THE SAFE PRESCRIBING OF OPIOID MEDICATIONS IN NON-CANCER PAIN: USING OPIOID MEDICATION IN A TROUBLED TIME

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Objectives

At the end of this presentation, the participant will be able to:
- Discuss the best practices for prescribing opioid medications
- Discern why buprenorphine is a safe pain medication
- Discuss the place of co-prescribing naloxone or patients being prescribed chronic opioid therapy (COT) for chronic non cancer pain (CNCP)
Use of Opioids in Chronic Pain: Balancing Act

- Pain as the 5th vital sign
  - Starting in 2001, the Joint Commission has now officially recognized that pain is a major health problem and "patients have the right to appropriate assessment and management of pain"

A Balancing Act: Public Health

- A crisis of abuse of prescription opioid medication
- New Mexico is in top #3 in United States in accidental OD rates with prescription opioid medication
- Yet NM providers prescribe less than the national median amount of opioid medication
Drug Overdose Death Rates
New Mexico and United States,
1990-2014

Deaths per 100,000 persons

Year


New Mexico
United States

Rates are age adjusted to the US 2000 standard population

Source: United States (CDC Wonder); New Mexico (NMDOH BVRHIS/SAES, 1990-1998, 2014; NM-IBIS, 1999-2013)
A Balancing Act: Patient’s Expectations

- Patient Expectations
  - of being pain free
  - of “magic bullet” medications
  - of unlimited supply of medications
    - opioids
  - of not having to do any work
    - physical therapy
    - behavioral health
  - of no consequences for their decisions
    - “being honest”
A Balancing Act: Provider’s Realities

- Provider’s realities
  - the incidence of alcoholism and addiction in the general population is 5%-10
  - one addict effects 7-10 people
  - the prevalence of current or past substance use disorders in patients receiving chronic opioids for CNCP may be ~ 40% or higher
  - the principles of chronic medication management are often forgotten when managing opiate medication
    - clash of providers & patient’s values

Basic Concepts of Prescribing Opioids

- Principles of medication management & prescribing
  - evidenced based medicine
  - efficacy and safety
- Use of corticosteroids as an analogy
  - control symptoms; often not curative
Controversy: Opiates for CNCP?

- There is not consensus among expert recommendations regarding the efficacy of opiate use in CNCP, for example:
  - Chou R et al. 2009: concludes chronic opioid therapy (COT) can be effective in selected patients
  - Manchikanti L et al. 2011: concludes there is only weak evidence for the use of COT

- There is insufficient evidence to determine the effectiveness of long-term opioid therapy for improving chronic pain, but emerging data support a dose-dependent risk for serious harms, such as overdose, mortality, and possibly fractures and cardiovascular events...

Place of Opioids in the Treatment of Chronic Pain

- Guidelines for starting opioids by indication, according to the American Academy of Pain Medicine
- Neuropathic, Chronic Back/Muscle, Inflammatory, or pain from Mechanical/Compressive Etiology:
  - Only after all non-opioid medications have been maximized
Prior to Initiating Opioid Medication
- Non opioid medication maximized
- SOAPP R screening test
- Controlled Substance Agreement (CSA)
- Review of NMBOP PMP report
- Baseline UDM
- Discuss risks and benefits of using controlled substances w/ patient
- Pause & think

Urine Drug Monitoring
- Suspected medication related aberrant behavior
- Fear of damaging provider-patient relationship
- Always make sure the test ordered will test for the medication in question
- Always document when patient last took a dose of the medication being tested
- High risk medication, not high risk patients
  - Good data drives good therapy
Types of Urine Drug Testing

<table>
<thead>
<tr>
<th>Immunoassay Presumptive Screen</th>
<th>GC-MS or LC-MS/MS Definitive Quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-office, point-of-care, or lab-based IA test</td>
<td>Laboratory test</td>
</tr>
<tr>
<td>Less specific and sensitive</td>
<td>Highly specific and sensitive</td>
</tr>
<tr>
<td>Results within minutes</td>
<td>Results in hours to days</td>
</tr>
<tr>
<td>Detects drug classes and few meds, illicit substances</td>
<td>Measures concentrations of all medications, illicit substances, and metabolites</td>
</tr>
<tr>
<td>Guidance for preliminary treatment decisions</td>
<td>Definitive identification and analysis</td>
</tr>
<tr>
<td>Cross-reactivity common: More false positives</td>
<td>False-positive results rare</td>
</tr>
<tr>
<td>Higher cutoff levels: More false negatives</td>
<td>False-negative results rare</td>
</tr>
</tbody>
</table>

