Pain Management

A Primer
Palliative Care

- Palliative
  - “Pallium” a cloak used in ancient Rome and Greek
  - To cover (treat) the effects (signs and symptoms) of an illness

- Care
  - Love
  - Concern
  - Compassion
Palliative Care

- Often equated with hospice
- Most clearly associated with cancer diagnoses
  - Can be associated with any chronic disease
- Developing as a specialty area in Medicine
- Primary aim is symptom control
  - Pain management
  - Dyspnea
  - Nausea and vomiting
Palliative Care

- Caring, competent physician
- Interdisciplinary team
- Symptom Management
- Patient and Family as a Unit of Care
Pain Management

Types of Pain

- Nociceptive/Somatic
  - Described as aching/stabbing/throbbing
    - Fracture Pain
    - Bone metastasis pain
    - Pain from cellulitis

- Visceral: pain in organs or viscera
  - Described as gnawing/cramping/aching
    - MI
    - Pancreatitis

- Neuropathic: from nerve injury
  - Described as sharp/burning/tingling
    - H zoster
    - Trigeminal neuralgia

- Complex Regional Pain Syndromes
Pain Management

- **Evaluation of Pain**
  - Believe pain
  - Evaluation of each [pain] location separately
  - Assessment of pain
    - Etiology
    - Intensity
    - Quality
    - History
      - Onset/Duration
      - Location
      - Precipitating factors
      - Relieving factors
  - Documented responses to therapy
  - Past history of ETOH/Drug use
Pain management

WHO Pain Treatment Ladder

**STEP ONE**
- non-opioid
- +/- adjuvant

**STEP TWO**
- weak opioid
- +/- non-opioid
- +/- adjuvant

**STEP THREE**
- strong opioid
- +/- non-opioid
- +/- adjuvant
Pain Management

**Opioid Prescribing**
- Around the Clock (ATC) dosing a must
- Remember the bowel regimen
- Watch for side effects
  - Sedation
  - Myoclonus
  - Constipation
  - Nausea/vomiting

**Opioid Titration**
- \( \text{ATC} + \text{PRN} = \text{TD} \) (total 24 hour dose)
- Each prn dose = 10-20% TD
- Increase TD by
  - Totaled amount of prn doses in 24 hour period or
  - 50-100% Pain 7-10
  - 25-50% Pain 4-6
  - 25% Pain 1-3

**Maintenance Therapy**
- Extended release preparations
- Rescue doses as needed of short acting preparations
Neurobiology of Pain

Chronic Pain-Synapse at Dorsal Horn

Nociceptor

Glutamate

Guanyl synthetase

Ca2+

K+

NO

Substance P

NK-1 receptor

AMPA receptor

NMDA receptor

Dorsal horn cell

PKC

Ca2+

Mg2+

NO synthetase

C-fos gene expression
# Pain Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>IM/SC mg</th>
<th>PO mg</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td>10</td>
<td>20-30</td>
<td>2-3:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>6:1</td>
</tr>
<tr>
<td><strong>Codeine</strong></td>
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<td>200</td>
<td>1.5:1</td>
</tr>
<tr>
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<td>15</td>
<td>30</td>
<td>2:1</td>
</tr>
<tr>
<td><strong>Hydromorphone</strong></td>
<td>1.5</td>
<td>7.5</td>
<td>5:1</td>
</tr>
<tr>
<td><em>Dilaudid</em></td>
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<tr>
<td><strong>Fentanyl</strong></td>
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*Based on single dose studies*

- Longer half life means relative potency increased when converting
Opioid Chemical Structures

Oxymorphone

Oxycodone

Hydromorphone

Codeine
## Pain Management

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<td><em>Duragesic</em></td>
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- Longer half life means relative potency increased when converting
Opioid Chemical Structures

Heroin

Fentanyl

Methadone
Morphine  Basic Pharmacology

- Rapid absorption: Peak levels 30-90 min
- VOD = 200 L (4L/kg)
- Total Body Clearance = 0.8-1.2 L/min
- Oral bioavailability = 20-40%
  - Significant first-pass metabolism
- Binds to albumin and δ globulin (20-40%)
- $T_{1/2} = 1.5-2$ hr
- Maximum solubility 62.5 mg/mL
  - Commonly comes out of solution at $T<16^\circ$ C
  - Maximum commercial concentration 50 mg/mL
Morphine: Metabolism

- Morphine-3-glucuronide (>50%)
- Morphine-6-glucuronide (5%)
<table>
<thead>
<tr>
<th>Method</th>
<th>Onset</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM/po/SQ</td>
<td>15-30 min</td>
<td>30-60 min</td>
</tr>
<tr>
<td>IV</td>
<td>Immediate</td>
<td>5-20 min</td>
</tr>
<tr>
<td>Rectal</td>
<td>10-15 min</td>
<td>6-8 hr</td>
</tr>
<tr>
<td>Epidural</td>
<td>5 min</td>
<td>30 min</td>
</tr>
</tbody>
</table>

