Pharmacology of Pain

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Learning Objectives

• Pain: Definition and Taxonomy
• Pain Assessment and Diagnosis
• Pharmacotherapy of pain
  • Non-Opioid Analgesics and Adjuvants
  • Opioid Management
    • Drug selection
    • Dosing
    • Management of the poorly responsive patient
    • Opioids and addiction
    • Management of opioid-related side effects

Simple Definition, Complex Meaning

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage”

Making a Pain Diagnosis

Determining the etiology/pathophysiology allows:

- A diagnosis/explanation for patient to understand their pain
- The clinician to use targeted and more effective therapies

**Do not just treat the symptom! Try to have a diagnosis**

Taxonomy of Pain

- **Nociceptive**
  - Somatic
  - Visceral
- **Neuropathic**
- **Mixed Nociceptive/Neuropathic**

**Taxonomy of Pain**

- **Nociceptive somatic pain**
  - Musculoskeletal injury
  - Generally well localized
- **Nociceptive visceral pain**
  - Thoracoabdominal visceral injury
  - Poorly localized; described as crampy pain (e.g. obstruction of hollow viscus), or as aching and stabbing (e.g. pain secondary to splenomegaly).
  - Often referred component
Taxonomy of Pain

• Neuropathic pain
  ▪ Sustained by neuroplastic changes in PNS & CNS
  ▪ “Burning,” “shock-like,” “electrical”
  ▪ Allodynia (pain induced by non-painful stimuli)

Taxonomy of Pain

• Idiopathic Pain
  ▪ Common in pts w/ Non-Malignant Pain
  ▪ In Cancer Pts -> lead to additional workup and a search for an underlying etiology

Pain Assessment

Diagnosis is in the History

• Characterize pain in full
  ▪ Quality & Location
  ▪ Timing & Intensity
  ▪ Alleviating & Exacerbating Factors, etc

• Diagnostic History
• Prior Pain Therapies
Pain Assessment

Medical and Social History

Thorough Physical Exam
If source unclear → Consider more data, labs/imaging etc if warranted
The Importance of a Differential Diagnosis

Therapeutic Strategies for Pain

Effective Treatment of Pain is More than Just Pharmacologics!
• Use Multimodal and Multidisciplinary Approaches
  • Cognitive Behavioral Therapies
  • Physical Therapy/OT
  • Acupuncture, Massage
  • Mind-Body Techniques
  • Interventional Procedures
  • Psychiatry
  • SW
  • Pharmacists
  • Chaplains
  • Others

Pharmacologic Treatment
Options are Broad

<table>
<thead>
<tr>
<th>Non-opioid analgesics</th>
<th>Opioid analgesics</th>
<th>Adjuvant analgesics</th>
</tr>
</thead>
</table>
| • NSAIDs
  • Acetaminophen    | • Codeine
• Hydrocodone
• Morphine
• Oxycodone
• Fentanyl
• Hydromorphone
• Methadone             | • Anticonvulsants
• Antidepressants
• Local anesthetic agents
• GABA agonists
• NMDA antagonists
• Others |
Non-opioid analgesics

Acetaminophen
- Analgesic for mild to moderate pain
- Antipyretic, Minimal anti-inflammatory effects
- Acts on central COX-3 enzymes
- Fewer adverse effects than other non-opioids
- Adverse effects
  - Risk for hepatotoxicity at high doses (>4000mg/d)
  - Increased risk with liver disease or chronic alcoholism
  - Rare renal toxicity
- No effect on platelet function
- IV formulation available ($$$)

Non-opioid analgesics

NSAIDs
More Potent Anti-Inflammatory Effects than Acetaminophen
- Inhibit cyclo-oxygenase (COX), reducing prostaglandin formation
- 3 isoforms of COX
  - COX-1: Constitutive, physiologic
  - COX-2: Inducible, inflammatory*
  - COX-3: Central, blocked by acetaminophen
- Drug-to-drug variation in toxicities partly determined by COX-1/COX-2 selectivity