Windows of Detection in Urine

- Indicates how long after administration a person excretes the drug and/or its metabolite(s) at a concentration above a specific test cutoff concentration
  - 1 to 3 days for most drugs and metabolites

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>Approximate Window of Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>3-5 days</td>
</tr>
<tr>
<td>THC*</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Benzodiazepines*</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Opioids*</td>
<td>~3 days</td>
</tr>
<tr>
<td>Cocaine (benzylecgonine metabolite)</td>
<td>2-3 days</td>
</tr>
</tbody>
</table>

*Long-term use of lipophilic drugs or longer-acting benzodiazepines can extend window of detection.


Initiating Opioid Medication

- Complete Critical 1st Assessment
- Start low and go slow
- Start on short acting (SA) opioid
- Reassess in ~ 2 weeks
- Caution
  - Fibromyalgia, Headache, IBS

Practical/General Dosage Range Guidelines for Use of Opioids in CNCP
(MME = Morphine Milligram Equivalent)

<table>
<thead>
<tr>
<th>Level</th>
<th>Daily MME Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>5 – 30 per day MME</td>
</tr>
<tr>
<td>Moderate</td>
<td>35 – 70 per day MME</td>
</tr>
<tr>
<td>Moderately High</td>
<td>75 – 90 per day MME</td>
</tr>
<tr>
<td>High</td>
<td>90-100 per day MME</td>
</tr>
</tbody>
</table>
### MME (Morphine Milligram Equivalent) Conversion Table

(All Conversion factors use Morphine as the Standard)

<table>
<thead>
<tr>
<th>Potency</th>
<th>Drug</th>
<th>Conversion Factor</th>
<th>Example: MME Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LESS</td>
<td>Codeine</td>
<td>.15</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>1</td>
<td>30 mg</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>1</td>
<td>30 mg</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td>1.5</td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone</td>
<td>3</td>
<td>10 mg</td>
</tr>
<tr>
<td>MORE</td>
<td>Hydromorphone</td>
<td>4</td>
<td>7.5 mg</td>
</tr>
</tbody>
</table>

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**Caution with Methadone**

- Variable half-life (8-59 hours) and duration (6-8 hours)
  - Dose q 6-12 hours
- Multiple drug interactions
  - Avoid w/ alcohol, azole antifungals, thioridazine
- Can ↑ QTc Interval @ ≈ 100mg/day
  - If ↑ QTc, Decrease dose
- Can accumulate in the elderly
- No changes in dose until 5-7 days after starting methadone

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### Dose: Methadone (possible)

#### Equianalgesic Doses

<table>
<thead>
<tr>
<th>Total Daily Dose Oral Morphine</th>
<th>EPERC Conversion (MSO₄: Methadone)</th>
<th>% of MSO₄ Dose (FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 MDE</td>
<td>3:1</td>
<td>20-30%</td>
</tr>
<tr>
<td>101-300 MDE</td>
<td>5:1</td>
<td>10-20%</td>
</tr>
<tr>
<td>300-600 MDE</td>
<td>10:1</td>
<td>8-12%</td>
</tr>
<tr>
<td>600-800 MDE</td>
<td>12:1</td>
<td>5-10%</td>
</tr>
<tr>
<td>800-1000 MDE</td>
<td>15:1</td>
<td>5-10%</td>
</tr>
<tr>
<td>&gt; 1000 MDE</td>
<td>20:1</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

### Data: Methadone

- NYT July 2012: Methadone accounted for 1/3 deaths from opioids in 2009
  - But only 2% of opioid prescriptions written
    - 1/3 patients prescribed methadone were opioid naive

- New Mexico
  - 1998-2002: 143/1120 (12.8%) drug related deaths caused by methadone
    - 75% from illicit drug use
  - 300% increase in prescribing of methadone in this time period
### Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Buprenorphine (SL &amp; Top)</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein Binding</td>
<td>96%</td>
<td>85%-90%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>SL: 29%; Top: ~ 15%</td>
<td></td>
</tr>
<tr>
<td>Half-life Elimination</td>
<td>SL: ~37 hrs; Top: ~26 hrs</td>
<td>8-59 hrs</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>10-30 min</td>
<td>30-60 min</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>6 hrs</td>
<td>4-8 hrs (single); 22-48 hrs (repeated)</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>SL: 30-60 min</td>
<td>1-7.5 hrs</td>
</tr>
<tr>
<td>Time to Peak Effect</td>
<td></td>
<td>3-5 days</td>
</tr>
<tr>
<td>Decreased Hepatic Fx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Renal Fx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geriatric</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2004. (Treatment Improvement Protocol (TIP) Series, No. 40.) 2
Pharmacology Available from: http://www.ncbi.nlm.nih.gov/books/NBK64236; Lexicomp; Epocrates; AHFS

