Opioid Training Institute (OTI): Pain Management vs. Diversion Part II

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Disclosure/Conflict of Interest

I, Timothy Atkinson, have no actual or potential conflict of interest in relation to this program.

Disclosures:

Axial Healthcare – Consultant

Daiichi Sankyo – Advisory Board

Purdue Pharma – Epidemiology Advisory Board

Honoraria – ACCP, PAINWeek, Auburn, Rockpointe
Objectives

• Explain appropriate use of opioids in the treatment of pain

• Discuss provider implemented strategies to ensure safe and effective pain management for patients in addiction recovery

• Demonstrate best practices in pain management, avoidance of addiction/diversion, and collaboration among healthcare providers
# Pain Scales

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Mild Pain</th>
<th>Moderate Pain</th>
<th>Severe Pain</th>
<th>Worst Possible Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Minion" /></td>
<td><img src="image2.png" alt="Minion" /></td>
<td><img src="image3.png" alt="Minion" /></td>
<td><img src="image4.png" alt="Minion" /></td>
<td><img src="image5.png" alt="Minion" /></td>
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</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
<th>10</th>
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</tbody>
</table>
Treatment of Chronic Pain Is a Low Priority

Incidence of chronic pain in US is greater than diabetes, heart disease and cancer combined.
Individual Response to Treatment

How the body alters the drug
Pharmacokinetics

Pharmacodynamics
How the drug affects the body

Pharmacogenetics
The science of how genetic variability impacts individual responses to medications

Visual summary
Chronic Pain Guidelines

Step 1
Self-management and optimized treatment of comorbidities

Step 2
Self-management and treating comorbidities
+ Non-pharmacologic therapy

Step 3
Self-management and treating comorbidities
+ Non-pharmacologic therapy
+ Non-opioid pharmacotherapy

Step 4
Self-management and treating comorbidities
+ Non-pharmacologic therapy
+ Non-opioid pharmacotherapy
+ Intensive Interdisciplinary Pain Rehabilitation
+/− Intermittent use of opioids for limited conditions (see p. 15)
30% Rule

Pain Medications

100%

Treatment Plan
Treatment Plan

- Pain Medications
- Physical Rehab
- TENS
- Pain Procedures
- Psychology
- Acupuncture

30% Rule
Non-Pharmacologic Therapy

Different days, different levels of pain may require different tools:

- Heat or Cold
- Stretching
- Exercise
- Biofeedback
- Music
- Relaxation
- Meditation

The toolbox way of thinking

- Reading
- Gardening
- TENS Unit
- Massage
- Acupuncture
- Chiropractor
Non-Opioid Pharmacotherapy

Nociceptive Pain:
- Acetaminophen
- NSAIDs
- Muscle relaxants
- Topicals
  - Diclofenac
  - Menthol-methyl salicylate

Neuropathic Pain:
- Anticonvulsants
- SNRIs
- TCAs
- Topicals
  - Lidocaine
  - Capsaicin
Opioid Candidate?

- Severe Pain Pathology?
  - Pain is NOT whatever the patient says it is!

- History of Substance Abuse or Aberrant Behavior?
  - Distant or Recent?

- Optimized Adjunct Analgesics for Pain Mechanism?
Paradigm Shift from Reducing Pain to Increasing Function

• Pain relief should improve function

• Lack of functional improvement always indicates treatment failure or other problems, e.g., misuse, diversion, addiction, mood disorders, side effects, etc.
Select Opioid Formulations

- Available with co-analgesic
  - Oxycodone, tramadol, codeine, hydrocodone
- Pure mu-opioid receptor agonists
  - Morphine, hydromorphone, fentanyl, oxycodone, hydrocodone
- Two or more mechanisms
  - Methadone, levorphanol
- Rapid onset (transmucosal)
  - Fentanyl