Non-opioid analgesics

NSAIDs
Adverse effects:
- GI & Renal toxicity
- Cardiovascular toxicity
- Bleeding diathesis
- COX-2 selective inhibitors (Celecoxib) have less GI & platelet effects, but risk of cardiovascular events
- Dose-dependent effects, with ceiling dose
- Marked individual variation in response to different drugs
Ketorolac

- Potent analgesic often used in the pain emergency setting
- Opioid-potency without sedation
- 15-30 mg IV every 6 hours
- Limited to 5 days duration due to enhanced side effect profile
- Oral form not as potent; limited to 5 days
- Can be significantly helpful in pain crises

Adjuvant Analgesics

- Drugs with other indications that may be analgesic in specific circumstances
  - Particularly useful for:
    - Neuropathic pain
    - Bone pain
    - Muscle spasm

Adjuvant Analgesics

- Anticonvulsants
- Antidepressants (TCAs, SNRIs)
- Corticosteroids
- alpha-2-adrenergic agonists
- Local anesthetics
- Topical agents
- GABA agonists
- NMDA receptor antagonists
- Cannabinoids
- Calcitonin
- Bisphosphonates
- Radiopharmaceuticals
Antidepressants and Anticonvulsants

A wide range of medications
Differing mechanisms to reduce neuronal excitability
Demonstrated to yield pain reduction of neuropathic pain

Anticonvulsants

Gabapentin
- FDA approved for Post-Herpetic Neuralgia (PHN)
- Binds to the alpha-2-delta subunit of the N-type calcium channels in neurons within the dorsal horn
- Starting dose: 100 mg three times daily or 300mg at bedtime.
- Dose increased as tolerated every 3 to 7 days until analgesia is achieved.
- Therapeutic range 1800-3600mg/d
- Saturable GI Transport Mechanism
- Renal-Dosing

Anticonvulsants

Pregabalin
- FDA approved for Diabetic Neuropathy, PHN, Fibromyalgia
- Same mechanism of action as gabapentin
- Dosing: Start at 50mg BID or TID, with the usual effective dose between 150mg-450mg BID.
- Perhaps more favorable side effect profile
- Less Renal Dose-Adjustment than Gabapentin
- No saturable GI transport mechanism

Many other 2nd line Anticonvulsants for neuropathic pain exist
Antidepressants

Tricyclic Anti-Depressants (TCAs)
- Lowest numbers needed to treat of neuropathics
- Lower doses for pain than as antidepressants (e.g., amitriptyline generally effective 50 to 100mg/day).
- Anticholinergic side effects:
  - 2° Amines (Nortriptyline) < 3° Amines (Amitriptyline)
  - Risks of sedation, dry mouth, cardiac issues, falls, etc

Antidepressants

Duloxetine
- Selective Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)
- FDA approved for: Diabetic Neuropathy, Fibromyalgia, Chronic Musculoskeletal Pain
- Dose: Start 20-30mg daily, increase to 60mg daily
- Risk in patients with hepatic dysfunction

*SSRIs lack significant efficacy in chronic pain
**All antidepressants and anticonvulsants carry warning about increase risk of suicidality.

Adjuvants for Bone Pain

Clinical scenario:

Pain crisis for a patient with extensive boney mets, aggressive opioid titration.