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### Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Buprenorphine (SL &amp; Top)</th>
<th>Methadone (po)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>CYP 3A4 to nor-metabolite</td>
<td>CYP 3A4, CYP 2B6, CYP 2C19</td>
</tr>
<tr>
<td>Drug Interactions: Avoid Concomitant Use</td>
<td>Azelastine, MAOI, Orphenadrine, Paraldehyde, Thalidomide</td>
<td>Alcohol, Azelastine, Benzodiazpines, QTc prolonging agents, Ketoconazole, Orphenadrine, Paraldehyde, Thalidomide</td>
</tr>
<tr>
<td>Drug Interactions: Metabolism</td>
<td>Substrate of CYP 3A4 (major); weakly inhibits CYP 1A2, CYP 2A6; CYP 2C19; CYP 2D6</td>
<td>Substrate of CYP 3A4 (major), CYP 2B6 (major), CYP 2C19 (minor), CYP2C9 (minor), CYP 2D6 (minor); Inhibits CYP 2D6 (moderate), CYP 3A4 (minor)</td>
</tr>
</tbody>
</table>

Lexicomp, AHFS, Epocrates
Buprenorphine & Methadone Mechanisms of Action

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Buprenorphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu Opiate</td>
<td>Partial agonist; High affinity; low-moderate activity</td>
<td>Agonist; High affinity</td>
</tr>
<tr>
<td>Kappa Opiate</td>
<td>Antagonist; High affinity; low-moderate activity</td>
<td>Agonist; Low affinity</td>
</tr>
<tr>
<td>NMDA</td>
<td>NMDA receptor blockade</td>
<td>NMDA receptor blockade</td>
</tr>
<tr>
<td>Serotonin Reuptake Inhibition</td>
<td>Weak serotonin reuptake inhibition</td>
<td></td>
</tr>
</tbody>
</table>


Head-Head Comparison

- Fifty-four patients with chronic pain and opioid addiction were randomized to receive methadone or buprenorphine/naloxone
- Both buprenorphine and methadone treatment resulted in a 12.75% reduction of pain after 6 months of treatment compared with the level of pain present at the initial visit
- Buprenorphine and methadone treatment were comparable in the amount of analgesia and functioning
- Buprenorphine treatment had a superior safety profile compared with methadone treatment
Which Medication to Use

**Buprenorphine (SL)**
- Buprenorphine is effective in treating neuropathic pain.
- Buprenorphine treats a broader array of pain phenotypes than do certain potent mu agonists, is associated with less analgesic tolerance, and can be combined with other mu agonists.
- Buprenorphine has a ceiling effect on respiratory depression & analgesia.
- Buprenorphine causes less cognitive impairment than do certain other opioids.
- Buprenorphine is not immunosuppressive like morphine and fentanyl.
- Buprenorphine does not significantly prolong the QTc interval, and is associated with less sudden death than is methadone.
- Buprenorphine is a safe and effective analgesic for the elderly.

**Methadone**
- Methadone is considered when:
  - Other opioids have been increased to high doses and are not working to relieve pain any more.
  - For specific pain types:
    - Neuropathic pain.
    - Complex regional Pain Syndrome.
- Methadone for pain treatment is not Methadone for opioid dependence.
- Methadone for opioid dependence:
  - Cravings and withdrawal symptoms in opioid dependence respond best to doses between 60-120mg daily.
  - In non-opioid dependent ("healthy") patients, pain relief is possible with doses between 5-50 mg daily.
- Methadone metabolism is complex:
  - It changes with time and dose.
  - Nonlinear pharmacokinetics.
  - Methadone interacts with many medications, primarily through the CYP P450 3A4, and 2D6 systems.

