Pain Management
Non-Opioid Options

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Disclaimer/Disclosure

- I, **Antony Pham**, have **no** financial disclosures or conflicts of interests to make for this ACPE Educational Program.
Objectives/Expectations

At the completion of this activity, the participant will be able to:

• Define and identify the importance of pain management in acute and chronic settings
• List different non-opioid treatment options for pain
• Indicate the use of opioids use in acute and chronic pain
• Identify potential side effects, misuse, and overdose of opioids
Pain - Definition

- “...an unpleasant sensory and emotional stimulus associated with actual or potential tissue damage...”

- Derived from Latin “peone” = penalty or punishment

- Inter-patient variability
  - “Pain is whatever the patient says it is”
Types of Pain

Nociceptive (perception)

- Protective and Physiologic
  - Provoked by tissue or organ damage
  - Musculoskeletal, inflammation, mechanical problems

- Somatic
  - Pain in skin, muscle, bone, joint
  - Described as aching, stabbing, throbbing, pressure

- Visceral
  - Pain in organs
  - Stomachache, headache
  - Described as gnawing, cramping, aching, sharp

Neuropathic

- Caused by nerve damage or hyper-excitability to CNS/PNS
  - Described as sharp, tingling, burning, shooting
  - Post-herpetic neuralgia (after shingles from the zoster virus)
  - Diabetic neuropathy (high glucose damages peripheral nerve fibers)
  - Fibromyalgia (widespread pain and fatigue)
  - Post-Stroke
Nociceptive & Neuropathic Pain

Nociceptive

Somatic

Visceral

Neuropathic

http://www.nepknowmore.ca/local/images/en/living_img01.gif
http://www.jadedragon.com/articles/headaches.html
Classification of Pain

**Acute**
- Usually nociceptive
- Useful pain, serves as warning (useful)
- Adaptive pain (protects the body)
- Noticeable signs (inflammation, trauma)
- Usually short in duration (less than 3-6 months)

**Chronic**
- Nociceptive or Neuropathic
- Lasting 3-6+ months
- Not useful pain (past normal healing)
- Can be maladaptive pain
- Signs often not noticeable (scars)

**Cancer**
- Both acute and chronic
- Related to tumor (organs, nerves)
- Related to therapy (mucositis, surgery)
The Burden of Pain

- Pain is the most common reason for medical help
  - 20-50% of patients seen in primary care
- May affect **100+ million people**
  - Of which, 5-8 million treated with opioids
- Annual cost of pain in the US = ~$600 billion
  - Healthcare expenses, lost income, lost of productivity

Assessing Pain

In 1999, JCAHO Pain standards revised

- Assess all hospital patients for pain

5th Vital sign

- Temperature
- Blood Pressure
- Heart Rate
- Respiratory Rate
- Pain
OPQRST – A Good Place to Start..

O: Onset
  • When did the pain begin

P: Palliative
  • What makes the pain better/worse?

Q: Quality
  • Describes the pain (sharp, shooting, tingling)

R: Radiation
  • Where is the pain (location)?

S: Severity
  • How does pain compare to previous pain (pain scale)?

T: Temporal
  • How does the pain change with time?
Pain Scales

**Numerical Rating Scale**

- **Verbal**
  - “What number describes your worst pain in the past 24 hours from 0 (no pain) to 10 (worst pain you can imagine)?”

- **Written**
  - “Circle the number that describes your worst pain in past 24 hours.”

- **Categorical Scale**
  - None (0)
  - Mild (1-3)
  - Moderate (4-6)
  - Severe (7-10)

Note: Pain is always SUBJECTIVE
X-rays/CT Scans can detect trauma
Vitamin B12 can detect neuropathic pain
Treatment Options for Pain

Pharmacological therapy is only ONE slice of the pie
Non-Pharmacologic Options

Behavioral
- Cognitive (modifying thoughts and awareness)
- Biofeedback (identifying triggers)
- Relaxation (controlled breathing, meditation, hypnosis)
- Psychotherapy and counseling

Physical medicine
- Aerobic exercise
- Stretching and range of motion
Acupuncture (needle penetration)

- Originated ~2000 years ago (one of the oldest medical procedures)
- Main concept:
  - Qi (chee) = vital energy that permeates all things (disharmony can block meridians).
  - Acupuncture restores proper flow of qi
- Adverse reactions
  - Minor bleeding (caution with anticoagulants)
  - Can be $60-100 per session (some insurances cover)
  - Generally safe (as long as the needles are clean)
  - Survey of 66,000 treatments reported no serious adverse effects
- Evidence
  - Difficulty in randomization
  - Meta-analysis of 6359 patients showed sham acupuncture have been shown to be no different than acupuncture.
  - Both better than no treatment
  - Remains inconclusive
Non-Pharmacologic Options

- Physical and Occupational therapy
- Chiropractic and Osteopathic
- Ultrasonic stimulation
- Electrical modulation
  - Transcutaneous Electrical Stimulation (TENS)
  - $30 on Amazon
Non-Pharmacologic Options

Thermal applications
- Hot/cold compresses
- Rule of thumb:
  - Cold (ice) for inflammation...usually first 48 hours (vasoconstricts)
  - Hot for chronic aches (vasodilates)

Interventional
- Nerve blocks
- Epidural steroid injections

Surgical
- Phantom limb pain (up to 60-80% after amputation)
Approaches to Acute Pain Management

Pain is ALWAYS subjective

- Clinician must accept the patient’s report of pain
- Attempt to make objective and categorize

Use a MULTI-MODAL approach

- Non-pharmacological treatment is MORE important than medications

Use STEP-WISE approach with medications

- Medication + dose to relieve pain without unmanageable side effects
- Goal is to manage pain while restoring function

Decide which route best suits the patient:

- PO/IV/SQ
- PR/TD/TM
- PCA
Pharmacological Options

Mild/Moderate Pain
- Non-opioid analgesic
  - APAP, Aspirin, NSAIDs, COX-2 Inhibitors
  - Tramadol

Neuropathic pain
- Anti-depressants (TCAs or SNRIs)
- Anti-epileptics (gabapentin, pregabalin)

Adjuvant
- Muscle relaxants
- Topical analgesics

Severe pain
- Opioids
WHO Pain Ladder (acute pain)

Very outdated (1980’s)

Adjuvant: Anti-depressants or Anticonvulsants (neuropathic pain) or Muscle Relaxants or Topicals