Team is getting ready to push 8 mg iv Dilauidid as you get to the bedside…
Adjuvants for Bone Pain

- NSAIDs
- Corticosteroids
- Bisphosphonates
  - Pamidronate
  - Zoledronic acid
- Rank-Ligand Inhibitors (ex, denosumab)
- Radioisotopes
  - Samarium
  - Strontium
  - Radium

Corticosteroids

Pain from:
- Bony Metastases, Cord Compression
- CNS Headaches 2/2 vasogenic edema/ICP
- Visceral inflammation (hepatic capsule stretch/IRP lymphadenopathy)

High doses (>16 mg/day) of dexamethasone are needed to in spinal cord compression, brain edema

Lower doses (2 to 16 mg/day) can be helpful in patients with other types of cancer pain

Risk/Benefit Ratio: increased infection risk, GI bleed, delirium, candida, insomnia, etc – may be helpful for other non-pain sx though

Corticosteroid Systemic Equivalence Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Equivalent Dose</th>
<th>Relative Anti-Inflammatory Potency</th>
<th>Relative Mineralocorticoid Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>25 mg</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4 mg</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75 mg</td>
<td>25 to 30</td>
<td>0</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.04-0.75 mg</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>
### Topical Analgesics

- May have local efficacy without systemic s/e
- Local Anesthetics
  - Lidocaine patches/Ointment
  - Lidocaine/Benadryl/Antacid
  - Viscous Lidocaine
- Diclofenac cream/patch
- Topical Capsaicin
- 0.1% Morphine in Intrasite gel
- Arnica

### Pharmacotherapy of Pain

#### Opioid Receptor Agonists

### Tramadol & Tapentadol

- Weak opioid receptor agonist with inhibition of re-uptake of serotonin (tramadol only) and norepinephrine
- Side effects: dizziness, constipation, sedation, nausea
- Reduces seizure threshold
- Combination with other opioids controversial
- Indicated for moderate to severe acute pain
  - Postoperative pain, osteoarthritis and low back pain
**Opioid Therapy: Drug Selection**

- Patient factors
- Drug pharmacokinetics
- Availability of appropriate dosing forms and routes of administration
- Cost

**Routes of Administration**

- Oral/SL and transdermal
  - Preferred for most patients
  - TD fentanyl not well absorbed in cachectic patients
  - If dysphagia or poor GI absorption—use SL, parenteral or TD route

- Transmucosal
  - Fentanyl for breakthrough pain (multiple brand name options)

- Parenteral
  - SQ and IV—for acute pain, feasible for long-term therapy
  - Avoid IM dosing of analgesics

**Routes of Administration**

- Rectal route
  - Limited use and absorption

- Intraspinal
  - Epidural and intrathecal (IT generally preferred for long term use)
Opioid Therapy: Drug Selection

Immediate-release preparations
- Acute pain
- Determining optimum dose during initial treatment of chronic pain
- “Rescue” dosing
- Can be used for long-term management in select patients

Opioid Therapy: Drug Selection

Immediate-release preparations
- Combination products
  - Acetaminophen/oxycodone
  - Acetaminophen/hydrocodone
  - Acetaminophen/codeine
  - *Use of combination agents controversial: FDA concerns with acetaminophen overdose
- Single-entity drugs,
  - morphine, oxycodone, oxymorphone, hydromorphone, fentanyl, methadone, codeine.
  - Tramadol, tapentadol

Opioid Therapy: Drug Selection

Extended-release preparations
- Preferred because of improved treatment adherence, maintenance of effective analgesic concentration, and the theoretically decreased risk in those with a h/o addiction
- Adjust dose q 2–3 d
**Opioid Therapy: Drug Selection**

Extended-release preparations
- Morphine Extended Release
- Oxycontin Extended Release
- Fentanyl Transdermal
- Oxymorphone Extended Release
- Hydromorphone Extended Release
- Buprenorphine Transdermal

Inherently Long Acting
- Methadone
- Levoorphanol

**Dosing Oral Opioids**

- For opioid naïve patient, Start with PRN short-acting opioid
- Add "background" (long-acting opioid) in dose equal to 60-75% of 24 hour dose of PRN opioid consumed
- Continue PRN opioid in dose equal to 10-15% of the 24 hour dose of background opioid
- Increase "rescue" dose as baseline dose increases

