CHRONIC PAIN MANAGEMENT

Betty J Harris, PharmD.
2014

Objectives

• Explain the consequences of untreated pain.
• Identify common causes of chronic non-malignant pain in adults.
• Identify steps to assessing pain, including cognitive impairment.
• Describe the pharmacodynamic and pharmacokinetic characteristics, and mechanism of action of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs).

Objectives

• List adverse effects and precautions, dosing guidelines and significant drug interactions associated with acetaminophen and NSAIDs.
• Describe the pharmacodynamic and pharmacokinetic characteristics, and mechanism of action, and role in chronic therapy of opioid analgesics.
• List adverse effects and precautions, dosing guidelines and significant drug interactions associate with the opioids.
• Given an actual or simulated patient with chronic pain, select an opioid based on patient and opioid related variables.
Consequences of untreated pain

- Depression, anxiety
- Falls
- Malnutrition
- Reduced cognition
- Increased healthcare costs
- Impaired sleep, functional disturbances
- Declines in socialization and recreational activities.
- Impact on family, friends and society

Effects of Chronic Pain on the Patient

Physical Functioning
- Mobility
- Sleep disturbances
- Fatigue
- Loss of appetite
- In Grey Matter

Social Functioning
- Diminished social relationships
- Sexual function/activity
- Recreational & social activities

Mood
- Depression
- Anxiety
- Anger
- Inability

Societal Consequences
- Health care utilization
- Disability
- Loss of work
- Substance abuse

Common chronic conditions in adults that typically cause pain

- Nociceptive Pain
  - Coronary artery disease
  - Low back pain from facet joint arthritis and spondylosis
  - Osteoarthritis
  - Osteoporosis
  - Paget's disease
  - Previous bone fractures
  - Rheumatoid arthritis

- Neuropathic pain
  - Central post stroke
  - Nutritional neuropathies
  - Peripheral neuropathies
  - Post herpetic neuralgia
  - Trigeminal neuralgia

- Mixed pain
  - Fibromyalgia
  - Myofascial pain
Clinical presentation

- Much of the assessment is subjective - from the patient
- Quality of life
- Four A's – chronic pain
  - Analgesia
  - Activity
  - Aberrant drug behavior
  - Adverse effects

Pain assessment through observation

- General impressions.
- Areas of redness, swelling.
- Atrophies muscles.
- Gait.
- Facial expression, grimacing, furrowed brow.
- Mood, appears anxious or flat affect.
- Body position, spontaneous movement, guarding positioning, limited movement.

“you can observe a lot just by watching”

– Yogi Berra
Treatment

Dosing Acetaminophen

<table>
<thead>
<tr>
<th>Population</th>
<th>Usual Dosing</th>
<th>MOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and Children ≥ 12 years of age</td>
<td>325-650 mg by mouth q4-6h IR or 1300 mg q6h XR</td>
<td>4000 mg (3,000 mg OTC)</td>
</tr>
<tr>
<td>Adults and adolescents ≥ 13 years of age, ≥ 50 kg</td>
<td>Up to 1000 mg Intravenously q6h</td>
<td>4000 mg</td>
</tr>
<tr>
<td>Adults and adolescents ≥ 13 years of age, ≤ 50 kg</td>
<td>15 mg/kg Intravenously q6h</td>
<td>75 mg/kg</td>
</tr>
<tr>
<td>Children 2-12 years of age</td>
<td>10 mg/kg by mouth q4-6h</td>
<td>75 mg/kg</td>
</tr>
<tr>
<td>Children &gt; 2-12 years of age</td>
<td>15 mg/kg Intravenously q6h</td>
<td>75 mg/kg</td>
</tr>
</tbody>
</table>

Caution with acetaminophen/peptic combination products (Wissin, Lortab, etc.)

