issues related to drugs prescribed for or related to the treatment of work-related injuries, including, but not limited to, the type, dosage and duration of prescriptions. The following shall apply:
Until then, what should you do?

Ask LOTS of questions (here are but a few):

- Have the usual first line oral meds been tried and failed?

- Is there DOCUMENTED evidence of intolerance of oral meds, or comorbid conditions that preclude the use of oral meds?

- Have commercially available topical meds been tried and failed?

- Are any of the ingredient meds in the compound a duplication of oral medication classes that the injured worker is already taking?

- Are the ingredient meds indicated/appropriate for the diagnosis?
Until then, what should you do?

More Questions…

- What do ODG/ACOEM have to say about these meds?

- Can the doc provide published literature showing efficacy of EACH medication in the compound?

- If this is a refill, is there objective evidence of pain improvement, such as a decreased opioid requirement?

- If this is a refill, is there specific documentation of qualified and quantified functional improvement?
Questions?