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Reassessment of Opioid Medication Regimen

4 A’s of monitoring opiate therapy

- Analgesia
- activities of daily living
- adverse effects
- aberrant drug-related behaviors
Reassessment of Opioid Medication Regiment

- Opioid Initiation Algorithm:
  - Does current opioid dose make sense; ie: 100-120 MME
    - Is medication strong enough?
      - ✓ If Not strong enough & Not lasting long enough
      - ↑ dose
    - Does medication last long enough?
      - ✓ If Strong enough but Not lasting long enough
      - ↓ dose interval
- ALWAYS Pause & think
- Consider adherence

Indications for LA Opioids

- Increase adherence
- When patient goes for an extended period of time and cannot take a SA opioid; ie: sleep, work
- Question of aberrant behavior
- > 6 doses of SA opioid/day
### Current Opioid ADFs: Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Opioid formulation</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical barriers</td>
<td>Prevent abusers from crushing or chewing their opioid to facilitate rapid release into the system</td>
<td>Does not deter abuse of intact tablets</td>
<td>Oxycontin©: oxycodone; forms viscous hydrogel</td>
</tr>
<tr>
<td></td>
<td>Prevent accidental crushing or chewing in compliant patients</td>
<td>Only 1 FDA-approved formulation available</td>
<td>Opana©: morphine; Exalgo©: Osmotic Extended-Release Oral Delivery System (OROS)</td>
</tr>
<tr>
<td></td>
<td>No AEs in compliant patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does not deter abuse of intact tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aversive components</td>
<td>May prevent abuse by chewing or crushing opioids</td>
<td>Potential for AEs in adherent patients who take the product as intended AES with intact tablets may prevent</td>
<td>Oxteca©: oxycodone; AVERSION technology impedes extraction of opioid</td>
</tr>
<tr>
<td></td>
<td>May limit abuse of intact tablets because taking too much will amplify niacin AEs</td>
<td>prevent appropriate dose increases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AES of niacin may not be sufficient to deter a motivated abuser</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No FDA-approved formulation</td>
<td></td>
</tr>
<tr>
<td>Sequestered antagonist</td>
<td>Prevents abuse by chewing or crushing opioids</td>
<td>Does not deter abuse of intact tablets</td>
<td>Embedda©: morphine/naltrexone</td>
</tr>
<tr>
<td></td>
<td>FDA-approved formulation available</td>
<td>Chewing or crushing the tablet may cause severe withdrawal symptoms</td>
<td>Targiniq ©: oxycodone/naloxone</td>
</tr>
</tbody>
</table>


### FDA Approved Abuse-Deterrent Extended Release Opioid Products

- Embeda: Morphine/naltrexone
- Targiniq: Oxycodone/Naloxone
- Oxycontin: Oxycodone reformulated
- Hysingla: Hydrocodone

Outcomes for LA vs. SA opioids

- Pain scores / severity
  - No difference when IR dosed around the clock
  - No difference in breakthrough dosing

- Patient preference
  - CR opioids scored statistically significantly better

- Sleep
  - CR opioids scored statistically significantly better

- Nausea
  - CR opioids scored statistically significantly better

- Somnolence
  - CR opioids scored statistically significantly better


However.....

- LA opioids may facilitate patient adherence with treatment, provide consistent levels of analgesic, and allow the patient to focus less on pain and pain medications
  - Goal of treating chronic pain is to reduce pain and improve functioning
  - Take pain medication like antihypertensive meds to let patient get on with life
  - With SAOs the pain medication is the center of the patient’s life

- LA opioids are more convenient for family, caregivers and staff
Opioids & Dangerous Medication Combinations

- **DO NOT USE CARISOPRODOL (Soma®)!!!**
- **METABOLIZED TO MEPROBAMATE WHICH IS AN ANXIOLYTIC**
  - **“HOLY TRINITY” (DEA) = CARISIPRODOL (Soma®) + Benzodiazepine + Opioid → ↑ risk of death drastically!!!**

Opioid Medication & Dangerous Drug Combinations

- Carisoprodol probably potentiates the inhibitory effects of GABA at the GABA-A receptor in the medulla similar to benzodiazepines.
- Tolerance to respiratory depression is incomplete, & may be slower than tolerance to euphoria
Opioids & Dangerous Medication Combinations

- BENZODIAZEPINES
  - GREATLY INCREASE THE RISK OF ACCIDENTAL OVERDOSE WHEN USED CONCOMITANTLY W/ OPIOID MEDICATION
  - AVOID, DON’T USE TOGETHER, STOP USING WITH OPIOID MEDICATION