January 2011 FDA mandated limiting acetaminophen to no more than 325 mg/tab or cap (5 year phase-in)

Acetaminophen pediatric dosing

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Dose and frequency</th>
<th>Maximum daily amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 years</td>
<td>≥ 43.6 kg</td>
<td>640 mg every 4 to 6 h</td>
<td>5 doses per day (5.7 g in 24 h)</td>
</tr>
<tr>
<td>11 years</td>
<td>&lt; 43.6 kg, ≥ 22.3 kg</td>
<td>400 mg every 4 to 6 h</td>
<td>5 doses per day (3.2 g in 24 h)</td>
</tr>
<tr>
<td>9 to 10 years</td>
<td>10.9 kg to 22.2 kg</td>
<td>400 mg every 4 to 6 h</td>
<td>5 doses per day (2.6 g in 24 h)</td>
</tr>
<tr>
<td>6 to 8 years</td>
<td>21.5 kg to 25.4 kg</td>
<td>520 mg every 4 to 6 h</td>
<td>5 doses per day (2.3 g in 24 h)</td>
</tr>
<tr>
<td>3 to 5 years</td>
<td>14.9 kg to 21.2 kg</td>
<td>240 mg every 4 h</td>
<td>5 doses per day (1.2 g in 24 h)</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>10.9 kg to 11.5 kg</td>
<td>160 mg every 4 h</td>
<td>5 doses per day (0.6 g in 24 h)</td>
</tr>
</tbody>
</table>
Drug Interactions with Acetaminophen

<table>
<thead>
<tr>
<th>Medication</th>
<th>Objective Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Acetaminophen</td>
<td>Increased risk of hepatotoxicity with large/chronic doses of barbiturates. Possibly reduced acetaminophen therapeutic effect.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Acetaminophen</td>
<td>Increased risk of acetaminophen-induced liver damage.</td>
</tr>
<tr>
<td>Hydantoins</td>
<td>Acetaminophen</td>
<td>Increased risk of hepatotoxicity; possibly reduced acetaminophen therapeutic effect.</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>Acetaminophen</td>
<td>Increased risk of hepatotoxicity; possibly reduced acetaminophen therapeutic effect.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Lamotrigine</td>
<td>With chronic acetaminophen use, may require lamotrigine dosage increase to maintain effect.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Warfarin</td>
<td>Weekly doses of acetaminophen of 2.25g or higher warrant INR monitoring and possibly warfarin dosage adjustment (increase).</td>
</tr>
</tbody>
</table>

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Agents

- Diclofenac*
- Indomethacin
- Sulindac
- Tolmetin
- Celecoxib **
- Meclizine
- Mefenamic acid
- Nabumetone
- Piroxicam
- Meloxicam
- Fenoprofen
- Flurbiprofen
- Ibuprofen ***
- Ketoprofen
- Naproxen
- Oxaprozin
- Etodolac
- Ketorolac ***

Drug Interactions with NSAIDs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Objective Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors, ARBs</td>
<td>NSAIDs</td>
<td>Reduced antihypertensive effect; risk of nephrotoxicity increased.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>NSAIDs</td>
<td>Increased risk of GI bleeding</td>
</tr>
<tr>
<td>Biologics, Corticosteroids, anticoagulants</td>
<td>NSAIDs</td>
<td>Increased risk of GI bleeding and GI ulceration</td>
</tr>
<tr>
<td>Hepatotoxic agents</td>
<td>NSAIDs</td>
<td>Increased risk of hepatotoxicity</td>
</tr>
<tr>
<td>SIBs</td>
<td>NSAIDs</td>
<td>Increased risk upper GI bleeding</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Antiangioteics</td>
<td>Increased risk of renal toxicity</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Diuretics, antihypertensives</td>
<td>Diminished antihypertensive effect</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Lithium, MAO</td>
<td>Reduced renal clearance; increased toxicity</td>
</tr>
</tbody>
</table>
Dosing Selected NSAIDs

<table>
<thead>
<tr>
<th>Generic Brand</th>
<th>Brand Name</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Catafam</td>
<td>50 mg three times a day</td>
</tr>
<tr>
<td></td>
<td>Voltaren XE</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Etodolac</td>
<td>X R</td>
<td>200 mg – 400 mg three times daily</td>
</tr>
<tr>
<td>Ibufrofen</td>
<td></td>
<td>400 mg – 800 mg three times daily</td>
</tr>
<tr>
<td>Naprosyn</td>
<td>Naprosyn</td>
<td>250 mg three times daily, 500 mg two or three times daily</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
<td>100 – 200 mg twice daily</td>
</tr>
</tbody>
</table>

Topical Treatments

Topical Diclofenac

- Flector (1.3%) topical patch – acute pain (sprains, strains and bruises)
- Pennsaid (1.5%) topical solution - OA
- Voltaren (1%) topical gel - OA
- Solaraze (3%) topical gel – actinic keratoses

Opioid history!