**Which opioid to start with?**

- Cost, patient history, patient experience, dose needed, route available
  - Renal function? PO?
- MSIR is the cheapest, but smallest tablet size is 15 mg (not for the opioid naïve!)
### Opioid Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>#</th>
<th>SWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine SR</td>
<td>15 mg q8 hrs</td>
<td>30</td>
<td>#90</td>
<td>$187.21</td>
</tr>
<tr>
<td></td>
<td>60 mg q8 hrs</td>
<td>30</td>
<td>#90</td>
<td>$532.39</td>
</tr>
<tr>
<td>Avinza (generic)</td>
<td>90 mg q 24 hrs</td>
<td>30</td>
<td>#30</td>
<td>$1672.92</td>
</tr>
<tr>
<td>Kadian</td>
<td>50 mg q 12 hrs</td>
<td>30</td>
<td>#60</td>
<td>$1173.07</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50 mcg/hr q72 hrs</td>
<td>30</td>
<td>#10</td>
<td>$263.60</td>
</tr>
<tr>
<td>Oxycontin</td>
<td>20 mg q 8 hrs</td>
<td>30</td>
<td>#90</td>
<td>$617.00</td>
</tr>
<tr>
<td></td>
<td>60 mg q 8 hrs</td>
<td>30</td>
<td>#95</td>
<td>$1497.06</td>
</tr>
<tr>
<td>Opana (Oxymorphone)</td>
<td>20 mg q 12 hours</td>
<td>30</td>
<td>#60</td>
<td>$604.50</td>
</tr>
<tr>
<td></td>
<td>16 mg q 24 hours</td>
<td>30</td>
<td>#30</td>
<td>$912.80</td>
</tr>
<tr>
<td>Methadone</td>
<td>10 mg q 8 hrs</td>
<td>30</td>
<td>#90</td>
<td>$39.80</td>
</tr>
</tbody>
</table>

### Opioid Titration and Responsiveness

- Ongoing titration is critical to successful therapy
- Increase dose until pain relief is adequate OR intolerable and unmanageable side effects occur
- No ceiling effect (well, sort of)
  - Hyperalgesia: increased perception of all stimuli to be painful
- Responsiveness of an individual patient to a specific drug cannot be determined

### Managing Poor Opioid Responsiveness

If dose escalation → adverse effects
- Better side-effect management
- Pharmacologic strategy to lower opioid requirement
  - Spinal route of administration
  - Add non-opioid or adjuvant analgesic
- Non-pharmacologic strategy to lower opioid requirement
  - “Opioid rotation”
### Equianalgesic Conversions

<table>
<thead>
<tr>
<th>Drug</th>
<th>SCI</th>
<th>IV</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>n/a</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>n/a</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
<td>varies</td>
</tr>
</tbody>
</table>

### Opioid rotation

- Conversion charts are based on large intra-individual variation in response to different opioids
- Reduce equianalgesic dose by 25%–50% to account for incomplete cross-tolerance
  - Reduce less if pain severe
  - Reduce more if medically frail
  - Reduce less (or not at all) if same drug by different route
  - Reduce methadone more: 50%–90%

### Transdermal Fentanyl

- For stable, chronic pain
- 12-24 hours for onset and discontinuation of action
- Heat increases absorption (caution if fevers!)
- Hydration, tattoos, and nutritional status may affect absorption
- Requires subcutaneous adipose tissue for absorption
- Must be opioid tolerant to start a patch
**Transmucosal Fentanyl:**

- For opioid tolerant cancer patients with incident pain (pain related to movement or other activity)
- Multiple agents
- Individual dosing - not equivalent to each other
- Short onset and duration of action
  - Apply lozenge to oral mucosa over 15 minutes
  - Apply dissolvable tablet between cheek and jaw
  - Apply film to inside of cheek
  - Place tablet under tongue
  - Nasal spray
  - SL spray
- TIRF REMS Access Program
  - Patient, Provider and Pharmacy enrollment required

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**Equianalgesic Conversions**

Manufacturer's Suggested Starting Doses of Transdermal Fentanyl:

<table>
<thead>
<tr>
<th>PO MSO4 (mg/day)</th>
<th>Fentanyl Patch (mcg/hr patch)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</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>
</tbody>
</table>

Alternate method:

When converting between fentanyl TD and morphine PO, use 1:2 ratio: 75mcg patch = 150mg oral morphine

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**Role of Methadone**

- Another useful long-acting drug
- Potency greater than expected based on single-dose studies
- Variable and unpredictable half-life (12-150 hrs)
- When used for pain: multiple daily doses, steady-state in 3-5 days to up to several weeks
- Close monitoring needed until steady-state approached to reduce risk of side effects
What makes Methadone different?

Chemical Structure
Dual mechanism of action: Opioid and NMDA receptor
Pharmacokinetics
Drug interactions
Cardiac Conduction abnormalities

Methadone: Basics

Long-acting opioid, mixture of d and l-isomers
Opioid Addiction vs Pain (script writing*)
Multiple binding sites:
- Mu-Opioid receptor (l-isomer)
- Blocks Serotonin & Norepinephrine reuptake (d-isomer)
- NMDA-receptor Antagonist (d-isomer)

When to consider Methadone?

Inadequate Pain Control w/ other opioids
Intolerable Side Effects w/ other opioids
Hyperalgesia or Tolerance to other opioids
Neuropathic Pain component
Renal Dysfunction
Patients w/ hx of Opioid/Heroin Abuse
**Methadone Conversion**

**Oral Morphine Equivalent Mg of oral Methadone**

<table>
<thead>
<tr>
<th>Oral Morphine Equivalent</th>
<th>Mg of oral Methadone</th>
<th>Mg of oral Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 mg/day</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>101-300 mg/day</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>301-600 mg/day</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>601-800 mg/day</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>801-1000 mg/day</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>&gt;1000 mg/day</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

IV methadone is twice as potent as oral methadone

**Based on data from Mercandante, 2001 and Ayonrinde, 2000**

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**Buprenorphine Patch (Butrans®)**

- Mixed agonist-antagonist
- Partial agonist at the mu-opioid receptor
- Antagonistic effect at kappa-opioid receptors
- Patch strengths: 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr and 20 mcg/hr

Patches are replaced every 7 days

<table>
<thead>
<tr>
<th>Prior Total Daily Opioid Dose</th>
<th>Buprenorphine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30 mg oral morphine equivalents per day (MED)</td>
<td>D/c all around-the-clock (ATC) opioids; initiate 5 mcg/hr patch; may be titrated every 72 hours</td>
</tr>
<tr>
<td>30-80 mg MED</td>
<td>Taper opioids to less than 30 mg MED; d/c all ATC opioids; initiate 10 mcg/hr patch; titrate q 72 hr</td>
</tr>
<tr>
<td>Greater than 80 mg MED</td>
<td>Consider alternative analgesic</td>
</tr>
</tbody>
</table>

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**Opioid-related Side Effects**

**Common**
- Constipation
- Somnolence, mental clouding

**Less common**
- Nausea
- Myoclonus
- Pruritis
- Urinary retention
- Sweating
- Amenorrhea
- Sexual dysfunction
- Headache
Treating Opioid-Related Side Effects

- Allow tolerance to the undesirable effect to develop (not constipation)
- Reduce the dose
- Change dosing intervals to achieve more consistent levels
- Try a different opioid (opioid rotation)
- Add another medication to manage the side effect
- Optimize the use of adjuvant analgesics to opioid spare

Constipation

**General Approach:**

- Increase fluid intake and dietary fiber
- Encourage mobility and ambulation if appropriate
- Ensure comfort and convenience for defecation
- Rule out and treat impaction if present
- No more docusate as a routine, first-line agent!