### Table of Select Non-Opioid Analgesics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Dose</th>
<th>Frequency</th>
<th>Maximum Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>500-1000mg</td>
<td>Q4-6H</td>
<td>4 grams</td>
<td>Liver toxicity in overdose</td>
</tr>
<tr>
<td>Aspirin</td>
<td>500-1000mg</td>
<td>Q4-6H</td>
<td>4 grams</td>
<td>GI, bleeding, renal</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200-400mg</td>
<td>Q4-6H</td>
<td>2400mg</td>
<td>GI, bleeding, renal</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250-500mg</td>
<td>Q6-8H</td>
<td>1500mg</td>
<td>GI, bleeding, renal</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>15-30mg</td>
<td>Q6H</td>
<td>150 mg first day then, 120mg thereafter. 5 day maximum</td>
<td>GI, bleeding, renal</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100-200mg</td>
<td>Q12H</td>
<td>400mg</td>
<td>GI (less), bleeding, renal, Cardiac/Stroke risk?</td>
</tr>
</tbody>
</table>
Acetaminophen (Tylenol)

- Most commonly administered OTC analgesic
- Known as paracetamol in Europe
- Useful in mild pain, headaches, fever
  - NO anti-inflammatory properties
- Commonly combined with opioids to reduce the opioid dose (difficult to titrate)
## Ex. Acetaminophen Combination Prescription Products

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Components</th>
<th>APAP strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol w/ Codeine®</td>
<td>APAP, Codeine</td>
<td>300mg</td>
</tr>
<tr>
<td>Lortab®</td>
<td>APAP, Hydrocodone</td>
<td>500mg</td>
</tr>
<tr>
<td>Norco®</td>
<td>APAP, Hydrocodone</td>
<td>325mg</td>
</tr>
<tr>
<td>Vicodin®</td>
<td>APAP, Hydrocodone</td>
<td>500, 750mg (ES)</td>
</tr>
<tr>
<td>Percocet®</td>
<td>APAP, Oxycodone</td>
<td>325, 500, 650mg</td>
</tr>
<tr>
<td>Ultracet®</td>
<td>APAP, Tramadol</td>
<td>325mg</td>
</tr>
<tr>
<td>Fioricet®</td>
<td>APAP, Butalbital, Caffeine</td>
<td>325mg</td>
</tr>
</tbody>
</table>

**FDA Update: March 26, 2014**

*All manufacturers have discontinued combination products with APAP >325mg*
Actions did not affect OTC acetaminophen products

- Maximum daily dose is still 4,000mg per 24hr period (FDA)
- Some manufacturers have changed their labels to decrease the maximum dose (3,000mg)
- Health care professionals may still prescribe the 4000mg daily maximum to patients (but are advised to use their own discretion and clinical judgment)

Liver Warning:

- Significant liver disease or heavy alcohol is a relative contraindication and the maximum dose is conventionally thought to be 2,000mg per day.

http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm
IV Acetaminophen (Ofirmev)

- Available for adults & children who are NPO/NPR
- Mainly used in surgical patients (perioperative)
- IV to PO conversion as soon as possible
  - Usually within 3 days (some institutions 24hrs)
- Cost per VA hospital:
  - **PO**: $.01 per 500mg tablet
  - **PR**: $0.25 per 625mg suppository
  - **IV**: $7 per 1000mg vial
NSAIDs

- Primarily used for mild to moderate pain
  - Anti-inflammatory at higher doses
- Ketorolac often used for severe pain (it works)
  - 5 day maximum (bleeding risks)
- Tissue injury, strains, sprains, headaches, arthritis, gout
- Synergistic with opioids

Common side effects:
- Bleeding (interfering with platelet aggregation)
- GI upset
- Nephrotoxic (reversible, vasoconstriction)
- CVD (interferes with ASA, potentiate heart failure, raises BP)
Tramadol and Tapentadol

**Not acetaminophen**
- Can be an option in cirrhosis/alcoholic patients

**Not an NSAID**
- Can be an option in GI bleeds/ARF
- Note: Avoid in severe renal impairment

**Not a true opioid**
- Binds to the mu-receptor + inhibits serotonin/NE
- Similar side effects as opioids (but less)

**Dosing**
- Tramadol (Ultram) 25mg PO Q4-6H (max 300mg)
- Tapentadol (Nucynta) 50mg PO Q4-6H (max 600mg)

Note: Risk of interaction with serotonergic drugs (serotonin syndrome)
Neuropathic Pain

Anti-depressants (TCAs)
- Neuropathic Pain
  - Amitriptyline
  - Doxepin
  - Imipramine
  - Nortriptyline
  - Desipramine

Anti-depressants (SNRIs)
- Neuropathic Pain
  - Duloxetine
  - Milnacipran
  - Venlafaxine

Anti-convulsants
- Neuropathic Pain
  - Gabapentin
  - Pregabalin
  - Carbamazepine
Anti-depressants for Pain

Considered 1\textsuperscript{st} or 2\textsuperscript{nd} line for neuropathic pain

Analgesic effect appears sooner vs. anti-depressant effects

Doses are lower for pain vs. depression

All TCAs are used off-label for pain (no FDA indication)

Some SNRIs (duloxetine & milnacipran) have FDA indications

Structurally similar agents
## TCAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Doses for Pain</th>
<th>Frequency</th>
<th>Maximum Dose</th>
<th>Side effects</th>
</tr>
</thead>
</table>
| Amitriptyline (Elavil) | 25-50mg                 | daily     | 150mg/day    | • Anticholinergic   
 • Orthostatic hypotension  
 • QT prolongation  
 • Sedation |
| Desipramine (Norpramin) | 25mg                    | daily     | 150mg/day    |                                                   |
| Imipramine (Tofranil)  | 50mg                    | daily     | 150mg/day    |                                                   |
| Nortriptyline (Pamelor)| 10-20mg                 | daily     | 160mg/day    |                                                   |

Should all be taken at bedtime for sedation reasons
### SNRI’s

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Doses for Pain</th>
<th>Frequency</th>
<th>Maximum Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duloxetine (Cymbalta)</strong></td>
<td>60mg</td>
<td>daily</td>
<td>120mg/day</td>
<td>• Headache • Drowsiness • Weight loss</td>
</tr>
<tr>
<td><strong>Milnacipran (Savella)</strong></td>
<td>50mg</td>
<td>Twice daily</td>
<td>200mg/day</td>
<td>• Headache • Hot flashes • Nausea</td>
</tr>
<tr>
<td>Approved only for Fibromyalgia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Venlafaxine (Effexor)</strong></td>
<td>37.5 – 75mg</td>
<td>daily</td>
<td>225mg/day</td>
<td>• Headache • Drowsiness • Sweating • Weakness • Hypertension</td>
</tr>
</tbody>
</table>
Anti-convulsants for Pain

Considered 1\textsuperscript{st} or 2\textsuperscript{nd} line for neuropathic pain

Binds to calcium channels to inhibit neurotransmitter release

Used for diabetic neuropathy, post-herpetic neuralgia, fibromyalgia

Pregabalin may work faster than gabapentin

Pregabalin is a Schedule V medication (euphoria)