- Ancient Egyptian papyrus records report the use of opium (3400 BC in Mesopotamia)
- Opium – refers to a mixture of alkaloids from the poppy seed
- Opiates – naturally occurring alkaloids such as morphine and codeine
- Opioid – describes all compounds that work at opioid receptors (morphine – prototypical opioid)
- Narcotic – originally used to describe medications for sleep, then opioids, now all drugs that are abused
Opioid Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Effects</th>
</tr>
</thead>
</table>
| Mu       | Brain    | • Suprapontal analgesia  
           | Medial thalamus         | • Respiratory depression, urinary retention  
           |                        | • Euphoria, sedation, pruritus, anorexia  
           |                        | • Overdose gastrointestinal toxicity, vomiting  
           |                        | • Physical dependence |
| Kappa    | Limbic and other diencephalic areas, brain stem, spinal cord | • Spinal analgesia  
           |                        | • Sedation, dysphoria, miosis, euphoria, diaphoria |
| Delta    | Brain    | • Effect most well studied; analgesia  
           |                        | • Possibly psychotomimetic and dysphoric effects |
| Sigma    | Not considered opioid receptors any longer | • Psychomimetic effects  
           |                        | • Opiophobia  
           |                        | • Stress-induced depression |


Opioid Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Phenanthrenes | • Morphine  
                  | • Codeine  
                  | • Hydromorphone  
                  | • Levorphanol |
|            | • Oxycodone  
                  | • Hydrocodone  
                  | • Oxymorphone  
                  | • Buprenorphine  
                  | • Nadalorphine  
                  | • Butorphanol |
| Benzomorphines | • Pentazocine |
| Phenylperidines | • Fentanyl, alfentanil, sufentanil  
                  | • Meperidine |
| Oxyphenylpiperazines | • Methadone  
                               | • (Propoxyphene) – off market |


Opioid Classification - Actions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
<th>Action</th>
</tr>
</thead>
</table>
| Opioid Agonists | Morphine  
                  | Fentanyl  
                  | Hydromorphone  
                  | Oxycodone  
                  | Methadone  
                  | etc. |
|                | • Stimulate opioid receptors.  
                  | • Differences in activity and efficacy appear to be related to the relative stimulation of the various opioid receptors, and genetic differences in opioid receptor sensitivity. |
| Opioid Partial Agonists | Buprenorphine  
                         | • Has a high affinity, but low efficacy at the mu receptor where it yields a partial effect |
| Opioid Agonist-Antagonists | Pentazocine  
                                   | • Poor mu opioid receptor efficacy  
                                   | • Kappa agonist properties |
| Opioid Antagonists | Naltrexone  
                         | Nalmefene  
                         | Butorphanol  
                         | • Competitive antagonists at the mu, kappa and delta receptors |

Pick an opioid...any opioid?


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First Line Opioids

- Morphine
- Oxycodone
- Hydromorphone
- Methadone
- Buprenorphine
- Fentanyl

Pain Pract 2008;9:287-313

Considerations in Opioid Selection?

- Patient-related variables
  - Assessment information about patient’s pain complaint
  - Specific information about the patient’s pre-existing conditions that may alter the expected dosing and effects (both therapeutic and toxic) prior to selection of pharmacotherapy

- History of codeine allergy?
Considerations in Opioid Selection?

- Agent/Drug-related variables
  - Characteristic properties of a medication that affects its use in a given situation, including pharmacodynamic and pharmacokinetic parameters, dosage formulations or routes of administration, adverse effects, and costs (cost of medication, administration and monitoring).
  - Cross-allergenicity with codeine?

Morphine

- Agonist at μ and κ opioid receptors
- Metabolized in the liver to morphine-3-glucuronide (M3G, 55%) and morphine-6-glucuronide (M6G, 10%). 10% eliminated unchanged.
  - Both pharmacologically active
    - M6G analgesic; both can cause toxicity
  - Accumulated in renal impairment and may cause toxicity
  - Reduce dose/avoid in renal impairment

See “Pharmacokinetic References” at end of slides.

