Opioids
Pharmacologic principals important in primary care

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Opiates
• Present in opium from seedpod of Papaver somniferum
• Morphine, codeine

Opioids
• Are manufactured
• Semisynthetic: derived from an opiate
• Fully Synthetic: synthesized to have function similar to natural opiates

Opiates & Opioids

Mu & Kappa Receptors
• Found in many sites: pre- and post-synapse in periphery, spinal cord dorsal horn, brain stem, midbrain, thalamus, cortex...
• Receptor subtypes and genetic pleomorphism
  – Not all patients respond to the same opioid in the same way
  – Not all pain responds to same opioid in the same way
  – Incomplete cross-tolerance between opioids
• Mu agonists: analgesia, decrease resp-pulse-BP, sedation, euphoria, N/V/C, miosis, mood/anxiety
• Kappa agonists: same except less analgesia & VS depression, different euphoria, antagonist at mu, high dose leads to dysphoria … even psychosis

Activation of Mu Receptors
• Inhibit activation of nociceptors
• Inhibit cells that release inflammatory mediators
• Inhibit terminals of C-fibers in the spinal cord
• Prevent ascending transmission of pain signal
• Turn on descending inhibitory systems

Function at Receptors: Full Agonists

<table>
<thead>
<tr>
<th>Mu receptor</th>
<th>Full agonist binding ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>activates the mu receptor</td>
</tr>
<tr>
<td>2</td>
<td>is highly reinforcing</td>
</tr>
<tr>
<td>3</td>
<td>is the most abused opioid type</td>
</tr>
<tr>
<td>4</td>
<td>includes heroin, methadone, &amp; others</td>
</tr>
</tbody>
</table>
**Function at Receptors: Partial Agonists**

**Mu receptor**
- Partial agonist binding ...
- activates the receptor at lower levels
- is relatively less reinforcing
- includes buprenorphine
- unusual mu agonists: tramadol and tapentadol

**Receptor Affinity**
- **AFFINITY** is the binding strength with which a drug physically binds to a receptor
  - Buprenorphine's affinity is very strong and it will displace full agonists like heroin and methadone
  - Note receptor binding strength (strong or weak), is **NOT** the same as receptor activation (agonist or antagonist)

**Full Agonist**
- Bup affinity is higher
- Therefore Full Agonist is displaced

**Receptor Dissociation**
- **DISSOCIATION** is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine's dissociation is slow
  - Therefore Buprenorphine stays on the receptor a long time and blocks heroin or methadone from binding

**Perfect Fit - Maximum Opioid Effect**
- Empty Receptor
- Opioid
- Opioid receptor unsatisfied -- Withdrawal
- As someone becomes “tolerant” to opioids their opioid receptors become less sensitive. More opioids are then required to produce the same effect. Opioids can produce a strong but shortlived euphoria, but when opioids activate a small number of opioid receptors, the body feels pain. This is withdrawal.

**Empty Receptor**
- Opioid Receptor in the brain
- Withrawal Pain

**Perfect Fit - Maximum Opioid Effect**
- Empty Receptor
- Opioid
- Strong Euphoric Opioid Effect

**Withdrawal Pain**
- Opioid Receptor in the brain

**Intrinsic Activity: Full Agonist (Morphine), Partial Agonist (Buprenorphine), Antagonist (Naloxone)**

- Intrinsic Activity:
  - Full Agonist (Morphine)
  - Partial Agonist (Buprenorphine)
  - Antagonist (Naloxone)
Opioids replaced and blocked by buprenorphine. Buprenorphine competes with the full agonist opioid for the receptor. Since buprenorphine has a higher affinity (stronger binding ability) it expels existing opioids and blocks others from attaching. As a partial agonist, the buprenorphine has a limited opioid effect, enough to stop withdrawal but not enough to cause intense euphoria.

Imperfect Fit – Limited Euphoric Opioid Effect

Over time (24-72 hours) buprenorphine dissipates, but still creates a limited opioid effect (enough to prevent withdrawal) and continues to block other opioids from attaching to the opioid receptors.

Buprenorphine Still Blocks Opioids as It Dissipates

Opioid Responsiveness
- Degree of pain relief with maximum opioid dose in the absence of side effects i.e. sedation
- Not all pain is opioid responsive
  - Varies among different types of pain
  - Varies among individuals
- Emerging research – allelic variants in the genes involving opioid and nonopioid systems, drug-metabolizing enzymes and transporters

Opioids and euphoria: the dopamine surge

Activation of the reward pathway by addictive drugs

Tolerance
- Differential tolerance:
  - Rapid to euphoria, depressed VS, sedation
  - Slow partial to analgesia
  - None to constipation and miosis
- Loss of tolerance is rapid:
  - Gaps in treatment require re-set to low dose
  - Risks escalate with erratic adherence

Physical dependence
- Normal brain effect
- Daily use if long half life or ER/LA opioids
- BID or TID use of any opioids
- 2-3 weeks = some physical dependence
- More dependence = higher dose, more potent opioids, longer duration
**Hyperalgesia: Can Opioids Worsen Pain?**

- In animal studies, chronic opioid administration resulted in increased pain sensitivity versus placebo.
- Patients on methadone maintenance show enhanced pain sensitivity versus controls.
- Does release of peptides, “antiopioids,” increase levels of dynorphin?
- Does neuroadaptation to chronic opioid administration occur?