- Immediate release without co-analgesic
  - Tramadol, oxycodone, Tapentadol, hydrocodone, hydromorphone, oxymorphone, others
- Modified release (long acting)
  - Morphine, methadone, oxycodone, hydromorphone, hydrocodone, others
- Partial agonists
  - Tramadol, pentazocine, butorphanol
- Partial agonists/antagonists
  - Buprenorphine
## OPIOID PHARMACOLOGY & PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Phenanthrenes</th>
<th>Equivalent Doses (mg)</th>
<th>µ-opioid Rec BA</th>
<th>Receptor Binding</th>
<th>Duration of Action (hrs)</th>
<th>Half-life $T_{1/2}$ (hrs)</th>
<th>Time to Steady State (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>75-120/130-200</td>
<td>+/-</td>
<td>µ</td>
<td>4-6</td>
<td>2.5-3.5</td>
<td>20</td>
</tr>
<tr>
<td>Morphine</td>
<td>10/30</td>
<td>+</td>
<td>µ</td>
<td>IR: 4</td>
<td>2-4</td>
<td>20</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A/30</td>
<td>+</td>
<td>µ</td>
<td>4-6</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5/7.5</td>
<td>++</td>
<td>µ</td>
<td>3-5</td>
<td>1-3</td>
<td>15</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A/20</td>
<td>+</td>
<td>µ</td>
<td>3-6</td>
<td>2-3</td>
<td>15</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1/10</td>
<td>+</td>
<td>µ</td>
<td>4-6</td>
<td>7-9</td>
<td>36</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.3/N/A</td>
<td>+++</td>
<td>µ, K</td>
<td>6-8</td>
<td>24-42</td>
<td>120-294</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2/4</td>
<td>++</td>
<td>µ, K$_3$, NMDA, NE</td>
<td>6-15</td>
<td>11-16</td>
<td>80</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Phenylpiperidines</th>
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</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>100/300</td>
<td>-</td>
<td>µ, δ</td>
<td>2-5</td>
<td>2.5-4</td>
<td>20</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>**</td>
<td>+++</td>
<td>µ</td>
<td>IM: 1-2</td>
<td>IV: 2-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TD: 48-72</td>
<td>TD: 17-22</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Diphenylheptanes</th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>3.75/7.5</td>
<td>++</td>
<td>µ, NMDA, NE</td>
<td>4-8</td>
<td>8-59</td>
<td>40-295</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol</td>
<td>N/A/100</td>
<td>-</td>
<td>µ, NE</td>
<td>4-6</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>
## Managing Opioid Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Increase fluid intake; use of cathartics, stool softeners, PAMORAs, and nonopioid analgesics</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Switch opioid v. use antiemetic / Lower dose</td>
</tr>
<tr>
<td>Itching</td>
<td>Switch opioid; antihistamines</td>
</tr>
<tr>
<td>Edema and sweating</td>
<td>Switch opioid</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Anti vertiginous agents</td>
</tr>
<tr>
<td>Confusion</td>
<td>Titrate dose; switch opioid; add neuroleptic</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
<td>Endocrine monitoring; testosterone replacement</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Switch opioid</td>
</tr>
<tr>
<td>Risk of falling for the elderly</td>
<td>Lower dose; use nonopioid analgesics</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Reduce dose or discontinue</td>
</tr>
</tbody>
</table>
Unique Characteristics of Opioid Formulations
Chemical Classes of Opioids

**PHENANTHRENES**
- Morphine
- Codeine
- Hydrocodone*
- Hydromorphone*
- Levorphanol*
- Oxycodone*
- Oxymorphone*
- Buprenorphine*
- Nalbuphine
- Butorphanol*
- Naloxone*
- Heroin (diacetyl-morphine)

**BENZOMORPHANS**
- Pentazocine
- Diphenoxylate
- Loperamide

**PHENYLPIPERIDINES**
- Meperidine
- Fentanyl
- Alfentanil
- Remifentanil

**DIPHENYLHEPTANES**
- Methadone
- Propoxyphene

---

**Rx EXAMPLES >**
- Morphine
- Pentazocine
- Meperidine
- Methadone
- Codeine
- Diphenoxylate
- Hydrocodone*
- Hydromorphone*
- Levorphanol*
- Oxycodone*
- Oxymorphone*
- Buprenorphine*
- Nalbuphine
- Butorphanol*
- Naloxone*
- Heroin (diacetyl-morphine)