Carbamazepine approved for Trigeminal Neuralgia (5\textsuperscript{th} cranial nerve)
## Anti-convulsants for Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Doses for Pain</th>
<th>Frequency</th>
<th>Maximum Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gapabentin (Neurontin)</strong></td>
<td>300mg</td>
<td>daily</td>
<td>3600mg/day</td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Sedation</td>
</tr>
<tr>
<td><strong>Pregabalin (Lyrica)</strong></td>
<td>75mg</td>
<td>Twice daily</td>
<td>600mg/day</td>
<td>• Peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Drowsiness</td>
</tr>
<tr>
<td><strong>Carbamazepine (Topamax)</strong></td>
<td>100mg</td>
<td>Twice daily</td>
<td>1200mg/day</td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Nausea</td>
</tr>
</tbody>
</table>
Muscle Relaxants

Antispasmodics (skeletal muscle relaxants)

Effect may be more from sedation

May cause CNS depression (careful in combination)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Doses</th>
<th>Frequency</th>
<th>Maximum Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenzaprine</td>
<td>5mg</td>
<td>TID</td>
<td>30mg/day</td>
<td>• Drowsiness</td>
</tr>
<tr>
<td>(Flexeril)</td>
<td></td>
<td></td>
<td></td>
<td>• Low muscle tone</td>
</tr>
<tr>
<td>Baclofen</td>
<td>5mg</td>
<td>TID</td>
<td>80mg/day</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>(Lioresal)</td>
<td></td>
<td></td>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>1500mg</td>
<td>QID</td>
<td>6000mg/day</td>
<td></td>
</tr>
<tr>
<td>(Robaxin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaxalone</td>
<td>800mg</td>
<td>QID</td>
<td>3200mg/day</td>
<td></td>
</tr>
<tr>
<td>(Skelaxin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Don’t forget your Topical Options..

### NSAIDs
- Diclofenac 1.5% topical (Voltaren Gel)

### Local Anesthetics
- 5% Lidocaine patch or gel
  - Good for localized neuropathic pain

### Counterirritants
- Capsaicin 0.025% cream (Zostix)
- Methylsalicylate 15% cream (BenGay)
- Menthol 2.5% cream (Icy Hot)
- Camphor 11% (Tiger Balm)
Pain Management: Opioid Use & Abuse

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Opium Poppy Plant

The Good

The Bad

The Ugly
Opium/Opiates/Opioids

Opium poppy seeds discovered in 1,800’s

• Ingestion found to relieve severe pain

Morphine prototypical opioid agonist

• Remains the standard for analgesics
• Naturally found in opium poppy (opiate)
• All new opioids are compared to morphine

Opioids

• Blanketed term for any drug that binds opioid receptors
• Opiates = naturally found or synthesized with naturally found opium
  • Ex. Morphine, codeine, oxycodone
• Synthetic opioids
  • Ex. Fentanyl, methadone
Opioid Receptors

- Three opioid receptors:
  - mu (μ)
  - delta (δ)
  - kappa (κ)

- Mechanism of Action:
  - All opioids produce effects through binding **mu-receptors**
    - Full agonists
    - Partial agonists
    - Mixed (partial agonists/antagonists)
    - Antagonists

mu receptors found throughout the body (CNS + PNS + Stomach)

Note: we have endogenous opioids called “endorphins”

<table>
<thead>
<tr>
<th>Opioid</th>
<th>mu (µ)</th>
<th>delta (δ)</th>
<th>kappa (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>++++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>(full)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>±</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>(partial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>±</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>(mixed)</td>
<td>(mixed)</td>
<td>(mixed)</td>
</tr>
<tr>
<td>Naloxone</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylnaltrexone</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Binding:** mu receptors  
**Desired:** analgesia  
**Other Effects:** bradycardia, sedation, euphoria, respiratory depression, dependence, miosis
Full opioid agonists do NOT have a “ceiling” effect.

Physiological response to constant binding of mu receptors = more receptors will be produced.

Key opens lock.

http://www.buppractice.com/node/1374
Questions

- What is the maximum daily dose of morphine?

- What would be expected to result from more mu receptors being produced?
Medical Uses of Opioids

<table>
<thead>
<tr>
<th>Condition</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe acute pain</td>
<td>• #1 reason patients seek medical attention</td>
</tr>
<tr>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td>• Trauma</td>
</tr>
<tr>
<td></td>
<td>• Opioids indicated</td>
</tr>
<tr>
<td>Severe cancer pain</td>
<td>• Opioids indicated</td>
</tr>
<tr>
<td>Severe chronic pain</td>
<td>• Very controversial</td>
</tr>
<tr>
<td>Cough suppressant</td>
<td>• Dry, non-productive</td>
</tr>
<tr>
<td></td>
<td>• Example: promethazine + codeine syrup</td>
</tr>
<tr>
<td></td>
<td>• Dextromethorphan is a derivative of opioids</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>• Tincture of Opium</td>
</tr>
<tr>
<td></td>
<td>• Loperamide is a derivative of opioids</td>
</tr>
<tr>
<td>Sedation</td>
<td>• Palliative care</td>
</tr>
<tr>
<td>Detoxification</td>
<td>• Opioid abuse</td>
</tr>
</tbody>
</table>
Common Opioids

- Codeine
- Hydrocodone
- Morphine
- Oxycodone
- Hydromorphone
- Fentanyl

All C-II medications
Codeine

How Supplied

• PO Only
  • Tablet (15, 30, 60mg)
  • Oral solution (promethazine 6.25mg + codeine 10mg) per 5ml

Typical starting dose

• 30mg PO Q6hrs PRN
• 5ml PO Q 6hrs PRN

Comments

• Used mainly for mild pain or cough (off-label)
• Antitussive effects directly suppresses cough reflex in the medulla
• Converted to active morphine via CYP2D6
• CYP2D6 polymorphisms and drug interactions may affect response
• “Ultrametabolizers” may have increased opioid effect
• Renal impairment: Initiate at 50% of normal dose and titrate
• Hepatic impairment: No studied
Hydrocodone

How Supplied

- PO Only
  - In combination with APAP
  - Immediate release
  - Extended release (not used PRN)

Typical starting dose

- Vicodin (with APAP) 5mg PO Q6hrs PRN
- Hysingla ER 20mg PO daily (up to 120mg tab)!
- Zohydro ER 10mg PO Q12H (up to 50mg tab)!

