Pain Management
Targeting all of the Receptors

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Department of Pharmacy
Middlesex Hospital
Conflicts of Interest

• The speaker has taken part in programs sponsored by Cadence Pharmaceuticals and Cubist Pharmaceuticals
Objectives

• Describe pain receptors and how medications affect the pain experience
• Describe multimodal pain therapy
• Describe tools for the clinician to monitor patients
Pop Quiz

• Which are you most concerned about giving a patient? (no hepatic or renal disease)
  – 1 mg IV Hydromorphone
  – 20 mg Oral Oxycodone Immediate Release
Getting back to the basics

• Pain
  – An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in such terms as damage
Different Types of Pain

- Visceral Pain
- Somatic Pain
- Neuropathic Pain
  - pain arising as direct consequence of a lesion or disease affecting the somatosensory system
- Complex Regional Pain Syndrome
  - Malfunction of nervous system after a traumatic injury. Pain persists after injury has healed and may be greater in intensity than original.
It’s not all about the opioids

• But many individuals think so
• \( \mu, \kappa, \delta \)
• MOP, KOP, DOP
• NOP
μ Receptor (MOP)

- The receptor we most often associate with effects of opioids
- Receptors primarily in brainstem and medial thalamus
- μ1
  - Analgesia
- μ2
  - Sedation, respiratory depression, bradycardia, nausea, vomiting, decreased gastric motility, urinary retention
κ Receptor (KOP)

- Receptors located in the limbic and other diencephalic areas, brainstem, & spinal cord
- Spinal analgesia, diuresis, dysphoria, dyspnea
δ Receptor (DOP)

- Mainly in the brain
- Spinal & supraspinal analgesia
- Decreased gastric motility
Nociceptin (NOP)

- Discovered in 1994
  - Aka ORL-1
- Analgesia, hyperalgesia
- Allodynia (concentration dependent)

- Effects at this receptor are not reversible by naloxone
Agonist/Antagonists

- Not all opioids are pure agonists
- Not all are antagonists
- Some do both
<table>
<thead>
<tr>
<th>Endogenous Peptides</th>
<th>Mu ((\mu))</th>
<th>Delta ((\delta))</th>
<th>Kappa ((\kappa))</th>
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<table>
<thead>
<tr>
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<th>Delta ((\delta))</th>
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<tr>
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<td>Fentanyl</td>
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<tr>
<td>Meperidine</td>
<td>Agonist</td>
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<td>Methadone</td>
<td>Agonist</td>
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<th>Delta ((\delta))</th>
<th>Kappa ((\kappa))</th>
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<tr>
<td>Naltrexone</td>
<td>Antagonist</td>
<td>Weak Antagonist</td>
<td>Antagonist</td>
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</table>
Buprenorphine

- Partial agonist at $\mu$ receptors
- Antagonism at $\kappa$, $\delta$ receptors
- Activates NOP
  - Thought to counteract “rewarding” actions of morphine
- Strong binding affinity to $\mu$ receptors
- Available as a patch (Butrans)
- Also as a tablet/film
  - Suboxone has naloxone as a component
Full Agonists

• Morphine
  – Caution with renal impairment (morphine-6 glucuronide)
  – IV is 3X as potent as PO form
• Hydromorphone (Dilaudid)
  – Minimal renal clearance (chronic use can accumulate)
  – IV is 5X as potent as PO form
• Oxycodone
  – Renally eliminated, much safer than morphine
  – 1-1.5X as potent as PO Morphine
• Oxymorphone (Opana)
  – Dose reduction in renal failure
  – Contraindicated for mod-severe hepatic
  – Twice as strong as Oxycodone
• Hydrocodone
  – Renally eliminated, much safer than morphine
  – About as potent as Oxycodone
• Fentanyl
  – Extremely potent
  – Safe for renal
  – Available as patch, buccal tablet, oralet ("lollipop"), nasal spray, injectable
## ADULT OPIOID EQUIANALGESIC DOSING TABLE