---

**X-SENSITIVITY >**

<table>
<thead>
<tr>
<th>PROBABLE</th>
<th>POSSIBLE</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
</table>

- See separate slide for tapentadol & tramadol

*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group*

Chemical Classes of Opioids (continued)

Phenylpropyl Amine Class

**Tapentadol**

Tapentadol is a 3-((1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl)phenol monohydrochloride.

**Tramadol**

Tramadol is a (±)cis-2-[[dimethylamino)methyl]-1-(3-methoxyphenyl cyclohexanol hydrochloride.
# Tramadol vs. Tapentadol

<table>
<thead>
<tr>
<th>Properties</th>
<th>Tramadol</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu Binding Affinity</td>
<td>6000x less than morphine</td>
<td>18x less than morphine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Significant CYP 450 2D6, 3A4</td>
<td>Conjugation, O-Glucuronide</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Neuroamine Activity</td>
<td>5-HT / NE</td>
<td>NE, almost no 5-HT</td>
</tr>
</tbody>
</table>

- Combined mechanism delays development of tolerance
- Morphine develops tolerance 2.5 times faster than tapentadol
# Tapentadol Clinical Trials

**Compared Adverse Effects Profiles for Tapentadol and Oxycodone in Phase III Clinical Trials**

<table>
<thead>
<tr>
<th>Phase III Clinical Trials</th>
<th>Study Population</th>
<th>Gastrointestinal (GI)</th>
<th>Central Nervous System (CNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Immediate-Release (IR)</td>
<td></td>
<td>Tap</td>
<td>Oxy</td>
</tr>
<tr>
<td>Harrick et al.</td>
<td>End-stage Joint Disease</td>
<td>18%</td>
<td>41%</td>
</tr>
<tr>
<td>Daniels et al.</td>
<td>Bunionectomy</td>
<td>49%</td>
<td>67%</td>
</tr>
<tr>
<td>Hale et al.</td>
<td>Lower Back Pain &amp; Osteoarthritis</td>
<td>18%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended-Release (ER)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buynak et al.</td>
<td>Lower Back Pain</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>Afilalo et al.</td>
<td>Knee Osteoarthritis</td>
<td>22%</td>
<td>37%</td>
</tr>
<tr>
<td>Schwartz et al.</td>
<td>Diabetic Peripheral Neuropathy</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td>Wild et al.</td>
<td>LBP &amp; OA; LT Safety &amp; Efficacy</td>
<td>18%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Tap = Tapentadol; Oxy = Oxycodone; N/A = Not Available due to lack of reporting
Opioid Red Flags

- 2 short-acting opioids
- No appointment with PCP in last year
- No PDMP or UDS within a year
- Carisoprodol, Benzodiazepine, and Short-acting opioid
- Morphine SR QID or PRN
- Oxycodone CR QID or PRN
Opioids for Chronic Pain

- Short-acting (immediate release)
  - Higher peaks, higher toxicity profiles
  - Intermittent effect on hypoadrenal axis
  - Possible lower overall 24 hour dose
  - Consider toxicity if combo w/ ASA, IBU, or APAP

- Long-acting (ER-LA)
  - Generally have lower Cmax
  - Sleep through night, but greater effect on REM sleep
  - Continuous effect at hypoadrenal axis
Periodic Table of Pain Meds