Comments

- Used in moderate pain
- Converted to hydromorphone by CYPD6
- ER formulations are intended as abuse deterrent preparations
- 1:1 conversion between IR and ER
- No active metabolite (preferred in renal insufficiency)
- Renal impairment: Initiate at 50% of normal dose
- Hepatic impairment: Initiate at 50% of normal dose if severe
Morphine

How Supplied

- IV or SQ or PCA
- PO
  - Immediate Release
  - Controlled Release (MS Contin)
  - Sustained Release (Kadian/Avinza)

Typical starting dose

- Morphine sulfate 2-5mg IV/SQ Q2hrs PRN
- Morphine sulfate 5-10mg PO Q4hrs PRN
- MS Contin 15, 30, 60…200mg PO BID (not PRN)
- Kadian10, 20, 30…200mg PO daily (not PRN)

Comments

- Used for moderate to severe pain
- Standard to compare all opioids
- 1:1 conversion between IR and ER (3:1 with PO to IV)
- Fast onset for IV (5mins)
- PO onset (1hr)
- Can be used continuously in cancer pain or palliative care
- Renal impairment: Initiate at lowest dose and titrate
- Hepatic impairment: No recommendations
Oxycodone

How Supplied

• PO Only
  • Immediate release or in combination with APAP
  • Controlled release (not used PRN)
  • Extended release + APAP (not used PRN)

Typical starting dose

• Percocet 5/325mg PO Q6hrs PRN
• Oxycontin 10, 20, 30…80mg PO BID
• Xartemis 15/325mg PO Q12H

Comments

• Used in moderate-severe pain
• IR also available with ibuprofen or aspirin
• CR and XR are abuse deterrent preparations
• Renal impairment: initiate at the lowest dose and titrate as indicated
• Hepatic impairment: initiate at 50% of usual dose
Hydromorphone

How Supplied

- Dilaudid
- IV or SQ
- PO

Typical starting dose

- 0.2mg IV Q2hrs PRN
- 2-4mg PO Q4hrs PRN

Comments

- Very potent opioid (severe pain)
- IV onset (5mins)
- PO onset (30mins)
- Commonly used in patient controlled analgesia (PCA)
- Commonly used in cancer pain or palliative care
- No active metabolite (preferred in renal insufficiency)
- Renal impairment: Initiate at 50% of normal dose
- Hepatic impairment: Initiate at 25-50% of normal dose
Fentanyl

**How Supplied**

- IV (Dilaudid) 1mcg/kg IV x 1
- Transdermal (Duragesic) 25mcg/hr patch Q72H
- Transmucosal (Actiq) Lozenge 200mcg PO x 1
- Nasal Spray (Lazanda) 100mcg spray in one nostril x 1
- Buccal Tablet (Fentora) 100mcg PO x 1
- Sublingual spray (Subsys) 100mcg spray x 1

**Comments**

- Most potent opioid (doses are in mcg and NOT mg)
- Mainly used in cancer pain or palliative care (sedation)
- No active metabolite (preferred in renal insufficiency)
- Renal impairment: Reduce patch dose by 50%
- Hepatic impairment: Reduce patch dose by 50%
Starting Opioids...Not so fast!

**Define Treatment Success:**
- Weigh expected benefits vs. risks **carefully** before initiating opioids
- Relieves pain while body heals and improves function

**Opioids do not eliminate the pain:**
- Decreases the unpleasantness of pain (perception)
- Patients will report that although pain is still present
  - It bothers them less
- Allows patient time to heal and improve function

**Short acting**
- Can be used for severe acute pain
- Start with the lowest dose
- Start with easiest route (PO/IV/PR/PCA)

**Long acting**
- Not recommended upon initiation
- Avoid in opioid-naïve patients
- Not used PRN
- Reserved Cancer pain or palliative care
- Controversial for chronic pain
Short-term Opioids for Acute Pain (severe)

If necessary, give pain medication **around the clock**

- Example:
  - Morphine Sulfate Extended Release 30mg PO Q12H

Give short acting pain medication **PRN** for breakthrough

- If possible, use the same opioid for short and long acting
- Doses should be 10-20% of total 24-hour oral dose every 1-2 hour PRN
- Example:
  - Morphine Sulfate Immediate Release 5mg PO Q 2 hours PRN pain

Ongoing need of rescue doses may indicate a need to readjust ATC dose

Opioids for acute pain should only be given until function is restored (> 7 days rarely needed)
Opioid Rotation

Converting between Opioids

- Common in practice
- Tolerance to one opioid
- Intolerable side effects
- Lack of desirable effects
- Insurance coverage
Example: Different Potencies

Potency
# Opioid Equivalence Chart

<table>
<thead>
<tr>
<th>Opioid</th>
<th>IV (mg)</th>
<th>PO (mg)</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
<td>3-4h</td>
</tr>
<tr>
<td>Tramadol</td>
<td>---</td>
<td>50-100</td>
<td>3-7h</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>---</td>
<td>30</td>
<td>3-5h</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>3-4h</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>---</td>
<td>20</td>
<td>3-5h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>2-3h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 (100mcg)</td>
<td>---</td>
<td>1–3h</td>
</tr>
</tbody>
</table>

All opioids are considered equipotent at these doses. Can use to convert between opioids.
Opioid Conversion

Determine the 24hr total dose of current opioid

Calculate the equianalgesic dose for “new” opioid using chart

Reduce the dose by 25-50% to allow for incomplete cross-tolerance between opioids (if pain was adequately controlled)

Divide the total daily dose of new opioid by number of doses given per day

During the first 24hrs, titrate up if pain still present

Recommended to convert to MORPHINE EQUIVALENT DOSE first (MED)

Keep in mind: All conversions are ESTIMATES (not exact)

WL is a 77 y.o. female hospitalized for pain management

- 10/10 diffuse cancer pain
- A PCA was initiated to manage her pain

### PCA Order

<table>
<thead>
<tr>
<th>Drug</th>
<th>Basal rate (constant infusion)</th>
<th>Bolus Dose (patient controlled)</th>
<th>One hour limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone IV</td>
<td>0.4mg/hr</td>
<td>0.2mg/push</td>
<td>0.6mg (3 pushes)</td>
</tr>
</tbody>
</table>
PCA – Patient Controlled Analgesia

http://www.cwladis.com/math104/PCAdevice.jpg
Patient Case

- Over the past 24 hours
  - WL has received the full basal rate
  - Used PCA (bolus dose) a total of 14 times.

