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- Region XI-Area Agency on Aging
- Rocky Mountain Health Plans
- Senior CommUnity Care PACE
- St. Mary’s Hospital Foundation
- Technical College of the Rockies
- Tri-County Health Network
- Volunteers of America
- WCAHEC
Objectives

• Explain why rotation to a different opioid may improve pain control
• Identify the unique properties of methadone as a second-line pain management opioid
• Explain why combining multiple medications with different mechanisms of pain relief may be needed for complex pain syndromes
Video

- Patients with advanced disease
  Cancer
  Heart Failure
  Etc.
- Attitudes
- Distinguish Acute from Chronic
- Role of Combinations
Debrief

• Attitudes
• Distinguish Acute from Chronic
• Role of Combinations
# EQUIANALGESIC DOSING GUIDELINE FOR CHRONIC PAIN

## Changing Routes of Administration

<table>
<thead>
<tr>
<th></th>
<th>PO / PR</th>
<th>IV / SC / IM</th>
<th>Epidural</th>
<th>Intrathecal</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>0.1</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

## Changing Analgesics

### Opioids

<table>
<thead>
<tr>
<th>Oral / Rectal Dose (mg)</th>
<th>Analgesic</th>
<th>Parenteral SC / IV / IM Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>Meperidine</td>
<td>50</td>
</tr>
<tr>
<td>150</td>
<td>Tramadol</td>
<td>-</td>
</tr>
<tr>
<td>150</td>
<td>Codeine</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>Hydrocodone</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Morphine</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
<tr>
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<td>Oxymorphone</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Hydromorphone</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Levorphanol</td>
<td>1</td>
</tr>
</tbody>
</table>

- Fentanyl 0.050 mg

*1000 mcg = 1 mg; must convert to mg to calculate equianalgesic dose*

### Transdermal Fentanyl

- Morphine 50 mg PO in 24 hrs ≈ Fentanyl 25 mcg, transdermal patch q 72 hrs

## Methadone

### Daily Morphine Dose (mg/24 hrs PO)

<table>
<thead>
<tr>
<th>Morphine PO</th>
<th>Methadone PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>3</td>
</tr>
<tr>
<td>101-300</td>
<td>5</td>
</tr>
<tr>
<td>301-600</td>
<td>10</td>
</tr>
<tr>
<td>601-800</td>
<td>12</td>
</tr>
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<td>15</td>
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<tr>
<td>&gt;1001</td>
<td>20</td>
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</tbody>
</table>

### Conversion Ratios

- Morphine PO: Methadone PO

## Methadone SC Dosing

1. Convert from daily Morphine Equivalent PO Dose / 24 hrs to Methadone PO Dose / 24 hrs using the Methadone PO Dosing Table above
2. Then + 3 to convert to Methadone SC Dose / 24 hrs

## Adjusting for Incomplete Cross Tolerance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>100%</td>
</tr>
<tr>
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Ferris FD and Pirrello RD: Improving Equianalgesic Dosing for Chronic Pain Management, American Association for Cancer Education Annual Meeting, oral presentation, Cincinnati, Ohio, September 2005

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Case 1

- A 68 yo woman with metastatic breast cancer has continuous pain. You started Morphine 15 mg orally every 4 hours with 15 mg q 1 h prn. She reports pain is well controlled, but she has persistent pruritus.
Opioid Rotation

- Change to an opioid with different chemical structure
  - Resolve adverse effects
  - Improve analgesia
Do the math

• 15 mg q 4h = 6 x 15
  90 mg morphine / 24h

• Look at the equianalgesic table;
  15 mg morphine = 10 mg oxycodone

• Set up a ratio
  15 mg morphine / 10 mg oxycodone
  90 mg morphine / X mg oxycodone

Solve for ‘X’
Question 1

- $X = $

<table>
<thead>
<tr>
<th>90 mg</th>
<th>60 mg</th>
<th>30 mg</th>
</tr>
</thead>
</table>
Question 1

- $X = 
  \begin{align*}
  &90 \text{ mg} \\
  &60 \text{ mg} \\
  &30 \text{ mg}
  \end{align*}$
Equianalgesic Conversions

- Check your math with a friend
- Call pharmacy to help you
- Online calculators
Equianalgesic Conversions

- Correct for incomplete cross-tolerance
- If pain well controlled, decrease by 25-50%
- If pain no well controlled, may not need to decrease
Case 2