Morphine

- Use cautiously with hepatic impairment
  - Oral morphine may become more bioavailable
  - May require increase in dosing interval
- Available as:
  - SA tablets, capsules, oral solution, oral intensol
  - LA tablets, capsules
  - Rectal suppositories
  - Injectable formulation
Opioid-Induced Adverse Effects

- Gastrointestinal adverse effects
  - Nausea and vomiting
    - Rule out constipation-induced
    - Prophylaxis generally not indicated
    - Management: antipsychotic agents, prochlorperazine, metoclopramide, corticosteroids
  - Constipation
    - Prophylactic treatment essential!
    - Stool softener and laxative
    - Methylaltrexone

Benjamin R et al. Pain Physician 2009;11:S105-S120.
Swingle JM et al. Am Fam Physician 2008;74:1347-1354

Opioid-Induced Adverse Effects

- CNS adverse effects
  - Sedation, mental clouding, impaired psychomotor function
    - Sleeping off sleep deficit from unrelieved pain
    - Common with dosage initiation and increases
    - Tolerance may develop
    - Treatment: psychostimulants, antipsychotic agents

Benjamin R et al. Pain Physician 2009;11:S105-S120.
Swingle JM et al. Am Fam Physician 2008;74:1347-1354

Opioid-Induced Adverse Effects

- Cardiorespiratory
  - Cardiac effects of opioids
    - Methadone
    - (Buprenorphine??)
  - Respiratory depression
    - Hold dose, reduce dose
    - Opioid antagonist (try to avoid this!)
    - Monitor level of arousal BEFORE it gets to respiratory depression!

Benjamin R et al. Pain Physician 2009;11:S105-S120.
Swingle JM et al. Am Fam Physician 2008;74:1347-1354
Morphine

- Use cautiously with hepatic impairment.
  - Oral morphine may become more bioavailable.
  - May require increase in dosing interval.
- Available as:
  - SA tablets, capsules, oral solution, oral intensol.
  - LA tablets, capsules
  - Rectal suppositories
  - Injectable formulation

Other Opioid Adverse Effects

- Pruritus
- Immunologic effects
- Hormonal changes
- Hyperalgesia
- Bladder dysfunction

Monitor for Sedation

<table>
<thead>
<tr>
<th>Stage / Clinical Presentation</th>
<th>Action Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep, easy to arouse</td>
<td>Acceptable; no action necessary. May increase opioid dose if needed.</td>
</tr>
<tr>
<td>1. Awake and alert</td>
<td>Acceptable; no action necessary. May increase opioid dose if needed.</td>
</tr>
<tr>
<td>2. Slightly drowsy, easily</td>
<td>Acceptable; no action necessary. May increase opioid dose if needed.</td>
</tr>
<tr>
<td>arousable, drifts off to sleep</td>
<td></td>
</tr>
<tr>
<td>during conversation</td>
<td>Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory. Decrease opioid dose by 25-50% or notify prescriber. Consider administering a non-sedating, opioid-sparing nonopioid (acetaminophen, NSAID)</td>
</tr>
<tr>
<td>4. Somnolent, minimal or no</td>
<td>Unacceptable; stop opioid. Consider administering naloxone. Notify prescriber; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.</td>
</tr>
<tr>
<td>response to verbal or physical stimulation</td>
<td></td>
</tr>
</tbody>
</table>
**Buprenorphine**

- Partial agonist at the mu opioid receptor, antagonist at the kappa opioid receptor
- Metabolized to norbuprenorphine (weak mu agonist) and buprenorphine-3-glucuronide.
- Do dosage adjustment needed in renal impairment/failure or mild to moderate hepatic impairment.
  - Not evaluate in severe hepatic impairment.

**Buprenorphine**

- Available as sublingual (SL) tablets and injection.
  - SL tablets with and without naloxone.
- Available as transdermal formulation.
  - 5 mcg/hr; 10 mcg/hr; 20 mcg/hr.
  - May be started in opioid-naive patients.
- Approximately 75 times more potent than oral morphine.

**Fentanyl**

- Agonist at the mu opioid receptor.
- Metabolized by the liver to inactive metabolites; little parent drug excreted unchanged.
- Bolus doses require no dosage adjustment.
- Continuous infusion and transdermal fentanyl (TDF) doses should be reduced in severe renal impairment.
- Avoid TDF in severe hepatic disease.
**Fentanyl**

- Available as injectable, transmucosal, intranasal and transdermal formulations.
- All but injections may ONLY be used in opioid tolerant patients.
- Oral morphine $\geq 60$mg/day for $\geq 7$ days or equivalent opioid.
- Fentanyl is approximately 100 times more potent than morphine.