*The patient has responded and the medical team consults you to assist in converting WL to an oral morphine regimen*
Patient Case

Total hydromorphone PCA dose in previous 24 hours:
- Basal: 0.4mg/hr x 24hrs = 9.6mg IV hydromorphone
- Bolus: 0.2mg x 14 pushes = 2.8mg IV hydromorphone
- Total hydromorphone PCA dose = 9.6mg + 2.8mg = 12.4mg IV

Converting hydromorphone IV to morphine PO:
- Hydromorphone 1.5mg IV = Morphine 30mg PO (from conversion chart)
- 12.4mg hydromorphone IV = 248mg morphine PO

Reduce dose by 50% for incomplete cross-tolerance:
- Reduce by 50% (248mg x 0.5) = 124mg morphine
Patient Case

- Divide total dose given per day (given BID):
  - Morphine Sulfate Extended Release (MS Contin®) 60mg PO BID

- What PRN dose should be given to WL?
  - Give PRN dose (10-20% of total daily dose)
  - Morphine Sulfate Immediate Release 10mg PO Q2 hours prn pain
Opioids to Fentanyl Patch

- Determine the amount of total current opioid in last 24hr
- Select the transdermal fentanyl dose based on 24hr dose using conversion table
- For fentanyl dosage >100mcg/hr, multiple patches used
- Do NOT cut patches
- As needed short acting opioids should be prescribed in the first 24hr of switch
- Titrate patch dose based on total prn opioid required
- Duration is 72 hours (but some may require Q48hours)
# Fentanyl Patch Conversion

U.S. Labeling: Dose Conversion Guidelines: Recommended Initial Duragesic® Dose Based Upon Daily Oral Morphine Dose

<table>
<thead>
<tr>
<th>Fentanyl Patch</th>
<th>Morphine PO/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>25mcg/h</td>
<td>60-134mg</td>
</tr>
<tr>
<td>50mcg/h</td>
<td>135-224mg</td>
</tr>
<tr>
<td>75mcg/h</td>
<td>225-314mg</td>
</tr>
<tr>
<td>100mcg/h</td>
<td>315-404mg</td>
</tr>
</tbody>
</table>

12.5mcg/hr patch may be considered in morphine 45-59mg PO daily

- Not used for ACUTE pain
- Only when patients are on a stable dose with a pill burden
- Convert to MED first
- PRN opioids may be needed
- No need to reduce for incomplete cross-tolerance (already in table)
Fentanyl Patches (Duragesic)
# Fentanyl Patches: Patient Counseling

**Before applying:**
- Do not remove patch from pouch until ready to use
- Do not use patch if pouch seal is broken or damaged in any way
- Verify that you have the correct dose prescribed for you

**Preparing to Apply:**
- Choose time of day that is best for you to apply
- Change patch at the same time of day (3 days or 72 hours after you apply)

**Applying:**
- Find an area on: chest, back, flank or upper arm. Avoid hairy, oily, broken skin
- Open pouch, peel off liner, press onto skin and hold for 30 seconds, wash hands
- Apply patch in alternating sites every 72 hours

**Counsel points:**
- You may bathe, swim, and shower while wearing a patch. If the patch falls off before 72 hours, discard it and apply a new patch to a different skin site.

**Disposing:**
- Fold the patch in half and flush it down the toilet
Fentanyl Patch: Black Box Warning

- [U.S. Boxed Warning] Actiq®, Duragesic®, Fentora®, Onsolis™:
  - May cause potentially life-threatening hypoventilation, respiratory depression, and/or death
  - Actiq®, Duragesic®, Fentora®, Onsolis™ should only be prescribed for opioid-tolerant patients.
  - Risk of respiratory depression increased in elderly patients, debilitated patients, and patients with conditions associated with hypoxia or hypercapnia; usually occurs after administration of initial dose in nontolerant patients or when given with other drugs that depress respiratory function.
Opioid Tolerance

- Defined as*: 
  - Oral morphine 60 mg/day OR
  - Transdermal fentanyl 25 mcg/hour OR
  - Oral oxycodone 30 mg/day OR
  - Oral hydromorphone 8 mg/day OR
  - Equianalgesic dose of another opioid

*For at least 1 week

Reverse conversion (fentanyl patch to another opioid): Patch off for at least 18hrs before starting
Side Effects of Opioid Use

**Short-Term**
- Constipation
- Itching
- Nausea & Vomiting
- Respiratory Depression
- Sedation
- QT Prolongation

**Long-Term**
- Hyperalgesia
- Fractures and falls
- Opioid Use Disorder
Side Effects of Opioid Use

- Tolerance to side effects expected to develop over time
  - Except: Constipation (minimal tolerance develops)

- Constipation
  - Long recognized with chronic use (constipation, bloating)
  - Most common + most persistent side effect
  - Need bowel regimen for chronic opioid patients
  - Stimulant + stool softener + stimulant prn
  - Always use a stimulant if possible

- Senna 2 tabs PO QHS
- Docusate 100mg PO BID
- Bisacodyl 5mg PO PRN
## Persistent Opioid-Induced Constipation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage/Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal suppository</td>
<td>• PR daily</td>
</tr>
<tr>
<td>Lactulose</td>
<td>• 15-60ml PO daily</td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>• 240ml PO daily</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>• 8oz PO BID</td>
</tr>
<tr>
<td>Fleet enema</td>
<td>• PR daily</td>
</tr>
<tr>
<td>Milk of Magnesia</td>
<td>• 30-60ml PO daily</td>
</tr>
</tbody>
</table>
Methylnaltrexone (Relistor)

Opioid antagonist approved for:

- Opioid-induced constipation
  - In advanced illness unresponsive to laxatives (IV)
  - 0.15mg/kg (usually 10mg) SQ every OTHER day
  - Chronic non-cancer pain (PO or IV)
  - 450mg PO daily
  - All laxatives should be d/c before starting (can add back if no response)

- Blocks opioid binding at the mu receptor
  - Does not cross the blood brain barrier (only works peripherally in the GI tract)
  - Does not affect opioid analgesia
  - Does not induce symptoms of withdrawal

Side Effects

- Abdominal pain (29%) + flatulence (13%)
- ~$120 per IV dose (Lexi-Comp)
- ~$200 per PO dose

Methylnaltrexone for Constipation

http://www.medicalnewstoday.com/info/oic/treatment-for-opioid-induced-constipation.php
Naloxegol (Movantik)

Treatment of opioid-induced constipation with chronic non-cancer pain

- Peripheral opioid receptor antagonist which does not cross the BBB

Naloxegol 25mg PO QAM on an empty stomach

- Discontinue all laxatives prior to use
- May reintroduce after 3 days if suboptimal response

Side effects:

- Abdominal pain (12-21%)
- ~$10 per tab (Lexi-Comp)
Side Effects of Opioid Use

**Pruritis (itching)**

- Observed in 2-10% of patients on opioids
- Diphenhydramine 25mg PO Q 6H (antihistamine)
- Consider changing to another opioid
- Consider naloxone 0.4mg x 1 for relief of severe pruritis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pruritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>+++</td>
</tr>
<tr>
<td>Codeine</td>
<td>+++</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>+</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>+</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>+</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+</td>
</tr>
<tr>
<td>Methadone</td>
<td>+</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
</tr>
<tr>
<td>Naloxone</td>
<td>-</td>
</tr>
</tbody>
</table>
Side Effects of Opioid Use