- VOD = 200 L
- Total Body Clearance = 1 L/min
- Oral bioavailability = 62% IV dose
- T1/2 = 2.5 hr
Hydromorphone: Metabolism

Principally eliminated by metabolism in liver
Metabolites excreted in urine
3-glucuronide metabolite neuroexcitatory
Fentanyl  Basic Pharmacology

- Mu (μ1, μ2) receptor agonist
- Analgesia at 1.7 ng/mL
- Fentanyl plasma protein binding decreases with increasing ionization of drug
- Accumulates in skeletal muscle and adipose tissue
- Metabolized in the liver by N-dealkylation to norfentanyl and other inactive metabolites
# Fentanyl Duragesic® Conversion

<table>
<thead>
<tr>
<th></th>
<th>Equianalgesic dose IM (mg)</th>
<th>Equianalgesic dose PO (mg)</th>
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<tr>
<td>Morphine</td>
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<td>30</td>
</tr>
<tr>
<td>Dilaudid®</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Oral 24 hr Morphine (mg)</th>
<th>Duragesic Dose (microgram/hr)</th>
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</thead>
<tbody>
<tr>
<td>45-134</td>
<td>25</td>
</tr>
<tr>
<td>133-224</td>
<td>50</td>
</tr>
<tr>
<td>225-314</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>100</td>
</tr>
<tr>
<td>405-494</td>
<td>125</td>
</tr>
<tr>
<td>495-584</td>
<td>150</td>
</tr>
<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>
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*Just a Guide*

Fentanyl 25 microgram/hr = Morphine (parenteral) 25 mg/24 hr
## Fentanyl
Pharmakokinetics of Transdermal Duragesic® Dose

<table>
<thead>
<tr>
<th>Duragesic® Dose (microgram/hr)</th>
<th>Mean Tmax (SD) (h)</th>
<th>Mean C max (SD) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>36.1 (16)</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>50</td>
<td>34.8 (15.4)</td>
<td>1.4 (0.5)</td>
</tr>
<tr>
<td>75</td>
<td>33.5 (14.5)</td>
<td>1.7 (0.7)</td>
</tr>
<tr>
<td>100</td>
<td>36.8 (15.7)</td>
<td>2.5 (1.2)</td>
</tr>
</tbody>
</table>
25% of patients are admitted using Duragesic® as the primary method of pain control. Historical data indicates that only 8% can be maintained on Duragesic® alone for effective pain relief.
Fentanyl Duragesic®
Supplemental Opioid Need by Dose

Mean Supplemental Opioid Dose as Rescue (24 hr)
Methadone  Basic Pharmacology

- Rapid Absorption
- Partition Coefficient = 115
  - Octanol pH 7.4 buffer
- VOD = 400 L
- Total Body Clearance = 0.1-0.2 L/min
- Oral bioavailability = 90%
- Binds to plasma proteins
  - (μ1 acid-glycoprotein) 60-90%
- T1/2 = 25-45 hr
# Methadone Dose Equivalency

## Single dose studies

<table>
<thead>
<tr>
<th>Oral</th>
<th>Parenteral</th>
</tr>
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<tbody>
<tr>
<td>Morphine:Methadone</td>
<td>2:1</td>
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## Multiple doses studies

<table>
<thead>
<tr>
<th>Morphine:Methadone</th>
<th>Morphine &lt; 500mg/24 hr</th>
<th>Morphine &gt; 1000mg/24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5:1</td>
<td>10:1</td>
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Methadone  Basic Pharmacology

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# Opioid Antagonists

<table>
<thead>
<tr>
<th>Name</th>
<th>Principal Action</th>
<th>Isolated Organ Bioassay</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Μµ (µ1)</strong></td>
<td>Analgesia: supraspinal Bradycardia Hypothermia Urinary retention</td>
<td>Guinea pig ileum</td>
<td>Morphine Meperidine Sufentanil</td>
<td>Naloxone</td>
</tr>
<tr>
<td><strong>Μµ (µ2)</strong></td>
<td>Analgesia: spinal Respiratory depression Constipation</td>
<td></td>
<td></td>
<td>MethylNaltrexone</td>
</tr>
<tr>
<td>Delta (δ1, δ2)</td>
<td>Analgesia: spinal/supraspinal Respiratory depression</td>
<td>Mouse vas deferens</td>
<td>DPDPE Deltorphine DSLET</td>
<td>Naloxone Naltrexone</td>
</tr>
<tr>
<td><strong>Kappa (κ1-4)</strong></td>
<td>Analgesia: spinal/supraspinal Constipation Sedation</td>
<td>Rabbit vas deferens</td>
<td>Butorphanol Bremazaocine</td>
<td>Naloxone</td>
</tr>
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