Equivalency of opioid analgesics to 10 mg of parenteral morphine (IV = IM = Subq). Published tables vary regarding equianalgesic dosing. Clinical response should guide dosing for each individual patient. ER = extended-release formulation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral</th>
<th>Oral</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
<td>3-6 hr;</td>
<td>Standard for comparison. Multiple routes of administration available. Use caution in renal insufficiency, elderly. Also available in a once-daily formulation (Avinza N/A at MH).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ER: 8-12 hr</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
<td>3-5 hr</td>
<td>Preferred agent for patients with renal dysfunction. Multiple routes of administration.</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1 mg</td>
<td>10 mg</td>
<td>3-6 hr;</td>
<td>Oral bioavailability of oxymorphone tablets is increased when administered with food, administer 1 hr prior to meals or 2 hrs after meals. When converting to oxycodone, use a 1:2 conversion (10 mg oxymorphone = 20 mg oxycodone).</td>
</tr>
<tr>
<td></td>
<td>N/A at MH</td>
<td></td>
<td>ER: 8-12 hr</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A</td>
<td>20-30 mg</td>
<td>3-4 hr;</td>
<td>Percocet is oxycodone and acetaminophen (APAP). Maximum daily dose of APAP=4000 mg. OxyContin (Oxycodone ER) should be used around-the-clock and not for breakthrough pain. Safe in renal insufficiency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ER: 8-12 hr</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>30 mg</td>
<td>3-4 hr</td>
<td>Oral formulations only in combination with APAP (Vicodin).</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 mg</td>
<td>N/A</td>
<td>0.5-2 hr;</td>
<td>200 mcg oral transmucosal fentanyl (Actiq) → 2 mg IV morphine. Patch takes 12 - 16 hr to see analgesic effect. When patch is removed 50% of drug remains in the system after 17 hours. Drug interaction with MAO inhibitors. Patch is contraindicated in opioid-naive patients or patients with acute or unstable pain. Safe in renal insufficiency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transdermal Patch: 48-72 hr</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Variable</td>
<td>Variable</td>
<td>4-12 hr</td>
<td>May accumulate due to long half-life and result in delayed toxicity. Careful monitoring during titration phase.</td>
</tr>
<tr>
<td>Codeine</td>
<td>120-130 mg</td>
<td>200 mg</td>
<td>4-6 hr</td>
<td>Must be metabolized to be effective; about 10% of patients cannot metabolize. Often combined with APAP.</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>N/A at MH</td>
<td>130 mg</td>
<td>4-6 hr</td>
<td>Darvocet-N is propoxyphene and acetaminophen. Not recommended for chronic use. Can accumulate in renal failure leading to CNS depression &amp; seizures.</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100 mg</td>
<td>300 mg</td>
<td>2-4 hr</td>
<td>Restricted for pain, requires Anesthesia approval. Toxic metabolite causes CNS excitation, (mental status changes, tremors, seizures): Should not be administered for more than 1-2 days. Avoid in elderly or patients with renal or hepatic insufficiency. Drug interaction with MAO inhibitors.</td>
</tr>
</tbody>
</table>
Methadone

- $\mu$ receptor agonist
  - $R$ enantiomer 10X activity
- NMDA antagonist
- 5HT reuptake inhibition ($S$-enantiomer)
- NE reuptake inhibition ($S$-enantiomer)
- Conversions from other opioids can be challenging

**RESPECT IT**
Equianalgesic Dose of Morphine to Methadone

300mg Morphine = 60mg Methadone
302.5mg Morphine = 30mg Methadone
Acetaminophen

- Inhibits central prostaglandin synthesis and elevation of pain threshold
- Some effect on inhibiting cyclooxygenase
- Potentially indirect action of cannabinoid (CB1) receptors
IV vs PO vs PR

• IV acetaminophen has been demonstrated to attain higher serum & CSF levels in patients
• Levels > 15 mcg/mL thought to correlate with analgesia
• With dose limits on PR & PO dosing, very difficult to achieve therapeutic levels
APAP

- Max Dose: 4 grams/day
- Liver disease: 2 grams/day
- Commonly 1 gram IV every 6 hrs x 4 doses
- Then 650 – 975 mg PO every 6 hrs
- **SCHEDULED** not prn
COX Inhibition

• COX-1 – stomach, kidney, thromboxane
• COX-2 – inflammation
• NSAIDs
  – Provide non-specific cyclooxygenase inhibition, some provide different ratios of inhibition
• COX-2 Inhibitor
  – Celecoxib
    • Reduced GIB rates
    • Has not shown increased rate of MI (Rofecoxib, Valdecoxib)
    • 100 – 200 mg qd - bid
Corticosteroids