Respiratory Depression/Sedation

- Patients with cardiopulmonary disease more susceptible
  - Monitor vitals (BP, HR, RR)
- Tolerance develops over time
  - Lower dose/change opioids
- Naloxone for reversal (0.4mg may repeat)
- Avoid alcohol and other CNS depressants
- Caution with driving or operating machinery

*Benzodiazepines or other CNS depressants: [US Boxed Warning]:*

*Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.*
Side Effects of Opioid Use

Nausea/Vomiting

- Tolerance develops over time
- Dopamine-receptor antagonists if necessary
  - Prochlorperazine 10mg PO BID PRN
  - Metoclopramide 10mg PO PRN

Hyperalgesia

- Paradoxical response (more sensitive to pain)
- Caused by overexposure to opioids
- Consider opioid rotation
- Consider tapering off opioids
### QT Prolongation

- **Methadone & Oxycodone reported to prolong QT**
- **Caution with:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
<td>Hypokalemia, hypomagnesemia, hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Quinidine, Amiodarone, Sotalol</td>
</tr>
<tr>
<td>Antianginal</td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>Macrolides (erythromycin, clarithromycin, azithromycin)</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones (ciprofloxacin, levofloxacin)</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>First/Second generation antipsychotics (haloperidol, clozapine)</td>
</tr>
<tr>
<td></td>
<td>TCA’s (amitriptyline, clomipramine), SSRI’s (citalopram, fluoxetine etc)</td>
</tr>
<tr>
<td>GI drugs</td>
<td>Ondansetron, granisetron, dolasetron</td>
</tr>
</tbody>
</table>
Opioid Drug Interactions

**CYP 2D6**
- Involved in activating:
  - Codeine
  - Hydrocodone
  - Tramadol
- Common inhibitors:
  - Fluoxetine
  - Paroxetine
  - Citalopram

May diminish effect of opioid

**CYP 3A4**
- Interacts with Methadone
- Common inducers
  - Carbamazepine
  - Rifampin
  - St. John’s wort
- Common inhibitors
  - Fluconazole
  - Ritonivir
  - Amiodarone
  - Diltiazem

Some phenotypes are “Ultrarapid Metabolizers” leading to enhanced opioid effects
Discontinuing Opioids

**Ideal**
- Success of therapy
- Quick cessation
- Patient returns to normal daily function

**Less ideal**
- Failure of therapy (use alternatives)
- Intolerable side effects (opioid rotation)
- Agree on exit strategy (scheduled taper)
- Discuss withdrawal symptoms

**Not ideal at all**
- Opioid hyperalgesia
- Development of opioid use disorder

**Worse case**
- Overdose
- Death
The Controversy of Opioids for Chronic Pain

Chronic Pain

- Nociceptive or Neuropathic
- Lasting 3-6+ months
- Not useful pain (past normal healing)
- Signs often not noticeable (scars)
- May be due to maladaptive modulation

Weighing the use of Opioids

- Only used when:
  - Other alternatives have not provided sufficient pain relief
  - Pain is adversely affecting function
  - QOL and potential benefits outweigh the harms
  - May have unrealistic expectations from opioids
The Controversy of Opioids for Chronic Pain

- Opioids have not produced the desired outcome for chronic pain
  - Can worsen pain (hyperalgesia) and function

- Long-term opioid use has NOT been validated in trials
  - Most studies only go up to 6 weeks

- Escalated doses in chronic pain
  - Doses 50-100MED increases mortality 9 fold

- Extensive evidence shows the possible harms of opioids
  - Abuse, dependence, overdose, side effects, hyperalgesia

- Opioids controlling pain is no longer the ultimate goal
  - Substantial risk vs. uncertain benefits

There is ~100% agreement that the medical profession has become overly opioid-centric for chronic pain
Speaking of Dose Escalation...

New Opioid Formulations

- **2013: Zohydro® ER**
  - Hydrocodone ER 10, 15, 20, 30, 40, 50mg ER (BID)
  - Can be crushed

- **2015: Hysingla® ER**
  - Hydrocodone ER 20, 30, 40, 60, 80, 100, 120mg ER (once daily)
  - Abuse deterrent formulation

- **2014: Targiniq® ER**
  - Oxycodone 40mg + naloxone ER (BID)
  - Abuse deterrent formulation

Are we going in the wrong direction?
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>259 million</td>
<td>• Prescriptions written for opioid pain relief</td>
</tr>
<tr>
<td></td>
<td>• One RX for every adult to have a bottle of pills</td>
</tr>
<tr>
<td>300%</td>
<td>• Increase in prescription opioid sales in US since 1999</td>
</tr>
<tr>
<td></td>
<td>• No change in overall amount of pain</td>
</tr>
<tr>
<td>2 million</td>
<td>• Americans have abused or were dependent on opioids in 2013</td>
</tr>
<tr>
<td>17,000</td>
<td>• Died from overdoses related to opioids in 2014</td>
</tr>
</tbody>
</table>
Non-pharmacologic therapy and non-opioid therapy are preferred for chronic pain.

Only consider opioids if expected benefits for both pain and function outweigh the risks.

If used, should be combined with non-pharm + non-opioid therapy.

Before starting opioid therapy for chronic pain, providers should establish treatment goals (realistic) and consider how therapy will be discontinued.

Before starting opioid therapy, providers should discuss known risks and realistic benefits.
CDC 2016 – Opioids for Chronic Pain

4. Prescribe immediate-release opioids instead of extended release

5. Use the lowest effective dosage
   - Precautions when increasing dosage to >50MED per day
   - Avoid >90MED per day

6. If initiating for acute pain, 3 days or less will often suffice
   - More than 7 days rarely needed

7. Evaluate benefits and harms within 4 weeks of starting opioids and then every 3 months.
   - Reduce or discontinue if benefits do not outweigh the harm (decrease by 10% per week)
### CDC 2016 – Opioids for Chronic Pain

<table>
<thead>
<tr>
<th>Number</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Evaluate other risk factors for harm&lt;br&gt;• History of overdoses, substance abuse&lt;br&gt;• Offer naloxone if necessary</td>
</tr>
<tr>
<td>9</td>
<td>Review patient’s history of controlled substance prescriptions using state prescription drug monitoring programs</td>
</tr>
<tr>
<td>10</td>
<td>Use urine drug testing before and at least annually to screen for other controlled and illicit drugs</td>
</tr>
<tr>
<td>11</td>
<td>Avoid using opioids with benzodiazepines whenever possible</td>
</tr>
<tr>
<td>12</td>
<td>Offer or arrange buprenorphine or methadone with behavioral therapies for patients with opioid use disorder</td>
</tr>
</tbody>
</table>
## Potential Misuse of Opioids