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>T</td>
<td>Tylenol</td>
<td>2</td>
<td>Mp</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Motrin</td>
<td>3</td>
<td>Vt</td>
</tr>
<tr>
<td>4</td>
<td>Ul</td>
<td>Ultram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Co</td>
<td>Codeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Mtswad</td>
<td>Med that starts with a 'D'</td>
<td></td>
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<tr>
<td>7</td>
<td>Di</td>
<td>Dilaudid</td>
<td></td>
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<tr>
<td>8</td>
<td>N x</td>
<td>Naproxen</td>
<td>9</td>
<td>Lo</td>
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<tr>
<td>10</td>
<td>Sd</td>
<td>Stadol</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>Hy</td>
<td>Hydrocodone</td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>Di</td>
<td>Dilaudid</td>
<td></td>
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<tr>
<td>13</td>
<td>In</td>
<td>Indocin</td>
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<tr>
<td>14</td>
<td>Mc</td>
<td>Mobic</td>
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<tr>
<td>15</td>
<td>Da</td>
<td>Darvon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Ox</td>
<td>Oxycodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>M-Di</td>
<td>More Dilaudid</td>
<td></td>
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</tr>
<tr>
<td>18</td>
<td>Cx</td>
<td>Celebrex</td>
<td></td>
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</tr>
<tr>
<td>19</td>
<td>Fd</td>
<td>Feldene</td>
<td></td>
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<tr>
<td>20</td>
<td>Sx</td>
<td>Suboxone</td>
<td></td>
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<tr>
<td>21</td>
<td>Op</td>
<td>Oxymorphone</td>
<td></td>
<td></td>
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<tr>
<td>22</td>
<td>De</td>
<td>Demerol</td>
<td></td>
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<tr>
<td>23</td>
<td>To</td>
<td>Toradol</td>
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<tr>
<td>24</td>
<td>Ci</td>
<td>Clinoril</td>
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<tr>
<td>25</td>
<td>Nu</td>
<td>Nubain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Me</td>
<td>Methadone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Fy</td>
<td>Fentanyl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. That Sh*t don't work
2. Huh?
3. Weak Sh*t
4. My Kind of Pills
5. The IV “Noble Narcs”
Street Value

- Use Lebin et al
- Dasgupta et al
Please take a minute and calculate the opioid daily doses below to their morphine equivalent daily dose (MEDD)

**Morphine Equivalent Doses (MEQ)**

Fentanyl 75mcg/hr  Oxycodone 120mg

Hydrocodone 80mg  Hydromorphone 48mg  Methadone 40mg

<table>
<thead>
<tr>
<th></th>
<th>Physician</th>
<th>Pharmacist</th>
<th>NP/ PA</th>
<th>Overall</th>
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</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>180 ± 122 (150)</td>
<td>178 ± 128 (150)</td>
<td>157 ± 68 (150)</td>
<td>176 ± 117 (150)</td>
</tr>
<tr>
<td>Avg ± SD (Median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>91 ± 36 (80)</td>
<td>88 ± 43 (80)</td>
<td>83 ± 39 (80)</td>
<td>88 ± 42 (80)</td>
</tr>
<tr>
<td>Avg ± SD (Median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>200 ± 69 (192)</td>
<td>193 ± 40 (192)</td>
<td>184 ± 69 (192)</td>
<td>192 ± 55 (192)</td>
</tr>
<tr>
<td>Avg ± SD (Median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>214 ± 142 (160)</td>
<td>171 ± 107 (160)</td>
<td>185 ± 129 (160)</td>
<td>193 ± 201 (160)</td>
</tr>
<tr>
<td>Avg ± SD (Median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>170 ± 41 (180)</td>
<td>178 ± 35 (180)</td>
<td>167 ± 39 (180)</td>
<td>173 ± 39 (180)</td>
</tr>
<tr>
<td>Avg ± SD (Median)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Case Discussion: Fentanyl

Background: 83 year old woman with multiple comorbidities, some of which include COPD, CLBP, DM, HTN, CAD, PVD. Multiple back surgeries following MVA with crush injury 30 years ago. Over the last 12 months, she has been managed with escalating doses of fentanyl transdermal without benefit; she is currently prescribed fentanyl 75mcg/hr change Q72 hours.