**Opioid-Induced Hyperalgesia**

**Withdrawal**

- If physical dependence is established, abrupt cessation OR too rapid taper produces withdrawal:
  - Increased pain (musculoskeletal / cranial / abdominal)
  - Insomnia, anxiety, hyper-autonomic, mydriasis, rhinorrhea, N/V/D, piloerection, dysphoria

**“Complex Physical Dependence”**

Opioid Dependence vs Addiction: A Distinction Without a Difference?

**Opioid Addiction**

(Substance Use Disorder Moderate/Severe)

- The **intermittent inconsistent unpredictable repetitive loss of control** over the use of a euphoria producing drug (EPD) resulting in repeated adverse consequences, with craving for the EPD when abstinent.
- EPD’s:
  - **Opioids**
  - Stimulants
  - Sedative-hypnotics
  - Cannabinoids
  - Other (PCP, ketamine, etc)

**Chemical coping**

- Use of the opioid for mood or anxiety effects rather than for it’s intended analgesic effect – “misuse”
- Thought to be more likely in highly stressed, poorly coping individuals or family systems
- Not effective long-term
- Explore alternative strategies (medication and/or behavioral) for symptoms being self-medicated (sleep, “stress”, energy, dysthymia)
- Counseling (CBT/DBT/Trauma Processing)
What does this mean for primary care practice?

Efficacy of opioids in pain

- Acute pain syndromes: good data supporting strong efficacy
- Malignant pain syndromes: good data supporting strong efficacy
- Chronic pain syndromes: weak data supporting limited efficacy

Opioid Efficacy in Chronic Pain

- Most literature surveys & uncontrolled case series
- RCTs are short duration <4 months with small sample sizes <300 pts
- Mostly pharmaceutical company sponsored
- Modest pain relief
- Modest to no functional improvement
- Short term benefit at most
- Risks are much greater than originally thought

Opioid Efficacy in pain: Exploit Synergism with Adjuncts

- NSAIDs
  - Kolesnikov Y; Wilson R; Pasternak G; Anes analges. 2003
  - Jimenez-Andrade JM et al. Pharmacol Biochem Behav. 2003
- Antidepressants
  - Luccarini P; et al. Anesthesiology. 2004
- Antiepileptics
  - Turan A et al. Anesthesiology. 2004
  - Some emerging concern re: gabapentin
- Avoid concomitant benzodiazepines or other controlled drugs – especially carisoprodol

Opioids and patient risk

- Risky brains:
  - Poor adherence, psychiatric DX, impulsivity, SUD mild (“partiers”)
- High risk brains:
  - SUD moderate or severe, h/o OD, h/o diversion
- High Risk Brains + High Risk Drugs = High Risk Behaviors
  - SUD patients + chronic opioids = high risk of problem patient behaviors and patient / family / community / Rxer harm.

Opioids: the concept of limits

- Past: the brain has an unlimited capacity to produce tolerance
- Current:
  - Max opioid dose (≥200MED) Balantyne, NEJM 2003
  - Not all pain is opioid responsive (ORP)
  - ORP responds rapidly/chronically to low doses
  - MEQ and clinical “time outs”
    - Watershed doses: increased risk with ? benefit
    - CDC 50 MEQ / OH 80 / Wash 120
    - “TO” = Stop / Reassess / Proceed with caution
### Opioid Choice

#### Short-acting
- Tramadol
- Hydrocodone
- Hydromorphone
- Morphine
- Oxycodone
- Oxymorphone
- Tapentadol
- Etc. etc. etc.

#### Long-acting
- Slow-release delivery system
  - Transdermal fentanyl
  - Extended release morphine
  - Extended release oxycodone
  - Etc. etc. etc.
- Intrinsic pharmokinetic property
  - Methadone
  - Buprenorphine
  - Levorphanol

### Opioid Rotation
- Switch to another opioid as means of restoring analgesic efficacy or limiting adverse effects
- Based on large intra-individual variation in response to different opioids
- Different variants of mu-opioid receptors
- Based on surveys and anecdotal evidence
- Use equianalgesic table to calculate dose of new opioid
  - Determine clinically relevant starting point
  - Decrease equianalgesic dose by 25-50%

### Opioid Conversion Chart

<table>
<thead>
<tr>
<th>ANALGESIC ORAL</th>
<th>PARENTERAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
</tr>
<tr>
<td>Methadone</td>
<td>2-3:1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100-200 mcg [TM]</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>65-130</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100-150</td>
</tr>
</tbody>
</table>

*Inturrisi CE. The Clinical J of Pain. 2002*  
*Morphine/Methadone Conversion Guidelines*

<table>
<thead>
<tr>
<th>Morphine (mg)</th>
<th>Equivalent Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>2:3:1 (2-3 mg morphine:1 mg methadone)</td>
</tr>
<tr>
<td>31-99</td>
<td>4:1</td>
</tr>
<tr>
<td>100-299</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499</td>
<td>12:1</td>
</tr>
<tr>
<td>500-999</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>20:1</td>
</tr>
</tbody>
</table>

*Frisch and Cleveland. 2003*  

### Opioid Pharmacology Summary
- Misconceptions are common
- Good short term medications
- Dose response relationships – acute and malignant
- Chronic pain often non-responsive
- Tolerance (differential), dependence, complex physical dependence, chemical coping, hyperalgesia, abuse and addiction
- Not safe for SUD patients – especially long term
- Tapers / detoxes (coming soon to a lecture near you)
- There is no low abuse potential opioid or formulation!