Opioids & Dangerous Drug Combinations

- Benzodiazepines facilitate inhibitory effects of GABA on the respiration at the GABA-A receptor in the medulla
- Opioid-induced ventilatory depression results from slowed breathing frequency and reduced tidal volume, & also from a blunted ventilatory responsiveness to hypoxia and hypercapnia
- Together these mechanisms can potentiate each other or be synergistic & can be very dangerous very quickly
Populations At Risk for Accidental Overdose with Prescription Opioids

- Those with a Rx for Opioid Medication
- Patients taking opioids exactly as prescribed
- Patients taking opioids exactly as prescribed, and also taking other CNS depressants, Rx or non-Rx
- Patients altering the intended route of administration
- Those w/o a Rx for Opioid Medication
- Those using opioid prescribe for other
- Those who use illicit opioids

Potential Risk Factors for Opioid Overdose

- +PMH for substance abuse; including alcohol, tobacco, marijuana
- +PMH for non-medical use of opioids
- +PMH or current symptoms of behavioral disorders
- +PMH for obtaining opioid Rxs from multiple providers
- High opioid dose
- Opioid rotation
Potential Risk Factors for Opioid Overdose

- Use of methadone &/or ER opioid formulations
- Use of ER opioid + prn IR opioid
- Concomitant use of other CNS depressants (benzodiazepines; carisoprodal (Soma®); alcohol, etc)
- +PMH for hepatic &/or renal disease
- Presence of acute &/or chronic pulmonary disease including sleep apnea

Co-prescribing of Naloxone

- Risk assessment
  - Based on the Lazarus Project and other studies
  - Risk assessment & therefore prescribing of naloxone is based on dose of opioids & comorbidities
  - Assumes that this is a static system
  - Time consuming
- Universal Precautions
  - No risk assessment
  - Co-prescribing of naloxone is given to anyone on chronic opioid therapy
  - Assumes that this is a fluid system
  - Access
  - Collaborative Practice Protocols
Routes of Administration of Naloxone

- Injection w/ nasal atomizer
  - Recently FDA approved
  - “Rescue Kit” contains #2 x 2ml of 0.4mg/ml solution of naloxone

- Auto-injector
  - FDA approved
  - Evzio®
  - #2 x 0.4mg/ml for IM or SQ injection

Resources

- [http://stopoverdose.org/recources.htm](http://stopoverdose.org/recources.htm)
- [http://prescribetoprevent.org/prescribe-naloxone-now/](http://prescribetoprevent.org/prescribe-naloxone-now/)
Do’s & Don’ts With Opioid Medication

DO
- Emphasize the importance of sustained improvement in functional levels allowed by opioids
- Describe opioids as having potential to “take the edge off” of the pain to allow greater function

DO NOT
- Treat the Pain Scale ratings made by the patient (unclear value in chronic pain)
- Aim to remove all pain (to help patient “be out of pain”, “to have the pain gone”, to be “pain free”)

DO
- START with low dose short-acting, perhaps 2-3 tablets per day as needed prn (specify up to maximum of 2-3 tablets per day)
- Systemize decision process when filling or refilling opiate Rx
- Remove stigma

DO NOT
- Use higher dose short acting medications routinely > 6 doses daily
- Caution w/ opioid doses of 100-120 MME daily
- Caution w/ combination of benzodiazepines & opioid
- NEVER use Soma® (carisoprodol)
What I’m Not Saying; What I AM Saying

- What I AM NOT saying
  - do not use opiates
  - opiates are bad drugs

- What I AM saying
  - THINK when prescribing opiates

T.H.I.N.K

- **T**: take advantage of all resources
  - UDS, BOP PMP reports
- **H**: have data in hand
  - VAS (function, pain, sleep), UDS, BOP PMP reports
- **I**: intuition
  - SARS
- **N**: “NO” is a valid answer
  - do the NEXT right thing
- **K**: know the basics of chronic medication management
  - federal, state & local laws
Conclusions

- As with any medication utilized for chronic disease therapy, use of opioids is a double-edged sword.
- Approach the use of Chronic Opioid Therapy in CNCP the same as any other chronic medication used in any other chronic disease state.
- As with any medication, used for any chronic disease condition, safe and effective opioid therapy requires careful assessment of goals for therapy & ADRs, re-assessment.
- A systematic, data driven approach to prescribing & monitoring opioid therapy should be used to decrease any personal bias.
- Aberrant drug taking behavior is a continuum of behaviors and a predictable adverse event of opioid therapy.