- 62 yo man with advanced NSCLCa right upper lobe. Now, forearm has intermittent stabbing pain. His elbow ‘aches’ severely. His hand has severe burning. Rates pain 8 / 10 despite 900 tid of gabapentin and 200 mg bid SR Morphine.
- Increased apical mass ➔ plexopathy
- Mixed nociceptive & neuropathic pain
Opioids

• Nociceptive pain > neuropathic pain
  First-line for moderate to severe neuropathic pain
  Titrate to effect or intolerable side-effects
  Poor response, more likely neuropathic pain
Excitatory Amino Acid
NMDA-Glutamate Receptors

- ↑ glutamate & glycine
  - ➔ Change charge
  - ➔ Mg\(^{2+}\) released
  - ➔ channel opens
  - ➔ ↓ opioid responsiveness
  - ➔ allodynia
  - ➔ hyperalgesia
Methadone

• Racemic mixture
  Mu-agonist opioid +
  NMDA receptor antagonist

• Single opioid
  Titrate to effect or intolerable side-effects
  Long half-life; NOT first order kinetics
  Experienced palliative care, pain experts

• Coanalgesic 2.5 – 5+ mg q8h

• Cost PO << parenteral

Fast Facts, see www.eperc.mcw.edu/ff_index.htm
Methadone

• Could also convert to methadone as only long-acting opioid
• Would still need short acting opioid like morphine, NOT methadone, for breakthrough.
**CHANGING ROUTES OF ADMINISTRATION**

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**CHANGING ANALGESICS**

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**METHADONE**

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**METHADONE SC DOSING**

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Calculation

- 300 mg morphine SR bid =
  600 mg morphine / 24 hours

- Go to table for 600 mg morphine
  10 morphine = 1 morphine

Do the calculation
Methadone Calculation

\[
\frac{\text{Morphine} \ 600 \ \text{mg}}{\text{Methadone} \ X \ \text{mg}} = \frac{10}{1}
\]

- Solve for \( X \)
Question 2

• $X =$

<table>
<thead>
<tr>
<th>600 mg methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg methadone</td>
</tr>
<tr>
<td>6000 mg methadone</td>
</tr>
</tbody>
</table>
Question 2

- $X = \begin{array}{l}
600 \text{ mg methadone} \\
60 \text{ mg methadone} \\
6000 \text{ mg methadone}
\end{array}$
Convert over 3 days

- **Day 1: 1/3**
  - 10 mg methadone bid
  - 200 mg morphine SR bid
- **Day 2: 1/3**
  - 20 mg methadone bid
  - 100 mg morphine SR bid
- **Day 3: 1/3**
  - 30 mg methadone bid
  - Stop morphine
If methadone a co-analgesic

- Methadone 5 mg tid
- Continue morphine SR 300 mg bid
- If great analgesia, can titrate down on the morphine
Bone Pain...
Pathophysiology

• Direct stimulation of nociceptors
  Pressure from expanding mass in closed space

• Prostaglandin synthesis
  Chemical stimulation of nociceptors
  Inflammation ➔ edema ➔ pressure
Management

- Opioids
- Acetaminophen
- NSAIDs
- Dexamethasone
- Bisphosphonates
- Radiation
- Immobilization
Question 3

• When starting ibuprofen, an NSAID, for bone pain, start with

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg qid</td>
<td></td>
</tr>
<tr>
<td>400 mg qid</td>
<td></td>
</tr>
<tr>
<td>600 mg qid</td>
<td></td>
</tr>
<tr>
<td>800 mg tid</td>
<td></td>
</tr>
</tbody>
</table>
Question 3

• When starting ibuprofen, an NSAID, for bone pain, start with
  Green Card 200 mg qid
  Pink Card 400 mg qid
  **Yellow Card 600 mg qid CORRECT**
  Orange Card 800 mg tid CORRECT
Question 3

• When starting ibuprofen, an NSAID, for bone pain, start with
  - 200 mg qid
  - 400 mg qid
  - 600 mg qid
  - 800 mg tid
Neuropathic Pain...
Neuropathic Pain: Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system = disease =/= symptom
Patient Experience
( some – all – none )

Described as
- Burning
- Shooting
- Electrical
- Freezing
- Aching

Stocking-glove
Radiation

Associated
- Numbness, tingling
- Weakness, clumsiness
- Loss of reflexes
- Autonomic dysfunction

  Swelling, sweating, skin changes
Causes

- Chemotherapy
- Compression – disc, metastases
- Infection – HIV, herpes
- Infiltration – cancer
- Ischemia – compromised arterial or venous circulation, edema, pressure
- Metabolic injury – diabetes
- Transection – amputation
Chemotherapy-induced Peripheral Neuropathy