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**Hydromorphone**

- Agonist at the mu and kappa opioid receptors.
- Metabolized in the liver to hydromorphone-3-glucuronide, which is pharmacologically active.
- Moderate to severe renal failure increases hydromorphone area under the curve and half-life of elimination 2-4 fold, respectively.
- Reduce dose or avoid in renal impairment.

---

**Hydromorphone**

- Use cautiously with hepatic impairment.
- Oral hydromorphone may become more bioavailable with severe hepatic impairment.
- Available as oral tablets, long-acting tablets, oral solution, injectable formulation and rectal suppository.
### Methadone

- Agonist at the mu receptor, antagonist at the N-methyl-D-aspartate receptor (NMDA).
- Metabolized to inactive metabolites.
- No dosage adjustment is needed in renal impairment but use caution with end-stage renal disease.
- Half-life may be prolonged with hepatic impairment; allow extra time to achieve steady-state and dose with caution.

- Available as oral tablets, oral solution, concentrated oral solution and injectable formulation.
- Caution when switching from other opioids to methadone.
- Allow 4-7 days or longer to achieve steady-state; do not adjust dose before.

### Oxycodone

- Agonist at the mu opioid receptor.
- Metabolized in the liver to noroxycodone.
  - Threefold greater affinity for mu receptor than oxycodone but poorly penetrates CNS.
- Oxymorphone
  - Ten% of oxycodone excreted unchanged.
- Parent drug and active metabolites accumulates with renal impairment.
  - Use with caution and at lower doses.
Oxycodone

- Consider SA formulation in hepatic impairment.
- Available in SA tablets, capsules, oral solution, oral intensol, long-acting table.
- Injectable formulation not in the US.
- Frequently given in combination with acetaminophen (ie. Percocet®), and to a lesser extent with aspirin (ie. Percodan®).

Patient-Related Variables

- Age, race, body habitus
- Opioid-use history (naive, tolerant?)
- Ability to use/manipulate dosage formulation
- Renal and hepatic function
- History of opioid responsiveness in past (therapeutic or toxic; allergic)

Definitions Relating to Opioid Use

- Physical dependence - a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- Tolerance - a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

http://www.amapainsoc.org/advocacy/opioids2.htm
Neuropathic pain

- Examples:
  - Sciatica from nerve root compression.
  - Diabetic peripheral neuropathy.
  - Trigeminal neuralgia.
  - Post herpetic neuralgia.
  - Fibromyalgia syndrome

Fibromyalgia syndrome

- Wide spread musculoskeletal aching, stiffness and tenderness symptoms for 3 or more months.
- Widespread pain index that assesses the number of painful body areas.
- Assessment of the severity of fatigue, waking unrefreshed and cognitive symptoms.
Epidemiology:

- In the US estimated to be 2% to 5% of the adult population\(^1\).
- Only 1 in 5 is diagnosed and DX takes about 5 years\(^2\).
- Most patients are between 25 and 60 y/o\(^3\).
- Women more likely to be diagnosed than men.


Risk factors

- Relatives of FM patients are at a higher risk for FM\(^1\).
- Environmental factors\(^2\):
  - Physical trauma or injury
  - Infections (Lyme disease, Hepatitis C)
  - Other stressors
- Gender:
  - Women are diagnosed approximately 7 times more often than men\(^3\).


Overview of anticonvulsants used for neuropathic pain

<table>
<thead>
<tr>
<th>Agent (brand name)</th>
<th>FDA approval</th>
<th>Trials supporting efficacy in non-FDA approved indications</th>
<th>Drug Interactions</th>
<th>Reduce dose in chronic polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>gabapentin (Neurontin)</td>
<td>Yes</td>
<td>Clinical trials support efficacy in neuropathic pain syndromes</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>pregabalin (Lyrica)</td>
<td>Yes</td>
<td>Clinical trials support efficacy in neuropathic pain syndromes</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>carbamazepine (Tegretol, Equetro, Carbocarb)</td>
<td>Yes</td>
<td>Clinical trials support efficacy in trigeminal neuralgia</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