<table>
<thead>
<tr>
<th><strong>Tolerance (not addiction)</strong></th>
<th><strong>Dependence (not addiction)</strong></th>
<th><strong>Addiction</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diminished drug effect over time due to exposure</td>
<td>• Take to not experience withdrawal symptoms</td>
<td>• NOT PREDICTABLE (35-40% genetically linked)</td>
</tr>
<tr>
<td>• Need increased dose for same effect (dose escalation)</td>
<td>• PREDICTABLE with use</td>
<td>• Loss of control over drug use</td>
</tr>
<tr>
<td>• Physiological adaptation</td>
<td></td>
<td>• Compulsive drug use (euphoric effects)</td>
</tr>
<tr>
<td>• PREDICTABLE with use</td>
<td></td>
<td>• Drug seeking behavior without symptoms (psychological)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Passes legal limits (can’t control)</td>
</tr>
</tbody>
</table>
Two or more within a 12-month period

- Opioids taken in larger amounts than intended
- Persistent desire or unsuccessful efforts to cut down use
- Great deal of time spent to obtain/use/recover from effects
- Craving or urge to use opioids
- Failure to fulfill major obligations at work/school/home
- Continued use despite interpersonal problems
- Important activities given up due to use
- Opioid use in situations which are physically hazardous
- Continued use despite knowledge of problem
- Tolerance (dose escalation)
- Withdrawal (unable to stop)

# Opioid Withdrawal Symptoms

- **Due to abrupt cessation of opioids**
  - Directly related to dependence

- **Rarely seen with acute use (but can be present)**
  - Most commonly with chronic use or abuse

- **Uncomfortable but not life threatening**
  - Won’t die from withdrawal

- **Short acting can start hours after previous dose**
  - Ex. Heroin

- **Long acting can start days from previous dose**
  - Ex. Methadone

- **Naloxone can precipitate withdrawal immediately**
  - Better than overdosing!
Opioid Withdrawal Symptoms

Followed by months of fatigue, anhedonia, poor appetite, insomnia (not fun)
Opioid Withdrawal Scale

- Resting pulse (>120bpm)
- Sweating (stream off face)
- Restlessness (unable to sit still)
- Pupil size (very dilated)
- Bone or joint aches (rubbing joints)
- Runny nose (constant stream)
- GI upset (multiple episodes)
- Tremors in hands
- Yawning (several times)
- Anxiety
- Piloerection (prominent)

Mild
Moderate
Severe

Schuckit M. Treatment of Opioid-Use Disorder. NEJM. July 2016. 375;4. 357-366
Managing Withdrawal Syndrome

- **Used to relieve symptoms of withdrawal**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-agonist (off-label) for anxiety, piloerection, chills, increased HR</td>
<td>Clonidine 0.1mg PO Q4H up to 1mg/day</td>
</tr>
<tr>
<td></td>
<td><strong>Benzos can be used for insomnia, anxiety</strong></td>
</tr>
<tr>
<td></td>
<td>Lorazepam 1mg PO PRN</td>
</tr>
<tr>
<td></td>
<td>Temazepam 15mg PO QHS for sleep</td>
</tr>
<tr>
<td></td>
<td>Must be VERY careful if a patient is still using opioids</td>
</tr>
<tr>
<td></td>
<td><strong>Diarrhea</strong></td>
</tr>
<tr>
<td></td>
<td>Loperamide 4mg PO x 1 up to 16mg/day</td>
</tr>
<tr>
<td></td>
<td><strong>Pain</strong></td>
</tr>
<tr>
<td></td>
<td>Naproxen 500mg PO BID PRN with food</td>
</tr>
<tr>
<td></td>
<td><strong>Nausea</strong></td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine 5mg PO Q4H PRN nausea</td>
</tr>
</tbody>
</table>
Withdrawal Maintenance

Methadone

- Full long-acting opioid agonist
  - Active metabolite
- Only licensed treatment programs are permitted to prescribe for withdrawal
  - Methadone Clinic
- Can be prescribed for acute/chronic pain by any licensed clinician
- Typical maintenance doses:
  - 80-120mg daily for detox
- Typical pain dose:
  - 5mg PO BID or TID (much lower)
Withdrawal Maintenance

Buprenorphine
- Partial opioid agonist
- Can be prescribed in clinician’s office (must be certified)
- Typically sublingual (+/- naloxone)
- Can be used for pain (not first line)
- C-III (less abuse potential)

Formulations
- Buprenorphine IV or IM (Buprenex) for pain
- Buprenorphine + naloxone SL film (Suboxone) for opioid dependence
- Buprenorphine SL tablet (Subutex) for opioid dependence (not recommended)
- Buprenorphine transdermal patch (Butrans)
- Buprenorphine buccal film (Belbuca) for pain
Withdrawal Maintenance

Naltrexone

- Opioid antagonist
- Longer acting than naloxone
- Treatment of alcohol and opioid dependence
- Keeps patient off of opioids
- Blocks the effects of opioids (if administered)
- Do not administer
- At least 7 days opioid free
- Patient needs to be HIGHLY motivated
- 25mg PO x 1 (if no withdrawal may increase)
# Heroin (diacetylmorphine)

## DEA Schedule
- C-I drug (not legal to prescribe)
- High abuse potential

## Routes of Administration
- Intranasal (snorting)
- Intravenous (rapid/most dangerous)
- Smoking (free base form..."chasing the dragon")

## Properties
- Highly lipophilic (crosses the BBB in 15 seconds)
- Produces rapid euphoria (calming, intense rush)
- Half-life = 30mins (active metabolite includes morphine = pain relief)
- Tolerance builds fast

## Risks
- Mortality (respiratory depression)
- Infection (abscesses/Hep C/HIV/Endocarditis)
- Withdrawal
- Legal Problems

Often cheaper and more accessible than prescription opioids

Note: ANY opioid can be misused and abused
Notable Celebrity Opioid Overdoses

400,000 heroin users
4 million non-medical prescription opioid users
Death rates increased 400% from 2000-2014 (1,842 to 10,574)
Remember JCAHO mandated pain as the 5th vital sign in 1999? Increasing prescribing and misleading marketing of opioids for chronic pain

http://www.huffingtonpost.com/2014/02/21/america-heroin-charts_n_4817130.html
REMS

Risk Evaluation and Mitigation Strategies (REMS)

- Established by FDA in 2007

In response to public health crisis of addiction, misuse, abuse, overdose and death.