Current Status: To replace fentanyl, she is given a prescription of morphine SA 60mg 1 tablet PO TID. 3 days later….she died of an opioid overdose.

Question: What happened?

Additional Text: Take a minute, think about potential causes
Serum Fentanyl Concentrations Following Multiple Applications of DURAGESIC® 100mcg/h (n=10)

## Transdermal Fentanyl Conversion

### Conversion suggested in manufacturer’s package insert:

#### Conversion from Oral Morphine to Duragesic®

<table>
<thead>
<tr>
<th>Oral 24-hour morphine (mg/day)</th>
<th>Duragesic® dose (mcg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>50</td>
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<tr>
<td>225-314</td>
<td>75</td>
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<td>315-404</td>
<td>100</td>
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<tr>
<td>405-494</td>
<td>125</td>
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<tr>
<td>495-584</td>
<td>150</td>
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<tr>
<td>585-674</td>
<td>175</td>
</tr>
<tr>
<td>675-764</td>
<td>200</td>
</tr>
<tr>
<td>765-854</td>
<td>225</td>
</tr>
<tr>
<td>855-944</td>
<td>250</td>
</tr>
<tr>
<td>945-1034</td>
<td>275</td>
</tr>
<tr>
<td>1035-1124</td>
<td>300</td>
</tr>
</tbody>
</table>

### Donner & Colleagues, Breibart & Colleagues, American Academy of Hospice & Palliative Medicine suggested conversion:

#### Donner Recommended Conversion from Oral Morphine to Duragesic

<table>
<thead>
<tr>
<th>24-Hour oral morphine dose (mg/day)</th>
<th>Transdermal fentanyl dose (mcg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90</td>
<td>25</td>
</tr>
<tr>
<td>91-150</td>
<td>50</td>
</tr>
<tr>
<td>151-210</td>
<td>75</td>
</tr>
<tr>
<td>211-270</td>
<td>100</td>
</tr>
<tr>
<td>Every additional 60 mg per day</td>
<td>An additional 25 mcg per hour</td>
</tr>
</tbody>
</table>


Fentanyl **RED** Flags

- Lost patches/falling off
- Allergy to patch
- Side effects vanished within minutes of removing
- Large dose increases (must know conversions)
- Chewing or eating patches
If we’re going to use Fentanyl...

We Need to be **VERY** familiar with fentanyl equianalgesic conversions:
  - Patient Safety

q72h vs q48h — is q48h appropriate? Is it a dose increase?
  - 89% of total fentanyl in patch released in first 48h
  - 20% of patients describe patch wearing off third day
    - Not an increase for those patients

Patches falling off- Won’t be replaced
  - Put it back on, tape it- order tegaderm coverings

Contact dermatitis to patch adhesive- localized around patch?
  - Triamcinolone spray on skin, allow to dry, place patch (standard of care)
<table>
<thead>
<tr>
<th></th>
<th>Levorphanol</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacology:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid agonist activity</td>
<td>μ, κ₁, κ₃ &gt; κ₂</td>
<td>μ</td>
</tr>
<tr>
<td>NE reuptake blockade</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NMDA inhibition</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Pharmacokinetics:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>11-16 hours</td>
<td>15-60 hours</td>
</tr>
<tr>
<td>Duration of action</td>
<td>6-15 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Metabolic pathway</td>
<td>Phase II glucuronidation to levorphanol-3-glucuronide</td>
<td>3A₄, 2B₆, 2C₁₉ mediated N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP)</td>
</tr>
<tr>
<td>Opioid chemistry</td>
<td>Dehydroxylated phenanthrene</td>
<td>Diphenylheptane</td>
</tr>
<tr>
<td><strong>Dosing:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO equivalent dose to 30mg/day of PO morphine</td>
<td>4mg</td>
<td>7.5mg</td>
</tr>
<tr>
<td>Suggested starting dose in opioid naïve patients</td>
<td>1mg (1/2 x 2mg tablet) PO TID to QID (Maximum daily starting dose = 4mg) Titrated upward by up to 25% weekly, i.e. if starting at 1mg PO QID first week, increase to 1mg PO 5x daily at second week.</td>
<td>2.5mg (1/2 x 5mg tablet) PO TID (Maximum daily starting dose = 7.5mg) Titrated upward by up to 25% weekly, i.e. if starting at 2.5mg PO TID first week, increase to 2.5mg PO 4 or 5x daily at second week. (Note: As the dose increases, percentage of upward titration decreases due to complex pharmacokinetics)</td>
</tr>
</tbody>
</table>