• Potent suppressors of inflammatory response
  – Inhibit margination and subsequent cell migration to area of injury
• At higher doses, significant side effects
• Thinning of skin, osteoporosis, hypertension, hyperlipidemia, increased bgms, psychosis, HPA axis depression
• Doses > 10 mg prednisone equivalent rarely used to treat RA
5-HT/NE Reuptake Inhibition

- Antidepressants have been shown to be effective in treating neuropathic pain
- TCAs nonselectively inhibit reuptake of 5-HT & NE
  - Amitriptyline – tertiary amine, ACH SE
  - Nortriptyline – secondary amine, decrease SE
- Data lacking for pure SSRIs & pain
- SNRIIs (duloxetine, mirtazapine, venlafaxine, desvenlafaxine)
Topical Anesthetics

- Lidocaine, prilocaine
- Good for localized pain
  - Numbs the area
- Can utilize up to 3 patches of Lidoderm at a time
- On for 12 hrs, off for 12 hrs
Gabapentin

- Structurally related to GABA
- Binds neither GABA-A nor GABA-B
  - Increases GABA
- Has shown efficacy in neuropathic pain
- Mechanism of action is unclear
- Can cause sedation
- Titrate dosage to effect
- 100 mg TID (or 300 mg at HS)
- Recommended dose limit at 3600 mg/day
- Renally eliminated, reduce dose & frequency
Pregabalin

- Mechanism is not understood
- Increases neuronal GABA
- Appears to be more potent than gabapentin
- Initiate at 50 mg TID
- May increase to 100 mg TID
- Renally eliminated, decrease dose 50% for Est CrCl less than 60 mL/min
Muscle Relaxants

- Methocarbamol
- Carbamate derivative of guaifenesin
- Blocks spinal polysynaptic reflexes
- May be non-specific sedative
- Suggested that produced muscle relaxation w/o loss of consciousness
- 500 - 1000 mg 3-4x/day
  - (1500 mg TID max)
Tizanidine

- Mechanism unknown
- Not chemically related to other muscle relaxants
- Enhances efficacy of NSAIDs
- 2 mg every 8 hrs
- Max dose of 36 mg/day
- Reduce in presence of impaired renal ftn
  - Est CrCl less than 25 mL/min
- > 40% - Asthenia, Xerostomia, Somnolence, Dizziness
Baclofen

- Derivative of GABA
- Acts on spinal end of upper motor neurons
- 5 mg TID to start
- Typically 40 – 80 mg/day (10-20 mg 4x/day)
- Quadriplegia & Paraplegia – doses much higher
  - 40 mg 4-5x/day
- Renally eliminated – use with caution
- AEs – Somnolence, confusion, nausea
- Intrathecal – do not abruptly discontinue
- Withdrawal – high fever, altered mental status, exaggerated rebound spasticity, muscle rigidity
Metaxalone

- Mechanism unknown
- General depression of the nervous system
- 800 mg 3-4x/day
- Caution with hepatic dysfunction
- Leukopenia, hemolytic anemia, jaundice
- Renally eliminated, no guidance for renal dysfunction
Chlorzoxazone

• Mechanism not fully understood
• 250 – 750 mg 3-4x/day
• Lower doses recommended w hepatic dysfunction
• Discoloration of urine (yellow/orange)


Carisoprodol

- Metabolite of meprobamate
- Blocks interneuronal activity in spinal cord
- 250 -350 mg 3-4x/day
- No renal adjustments necessary
- Consider adjustments with hepatic failure
- Dizziness, somnolence
Cannabinoids

- Some data to support usage in pain management
- CT Law only allows for treatment for “spinal cord damage causing intractable spasticity”
Multimodal Treatment

• The use of different classes of analgesics and different sites of analgesic administration to provide superior dynamic pain relief with reduced analgesic-related side effects
Safe use of opioids in hospitals

While opioid use is generally safe for most patients, opioid analgesics may be associated with adverse effects, the most serious effect being respiratory...
Sentinel Alert

- Prompted due to increased numbers of opioid induced AEs, such as respiratory depression, death
- Identified lack of knowledge of potencies of different opioids
- Improper prescribing of multiple opioids
- Inadequate monitoring of patients
Guidance list