Overview of antidepressants used for neuropathic pain

<table>
<thead>
<tr>
<th>Agent</th>
<th>Blocks major</th>
<th>FDA approval</th>
<th>Task supporting efficacy in non-FDA approved conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>sertraline</td>
<td>Not approved for chronic pain</td>
<td>DM neuropathy, fibromyalgia</td>
</tr>
<tr>
<td>TRS</td>
<td>sertraline</td>
<td>Not approved for chronic pain</td>
<td>Neurogenic pain</td>
</tr>
<tr>
<td>SNRI</td>
<td>duloxetine</td>
<td>DM neuropathy, CRPS, CMAP, CINCH</td>
<td></td>
</tr>
<tr>
<td>NRI</td>
<td>venlafaxine</td>
<td>Not approved for chronic pain</td>
<td>DM neuropathy, polymyopathy, fibromyalgia</td>
</tr>
</tbody>
</table>


Comparative efficacy of diabetic neuropathic pain medications

<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Brand name and usual dose ranges (oral)</th>
<th>Clinical trials showing efficacy in pain (as compared to placebo)</th>
<th>Efficacy vs. current standard of care (only 3 out of 88 agents available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>venlafaxine (75-225mg)</td>
<td>1.25 (2.5 to 4.7)</td>
<td>1.25 (1.6 to 3.6)</td>
</tr>
<tr>
<td>Traditional analgesics</td>
<td>hydrocodone (5-15mg)</td>
<td>1.25 (2.5 to 4.7)</td>
<td>1.25 (1.6 to 3.6)</td>
</tr>
<tr>
<td>Newer analgesics</td>
<td>celecoxib (200-400mg)</td>
<td>1.25 (2.5 to 4.7)</td>
<td>1.25 (1.6 to 3.6)</td>
</tr>
<tr>
<td>SNRI</td>
<td>duloxetine (60-120mg)</td>
<td>1.25 (2.5 to 4.7)</td>
<td>1.25 (1.6 to 3.6)</td>
</tr>
<tr>
<td>SNRI</td>
<td>milnacipran (125-250mg)</td>
<td>1.25 (2.5 to 4.7)</td>
<td>1.25 (1.6 to 3.6)</td>
</tr>
</tbody>
</table>


OTHER ADMINISTRATION ALTERNATIVES
Intrathecal Drug Compounding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum concentration</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>100 mg/mL</td>
<td>100 mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>100 mg/mL</td>
<td>1 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50 mcg/mL</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>100 mg/mL</td>
<td>10 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>30 mg/mL</td>
<td>15 mg</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>50 mcg/mL</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.1 mg/mL</td>
<td>0.25 mg</td>
</tr>
</tbody>
</table>

Be VERY careful when converting directly TO or FROM intrathecally administered opioids.
Peripheral / Perineural Blockade

- May be used pre-operatively or peri-operatively
- Single dose vs. continuous peripheral infusion
- Safer than neuroaxial administration except higher risk of seizure

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Dosimetry</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>2 mL/qh</td>
<td>2-3</td>
<td>50-120</td>
</tr>
<tr>
<td>Lidocaine w/ epi</td>
<td>2 mL/qh</td>
<td>2-3</td>
<td>65-180</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>0.8 mL/qh</td>
<td>2-3</td>
<td>50-120</td>
</tr>
<tr>
<td>Mepivacaine w/ epi</td>
<td>0.8 mL/qh</td>
<td>2.3</td>
<td>90-180</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>27.5 mL</td>
<td>5-10</td>
<td>240-480</td>
</tr>
<tr>
<td>Bupivacaine w/ epi</td>
<td>27.5 mL</td>
<td>5-10</td>
<td>240-480</td>
</tr>
</tbody>
</table>

Learn More!

- American Society of Anesthesiology Guidelines for Perioperative Pain Management
  - 2012 available, 2004 freely available
  - http://www.asahq.org/PracticeAnaesthesia/FilesProductAndPracticeGuidelines/Products/PainManagement/ProductSummary/OverView.html
- VHA / DoD Clinical Practice Guidelines for Acute Post-Operative Pain
Breakthrough Pain

Table 4-1: Types of Breakthrough Pain (BTP)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Immediate release opoid on an as-needed basis. (Consider use of a noninvasive analgesic of nonopioid drug class.)</td>
</tr>
<tr>
<td>Incident pains with continuous component</td>
<td>Noninvasive analgesics (e.g., oral, sublingual, transdermal, or rectal) for incident pain. Noninvasive analgesics may also be used as second-line analgesics.</td>
</tr>
<tr>
<td>Incident pains without continuous component</td>
<td>Noninvasive analgesics (e.g., oral, sublingual, transdermal, or rectal) for incident pain. Noninvasive analgesics may also be used as second-line analgesics.</td>
</tr>
</tbody>
</table>