Role of NMDA

- Pain signals trigger release of glutamate into synaptic cleft
- Glutamate activates AMPA
  - Na & K channels
- Prolonged activation results in changes membrane polarization
- NMDA receptors activated when Mg$^+$ plug removed
- NMDA primed for glutamate activation
- Ca$^+$ influx activates Protein kinase C $\rightarrow$ releases NO
- NO closes K$^+$ $\rightarrow$ opioid resistance
- C-fos gene expression $\rightarrow$ neuroplasticity
Available NMDA Antagonists

• Clinical trial experience produced mixed results
  • Dextromethorphan
    • Morphine/Dextromethorphan discontinued in Phase III trials
      • Lack of benefit
      • Psychological adverse effects
  • Ketamine
    • Parenteral only; requires admission
    • Lower doses used in chronic pain than anesthesia
  • Memantine
    • Some success
    • Weak evidence
Comparison of Proposed Morphine to Methadone Conversion Parameters


<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine dose (mg/d)</td>
<td>30-90</td>
<td>&lt;100</td>
<td>30-90</td>
</tr>
<tr>
<td>Morphine: Methadone EDR</td>
<td>3.70:1</td>
<td>3:1</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td>91-300</td>
<td>101-300</td>
<td>91-300</td>
</tr>
<tr>
<td></td>
<td>7.75:1</td>
<td>10:1</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>301+</td>
<td>12:1</td>
<td>12:1</td>
</tr>
<tr>
<td>Population: Cancer-related pain and heroin maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ayonrinde (N = 14 patients)

Population: Neuropathic pain patients
Study: Prospective 6 month study

Mercadante (N = 52 patients)
Population: Palliative Care Units
Largest study to date. Result similar and strongly supportive of Ripamonti

Methadone **RED** Flags

- Methadone once daily
- No EKGs
- TCAs (QTc prolonging medications)
- Methadone PRN
- QTc >500ms
Abuse-deterrent formulations (ADFs)

*One Component to Address Prescription Opioid Crisis*

- Full impact cannot be realized until all opioids are abuse-deterrent
- FDA’s goal: ADFs for all major opioids
Common Routes of Administration or Abuse

- Crushing and swallowing
- Crushing and snorting
- Crushing and smoking
- Crushing and/or extracting for injection
- Oral intact
- Co-ingestion with alcohol/benzodiazepines
Speed of CNS Entry and Concentration Determines Liking

The “abuse potential” of a drug increases as the value of the AQ increases.

\[ \frac{C_{\text{max}}}{T_{\text{max}}} \]

In this ratio, as \( C_{\text{max}} \) INCREASES and as \( T_{\text{max}} \) DECREASES, the ratio becomes relatively larger, signaling potentially increased attractiveness as a drug of abuse.

Key Assessments

- Subjective Abuse Liability Assessments
  - Bipolar VAS
    - Drug Liking
    - TDA
  - Unipolar VAS
    - Drug High
  - Likert, T/F
  - ARCI, POMS
Abuse Deterrent Formulations of Opioids: Effectiveness and Value

Draft Evidence Report

May 5, 2017

Prepared for:

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
“…ADFs have the potential to substantially reduce the incidence of opioid abuse relative to non-ADF formulations among patients initially prescribed these drugs…

…but will also increase overall costs to the health system…”
Opioid Tapering
## Reasons to taper