- Requires manufacturers to fund accredited education on safe opioid prescribing

All Long-Acting opioid formulations on REMS

Providers recommended to:

- Train yourselves
- Counsel all patients of safe use, serious risk, storage, and disposal
- Evaluated patient’s therapeutic response
- Evaluate patient’s risk for opioid use/abuse
- Educate patient on safe use, storage, and disposal of opioids

http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avinza</td>
<td>Morphine sulfate extended-release capsules</td>
</tr>
<tr>
<td>Butrans</td>
<td>Buprenorphine transdermal system</td>
</tr>
<tr>
<td>Dolophine</td>
<td>Methadone hydrochloride tablets</td>
</tr>
<tr>
<td>Duragesic</td>
<td>Fentanyl transdermal system</td>
</tr>
<tr>
<td>Exalgo</td>
<td>Hydromorphone hydrochloride extended-release tablets</td>
</tr>
<tr>
<td>Kadian</td>
<td>Morphine sulfate extended-release capsules</td>
</tr>
<tr>
<td>MS Contin</td>
<td>Morphine sulfate controlled-release tablets</td>
</tr>
<tr>
<td>Nucynta ER</td>
<td>Tapentadol extended-release oral tablets</td>
</tr>
<tr>
<td>Opana ER</td>
<td>Oxymorphone hydrochloride extended-release tablets</td>
</tr>
<tr>
<td>OxyContin</td>
<td>Oxycodone hydrochloride controlled-release tablets</td>
</tr>
</tbody>
</table>
Prescription Monitoring Program (PMP)

- Signed by Governor Cuomo in 2012
- Aka I-STOP
- Collects and analyzes dispensed controlled substance data from pharmacies
- Available to practitioners and pharmacists online
- Identify potential diversion, abuse, doctor shopping, improper prescribing and dispensing
- Real time submission of data (schedule II, III, or IV)...may be 24hrs delayed
- Often flagged by patient paying in CASH
Drug deaths in 2013
- 2,175 total drug related deaths
- 40% more than in 2009

Opioid-related deaths
- 952 opioid-related deaths
- 30% more than 2009

Naloxone administered in 2014
- 11,992
- 57% more than in 2013
Outlines eligibility for registered opioid overdose prevention programs

- Trains overdose responders
- Substance abusers, family members, friends can be trained overdose responders
- Law enforcement and first responders (firefighters)

Responsibilities:

- Complete training of opioid overdose prevention program
- Refresher every 2 years
- Contacting EMS (911)
- Reporting all responses (record keeping)

Allows for non-patient specific prescriptions of naloxone

- Can have naloxone on hand (aka standing order)
- Naloxone kits may be “shared”
- Becoming similar to “epi” pen
Role of pharmacies

- May register as an opioid overdose prevention program
- May dispense naloxone to patient specific AND non-patient specific prescription

Liability

- A recipient (substance abuser, family member, friend), acting reasonably in good faith in compliance, shall not be subject to criminal, civil or administrative liability...
911 Good Samaritan Law

- Provides legal protection against criminal charges for possession of controlled substances to persons seeking assistance in good faith, as well as to the person who has overdosed.

Standing Orders

- Permits non-patient specific prescribing of naloxone
- Authorized pharmacies to dispense naloxone

Syringe Exchange Programs

- Provides new, sterile syringes free of charge
How to Recognize an Opioid Overdose

Heavy nodding, snoring, snorting

Unresponsiveness, shallow breathing, skin changes

Fatal overdose

Up to 3 hours (progression not instantaneous)
Miosis

- Constriction of the pupil (appears pinpointed)
- Opposite of mydriasis (dilation of pupil)
- Note: nicotine and cholinergic agents can also cause miosis
Responding to an Overdose

Check for Response

• Shake, Shout, Sternal Rub (grind knuckles into chest bone)

Call 911

• Report overdose
• Time & Location

Administer Naloxone

Resuscitation

• If not breathing, chest compressions (rescue breaths if properly trained)
What is Naloxone?

- First approved as Narcan in 1971
  - 80% was used for heroin overdoses

- Reverses opioid effects
  - Effective for 30-90mins

- Can cause sudden withdrawal (unpleasant)
  - Agitation, hypertension, violent behavior, fever, sweating

- Safe and effective
  - Not addictive

- Pure opioid antagonist at the opioid receptors
  - Inserting glue into a door lock
  - Does not prevent deaths caused by other drugs
    - Benzodiazepines
    - Alcohol
    - Cocaine
What is Naloxone?

### Indication
- Known or suspected overdose of opioids
- Natural or Synthetic
- Reversal of opioid activity
- Respiratory depression
- Itchiness, Nausea

### How supplied
- Injection (IV or IM or SQ)
  - 0.4mg x 1 (repeat dose every 2-3 minutes or increase to 2mg if inadequate response)
- Auto-injector
  - 1 dose (0.4mg) IM or SQ x 1 (may repeat every 2-3 minutes)
- Intranasal
  - 0.4mg x 1 (repeat dose every 2-3 minutes or increase to 2mg if inadequate response)

Lower doses recommended to prevent sudden opioid withdrawal
Naloxone (Narcan®)

IV or IM or Intranasally
Naloxone (Evzio®) – Auto Injector

http://images.rxlist.com/images/rxlist/evzio6.gif
Naloxone (Evzio®) – Auto Injector

1. Pull red safe-guard
2. Speaker will sound (injector is ready)
3. Inject into thigh
4. Hold for 5 seconds
5. May repeat if unresponsive
# Naloxone Prices

<table>
<thead>
<tr>
<th>Naloxone Product</th>
<th>Manufacturer</th>
<th>Previous price per year</th>
<th>Current Price (2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal</td>
<td>Amphastar</td>
<td>$20.34 (2009)</td>
<td>$39.60</td>
</tr>
<tr>
<td>1mg/ml vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>Mylan</td>
<td>$23.72 (2014)</td>
<td>$23.72</td>
</tr>
<tr>
<td>0.4mg/ml vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auto-Injector (Evzio)</td>
<td>Kaleo</td>
<td>$690 (2014)</td>
<td>$4500</td>
</tr>
<tr>
<td>2 pack pre-filled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal spray</td>
<td>Adapt</td>
<td>$150 (2015)</td>
<td>$150</td>
</tr>
<tr>
<td>Single use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Naloxone kits

- Advising clinicians to co-prescribe with long-term or high dose opioid use
Question

What happens if you administer Naloxone to a person NOT using opioids?

A. Withdrawal
B. Sedation
C. Pain Relief
D. Nothing
CVS, Walgreen’s (Duane Reade) began stocking naloxone in 2015

More than half of US states currently with access on shelves

Considered a “standing” order in most approved states
“Torture is the ability to remove pain, but the unwillingness to do so...”

~Anonymous

“Each day, ~7,000 people are treated in the Emergency Department for drug overdoses...”

-CDC
Remember: This all started from a plant