Table 4-2: Properties of Immediate-Release Opioids Used for Breakthrough Pain

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Onset of effect</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>30-60 minutes</td>
<td>4 hours</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30 minutes</td>
<td>4 hours</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 minutes</td>
<td>4 hours</td>
</tr>
<tr>
<td>Methadone</td>
<td>10-15 minutes</td>
<td>4-6 hours</td>
</tr>
</tbody>
</table>

McPherson – refer to references
McPherson – PPI information; refer to references

Table 5-3
Conversion from Oral Morphine to Duragesic

<table>
<thead>
<tr>
<th>Oral 24-hour morphine dose (mg/day)</th>
<th>Duragesic TDS dose (mg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-125</td>
<td>10</td>
</tr>
<tr>
<td>165-225</td>
<td>20</td>
</tr>
<tr>
<td>225-300</td>
<td>30</td>
</tr>
<tr>
<td>300-375</td>
<td>40</td>
</tr>
<tr>
<td>375-450</td>
<td>50</td>
</tr>
<tr>
<td>450-525</td>
<td>60</td>
</tr>
<tr>
<td>525-600</td>
<td>70</td>
</tr>
<tr>
<td>600-675</td>
<td>80</td>
</tr>
<tr>
<td>675-750</td>
<td>90</td>
</tr>
<tr>
<td>750-825</td>
<td>100</td>
</tr>
<tr>
<td>825-900</td>
<td>110</td>
</tr>
<tr>
<td>900-975</td>
<td>120</td>
</tr>
<tr>
<td>975-1,050</td>
<td>130</td>
</tr>
</tbody>
</table>

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Table 5-2
Dosage Recommended Conversion from Oral Morphine to Duragesic

<table>
<thead>
<tr>
<th>24-Hour oral morphine dose (mg/day)</th>
<th>Transdermal fentanyl dose (mg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-125</td>
<td>10</td>
</tr>
<tr>
<td>126-200</td>
<td>20</td>
</tr>
<tr>
<td>201-275</td>
<td>30</td>
</tr>
<tr>
<td>276-350</td>
<td>40</td>
</tr>
<tr>
<td>351-425</td>
<td>50</td>
</tr>
<tr>
<td>426-500</td>
<td>60</td>
</tr>
<tr>
<td>501-575</td>
<td>70</td>
</tr>
<tr>
<td>576-650</td>
<td>80</td>
</tr>
<tr>
<td>651-725</td>
<td>90</td>
</tr>
<tr>
<td>726-800</td>
<td>100</td>
</tr>
</tbody>
</table>

Every additional 10 mg per day
An additional 2.5 mg per hour

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Chronic Pain MGT

Table 6-15 Pharmacologic Management of Chronic, Noncancer Pain

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Nonopioids</th>
<th>Opioids</th>
<th>Other Medications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic</td>
<td>Antidepressants</td>
<td>Anticonvulsants</td>
<td>Anti-inflammatory drugs (nonsteroidal)</td>
<td>Neuropathic pain is a type of chronic pain that is characterized by a burning, aching, or tingling sensation.</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Antidepressants, opioids</td>
<td>Anticonvulsants, cannabinoids</td>
<td>Anti-inflammatory drugs (nonsteroidal)</td>
<td>Fibromyalgia is a chronic pain condition that is characterized by widespread muscle pain, stiffness, and tenderness.</td>
</tr>
<tr>
<td>Malignant</td>
<td>Antineoplastic agents</td>
<td>Cancer chemotherapy</td>
<td>Targeted therapy</td>
<td>Malignant pain is a type of chronic pain that is associated with the presence of a malignancy.</td>
</tr>
</tbody>
</table>

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Table of contents:

1. Introduction
2. Neuropathic Pain
3. Fibromyalgia
4. Malignant Pain
5. Overview of Pharmacologic Management
6. Acute Pain Management
7. Chronic Pain Management
8. Nonopioid Analgesics
9. Opioid Analgesics
10. Adjunctive Therapies
11. Assessment of Pain Management
12. Safety and Tolerance of Pain Medications
13. Ethics and Palliative Care
14. Future Directions in Pain Management
References


• Mease P.J. J Rheumatol. 2005;32(suppl 75):5-21.