<table>
<thead>
<tr>
<th>Lack of benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
</tr>
<tr>
<td>High dosage</td>
</tr>
<tr>
<td>Nonadherence to the treatment plan or unsafe behaviors</td>
</tr>
<tr>
<td>Substance use disorder</td>
</tr>
<tr>
<td>Opioid overdose</td>
</tr>
<tr>
<td>Comorbidities that increase risk</td>
</tr>
<tr>
<td>Concomitant medications that increase risk</td>
</tr>
<tr>
<td>Mental health comorbidities that can be worsened</td>
</tr>
</tbody>
</table>
Conditional probability of overdose or suicide death after opioid starts and stops

- **FY10 After discontinuation**
- **FY 10 After start in those who never discontinued**
- **FY13 After discontinuation**
- **FY 13 After start in those who never discontinued**

Deaths per 100,000 patients vs. Days after start or stop.
Key observations

• Risk of overdose or suicide death is elevated for approximately 6 months after either opioid starts or stops

• After stabilization, risk of overdose or suicide death among those who had an opioid prescription is the same regardless of whether they remain stably on or off opioids

• Pattern is stable from before Opioid Safety Initiative to the year after the Opioid Safety Initiative was started
May include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide

“Health Care professionals should not abruptly discontinue opioids in a patient who is physically dependent.”
CDC Clarifies Opioid Guidelines

• February 28, 2019

• Response to Letter from representatives of National Comprehensive Cancer Network, American Society of Clinical Oncology, and American Society of Hematology

• “The guideline is not intended to deny any patients who suffer from chronic pain from opioid therapy as an option for pain management”

• “CDC encourages physicians to continue to use their clinical judgement and base treatment on what they know about their patients, including the use of opioids if determined to be the best course of treatment.” (emphasis added)
Taper Considerations

- **25% of previous day’s dose is needed to prevent acute withdrawal**
- **Individualize to the patient**
- **Taper can be slowed but don’t reverse the taper**

**Determine goal**
- Reduction vs. cessation

**Medication**
- Use current meds
- Reduce dose then change frequency

**Speed of taper**
- Varies


Taper Speed

Discontinuation
- Unsafe or illegal behavior

Ultra-rapid taper
- Inpatient
- Significant comorbidities
- Medically dangerous situations
- Reduce every 1-7 days

Gradual dose reduction
- Most patients
- People who have been on opioids for long duration
- Can take larger initial cuts of 25-50%
- Typically 10-25% q2-4 weeks

Taper Case #1

- **Background:** Mr. Jackson is a 62 yo male with OA prescribed morphine SA 60 mg PO TID. He was listening to the news and heard some bad stuff about opioids.

- **Current status:** He is requesting an opioid taper.

- **Question:** How would you taper his meds?

- **Answer:**
  - Lots of answers
  - Work with patient to see what he’s comfortable with
  - Reduce by 15 mg every 4 weeks or more
  - Take an initial reduction of 45 mg/45 mg/60 mg then reduce by 15 mg/day
Taper Case #2

- **Background:** Mr. McDonald is a 64 yo male with lumbar stenosis currently prescribed oxycodone CR 20 mg PO BID and oxycodone/acetaminophen 5/325 mg PO QID PRN.

- **Current status:** Upon review of the PDMP, you find that that patient has been obtaining these same medications from another provider for the last year.

- **Question:** What would you do?

- **Answer:**
  - Discontinue opioids
  - Refer to BH
  - Offer OEND
  - Optimize nonpharm and nonopioid alternatives
Summary

• Effective treatment employs multimodal therapy potentially including interventional, nonpharmacologic, and nonopioid options

• Chronic pain assessment and treatment is function and goal-oriented

• Pain pharmacotherapy emphasizes evidence-based targeting of pain mechanisms

• Opioid therapy is reserved for severe refractory pain, emphasizing risk mitigation and individualized therapy as part of multimodal treatment

• Opioid tapering is not without risk and should involve shared decision-making, adjusting or slowing taper, and addressing mental health concerns
Thank You!

Questions?