- Screen pts for respiratory depression risk
- Assess pts previous use and/or abuse, identifying tolerance or naïveté
- Conduct full body skin assessment to ascertain if pt may have patch or pump
- Utilize individualized multimodal treatment plan
- Take extra precautions to pts that are new to opioids
Sentinel Event

- Consult a RPh or pain management specialist when converting opioids
- Avoid rapid dose escalation above routine dose levels in opioid tolerant pts
- Take extra precaution when transferring pts between units, facilities or home, as med effects can peak during transfer or shortly thereafter
- Avoid using opioids to meet an arbitrary pain rating or discharge date
Pasero Opioid Sedation Scale

- Chris Pasero & Margo McCaffrey
- Involves classic signs of opioid induced sedation, grading them
- Based on level of sedation, guides providers to proper course of action
POSS

S = Sleep, easy to arouse
  – Acceptable; no action necessary; may increase opioid dose if needed

1 = Awake and alert
  – Acceptable; no action necessary; may increase opioid dose if needed

2 = Slightly drowsy, easily aroused
  – Acceptable; no action necessary; may increase opioid dose if needed
POSS

• 3 = Frequently drowsy, arousable, drifts off to sleep during conversation
  – 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 25% to 50% or notify provider for orders; consider administering a non-sedating, opioid-sparing medication

• 4 = Somnolent, minimal or no response to verbal and physical stimulation
  – Unacceptable; stop opioid; consider administering naloxone; notify provider; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory
Screening
UDTs

- Random and/or scheduled
- Should be a component of agreement/policy
- Pill counts are a good idea also

<table>
<thead>
<tr>
<th>Risk</th>
<th>Number of Urine Drug Tests per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 or 4</td>
</tr>
<tr>
<td>High</td>
<td>4 or every month, office visit, or every drug refill</td>
</tr>
</tbody>
</table>
UDT Tips & Tricks

• Independent Lab
• Do not dispense Rx without notification from Lab of adequate urine specimen

• In your office
• Turn off water flow from sink
• Toilet water should have coloring agent added
• Pt should disrobe in exam room & put on gown
Positively Negative

- **FALSE POSITIVES**
  - Opioids
    - Dextromethorphan,
      Diphenhydramine,
      fluoroquinolones, poppy
      seeds, quinine, rifampin,
      verapamil
  - THC
    - Dronabinol, NSAIDs, PPIs
      (pantoprazole)
  - Benzos
    - Oxaprozin, sertraline

- **FALSE NEGATIVES**
  - Fentanyl
  - Oxycodone
  - Hydrocodone
  - Tramadol
  - Methadone

- Expanded Assays available (more $$$)
Welcome to CPMRS, Please login to Continue

Username*

Password*

Forgot/Reset Password?

Login

Not a member? Register

For registration questions, please contact the Administrator at: (860) 713-6073 or DCP Prescriptions@ct.gov

Please review and ensure your profile information is correct. After you login, click 'My Account' to review and update your profile.
<table>
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<tr>
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<tr>
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<tr>
<td>Tramadol</td>
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US Department of Health and Human Services, Center for Disease Control

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Active Cumulative Morphine Equivalent 528.26
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<th>Prescriber</th>
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<td>3852</td>
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Median Price Per Milligram:
Opioids in Tablet Form

Price in Dollars

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<tr>
<td>Buprenorphine</td>
<td>1.88</td>
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<tr>
<td>Oxymorphone</td>
<td>1.38</td>
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<tr>
<td>Methadone</td>
<td>1.00</td>
</tr>
<tr>
<td>Hydrocodone</td>
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</tr>
<tr>
<td>IR Oxycodone</td>
<td>1.00</td>
</tr>
<tr>
<td>ER Oxycodone</td>
<td>1.00</td>
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<tr>
<td>Morphine</td>
<td>0.53</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.1</td>
</tr>
</tbody>
</table>

- **Median Price Per Milligram**
  - **Buprenorphine**: 5.0
  - **Hydrocodone**: 6.5
  - **Hydromorphone**: 4.5
  - **Methadone**: 3.5
  - **Oxymorphone**: 3.0
  - **Oxycodone IR**: 1.5
  - **Oxycodone ER**: 1.0
  - **Morphine**: 0.5
  - **Tapentadol**: 0.1
  - **Tramadol**: 0.1
References

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