**Opioid-Related Constipation Pharmacologic Approaches**

<table>
<thead>
<tr>
<th>Agent (a) (e.g.)</th>
<th>Mechanism</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senna</td>
<td>Myenteric plexus stimulant</td>
<td>$</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>Muscle Stimulant; increased intestinal water and electrolyte levels</td>
<td>$</td>
</tr>
<tr>
<td>Milk of Magnesia</td>
<td>Osmotic</td>
<td>$</td>
</tr>
<tr>
<td>Mag Citrate</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>Lactose intolerance (?)</td>
<td>$</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Prokinetic</td>
<td>$</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>Chloride channel activation</td>
<td>$$$</td>
</tr>
<tr>
<td>Naloxegol</td>
<td>Peripheral opioid antagonist (tertiary)</td>
<td>$$$</td>
</tr>
<tr>
<td>Methylnaltrexone</td>
<td>Peripheral opioid antagonist (quaternary)</td>
<td>$$$$</td>
</tr>
</tbody>
</table>

Cost per month: $ $10 | $10-100 | $100-500 | $500+ $500
Methylnaltrexone for constipation

- Methylnaltrexone bromide: subcutaneous injection for treatment of opioid induced constipation in patients with advanced illness receiving palliative care
- Peripherally acting mu-opioid receptor antagonist
  - Limited effect on CNS opioid receptors
- Produces stool 30 min to 4 hours
- Dosed once every other day by SC injection

**Methylnaltrexone Dosing**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 84</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>84-136</td>
<td>8 mg</td>
</tr>
<tr>
<td>136-251</td>
<td>12 mg</td>
</tr>
<tr>
<td>&gt; 251</td>
<td>0.15 mg/kg</td>
</tr>
</tbody>
</table>

- For patients with a creatinine clearance less than 30 mL/min, reduce dose by 50%
- Available solution is 12 mg/0.6 ml

Nausea

**General Approach:**
- Hydrate as appropriate
- Good mouth care
- Correct contributory factors
- Adjust medication

**Pharmacologic Approach:**
- Vertigo → antihistamine (e.g. scopolamine, meclizine)
- Early satiety → prokinetic (e.g. metoclopramide)
- Dopamine antagonists (e.g. prochlorperazine, haloperidol, metoclopramide)

Somnolence or Cognitive Impairment

**General Approach:**
- Reassurance
- Education
- Treatment of potential etiologies

**Pharmacologic Approach:**
- If analgesia is satisfactory, a trial of opioid dose reduction by 25%
- If analgesia is satisfactory and the toxicity is somnolence, consider psychostimulant (e.g. methylphenidate or dextroamphetamine)
- Low dose antipsychotics may be used to treat opioid-induced delirium
**Pruritis**

- Most common with intraspinal opioids
- Usually involves face, neck, upper thorax
- May be CNS mediated vs. histamine-mediated
- Management:
  - Stop the opioid
  - Administer partial antagonist (nalbuphine 2.5-5 mg IV) or antihistamine (diphenhydramne 25 mg IV)

**Neurotoxicity: Delirium, Myoclonus, Hyperalgesia**

- Risk Factors:
  - High opioid doses and/or rapid dose escalation
  - Prolonged exposure to opioid
  - Dehydration
  - Renal Failure
- Management:
  - Opioid rotation (especially methadone)
  - Dose reduction
  - Hydration
  - Neuroleptics for delirium
  - Benzodiazepines to control myoclonus
  - Partial antagonist (nalbuphine 2.5-5 mg IV)

**Summary: Pharmacotherapy of Pain**

- Understand the pain syndrome
  - Neuropathic
  - Nociceptive (Visceral, Somatic/Inflammatory)
  - Idiopathic
- Consider co-analgesics and adjuvant medications for specific pain syndromes
  - Bone pain
  - Neuropathic pain
- Use opioids for moderate to severe pain
- Successful opioid therapy requires:
  - Proper opioid selection
  - Use of long-acting and short acting opioids for breakthrough pain
  - Titrating to desired effect, ongoing assessment
  - Treating opioid-related side effects