- Affect neuronal cell body, axonal transport system, myelin sheath, glial support structures

**Pure Sensory**

- Platins
  - Cisplatin
  - Oxaliplatin
  - Carboplatin

**Mixed Sensorimotor**

- Taxanes
  - Paclitaxel
  - Docetaxel

- Vinca-alkaloids
  - Vincristine

---

Management...
...Gabapentinoids

- **Pregabalin vs. gabapentin**
  - Easier to titrate
  - Faster onset
  - ↑ sleep, ↓ anxiety

- **Cost pregabalin >> gabapentin**

- **Trial gabapentin**
  - Start 100 – 300 mg qhs
  - Daily, increase 100 mg q8h
  - Effective 900 – 1800 mg / 24 hr
  - Max 3600 – 5400 mg / 24 hr

- **If ineffective, pregabalin**
  - Start 25 – 75 mg q12h
  - Increase 25 mg q12h
  - Effective 100 – 150 mg / 24 hr
  - Max 300 – 600 mg / 24 hr
Evidence…

- Therapies extrapolated from non-cancer pain
  - Diabetic peripheral neuropathy (DPN)
  - Post-herpetic neuralgia (PHN)
- Few RCTs
- Very few comparative trials
- Trial and error
Gabapentinoids...

- Act on voltage-gated Ca\textsuperscript{2+} channel, modulating alpha-2-delta protein
  - Positive RCT’s
    - Gabapentin: PHN, DPN, neuropathic cancer pain
    - Pregabalin: PHN, DPN, fibromyalgia
  - NNT less favorable than TCAs
- First-line 2\textsuperscript{o} safety
- Not hepatically metabolized
- No drug interactions
- Side effects usually tolerable

Antidepressants as Analgesics

**Efficacy** Noradrenaline (N) & Serotonin (S)

3º amine TCAs, amitriptyline (N & S RI)

≈ 2º amine TCAs, desipramine, nortriptyline (N RI)

> Mixed SNRIs, duloxetine, venlafaxine

> SSRIs, citalopram, paroxetine

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Side effects

Greatest = CNS, anticholinergic, nausea, CV

> Less

> Least = sexual

≈ Least = sexual

Antidepressants as Analgesics

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Greatest = CNS, anticholinergic nausea, CV
> Less
> Least = sexual
≈ Least = sexual

Antidepressants

- Desipramine 10 – 25 mg PO qhs
  Increase by 10 – 25 mg qhs every 3 – 5 days
  (t ½ up to 24 hrs)
- If dose > 100 mg qhs could be effect, assess blood levels for risk of toxicity
Anticonvulsants

- ↓ excitation (↓ Na⁺ / K⁺ flux)
- Limited data, trial-and-error
- Newer drugs have better safety profiles
  - Lamotrigine
  - Carbamazepine (PHN)
  - Topiramate
  - Phenytoin
  - Oxcarbazepine
  - Valproate
  - Tiagabine
  - Levetiracetam
  - Zonisamide
Anticonvulsants

- Carbamazepine 50 – 100 mg q12h
  Increase by 50 – 100 mg every 3 days
  $t_{\frac{1}{2}} = 12$ hrs

Monitor blood levels for risk of toxicity
## Opioids, Positive Trials

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Pain Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>PHN</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>DPN &amp; PHN</td>
</tr>
<tr>
<td>Methadone</td>
<td>Mixed neuropathic pain</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Peripheral &amp; central neuropathic pain</td>
</tr>
</tbody>
</table>

Morphine + gabapentin vs. morphine alone vs. gabapentin DPN or PHN

Systematic review of tramadol (5 trials)

Tough Cases

Like in Diabetes, or Hypertension, sometimes need combinations of medications with different mechanisms of action, e.g.,

- Opioid
- Gabapentin
- Desipramine
- Ibuprofen
Multiple Issues ➔
“Total Pain”

- Disease management
- Loss, grief
- End of life / death management
- Physical
- Psychological
- Social
- Practical
- Spiritual
Video
Discuss

• What is major barrier to managing the pain of advanced illness in your setting?
  Drugs?
  Attitudes?
  Team work?
Key Message

Bone, abdominal and neuropathic pain are frequently devastating and require a complex interdisciplinary approach to management.
Gandhi... *You need to be the change you want to see in the world*...
Palliative Care
Interdisciplinary Curriculum

A Joint Initiative of the
Palliative Medicine Faculty & Staff of

OhioHealth

The Ohio State University
Wexner Medical Center

Nationwide Children’s

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