Opioids

Pharmacologic principals important in primary care

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Opiates & Opioids

Opiates

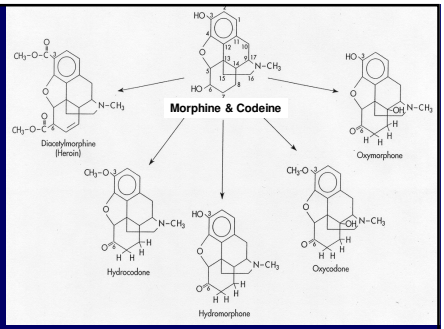
- Present in opium from seedpod of *Papaver somniferum*
- Morphine, codeine

Opioids

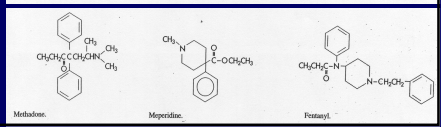
- Are manufactured
- Semisynthetic: derived from an opiate
- Fully Synthetic: synthesized to have function similar to natural opiates

Opioids

Natural Opiates & Semisynthetic



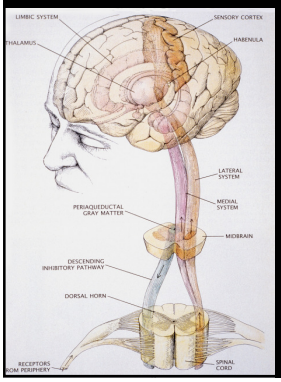
Synthetic



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 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

Mu receptor	Full agonist binding …

❶ activates the mu receptor

❷ is highly reinforcing

❸ is the most abused opioid type

❹ includes heroin, methadone, & others

Function at Receptors: Partial Agonists

Mu receptor — **Partial agonist binding …**

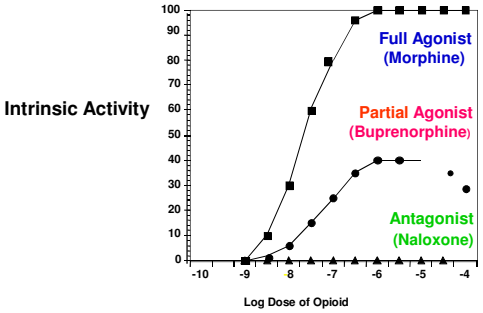
❶ activates the receptor at lower levels

❷ is relatively less reinforcing

❸ includes buprenorphine

❹ unusual mu agonists: tramadol and tapentadol

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



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)

Mu Receptor — **Full Agonist Bup affinity is higher**

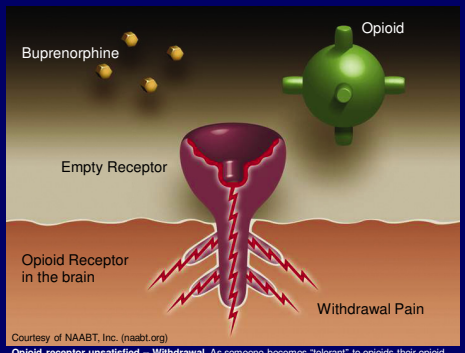
Therefore Full Agonist is displaced

Receptor Dissociation

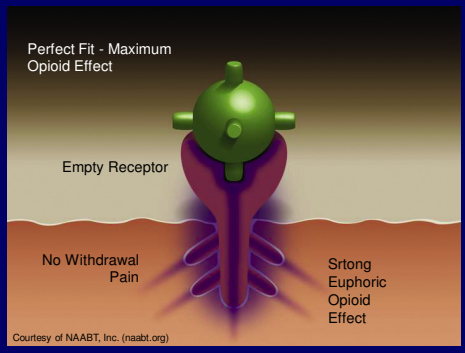
- **DISSOCIATION** is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine's dissociation is slow
  - Therefore Buprenorphine stays on the receptor a long time and blocks heroin or methadone from binding

Mu Receptor — **Bup dissociation is slow**

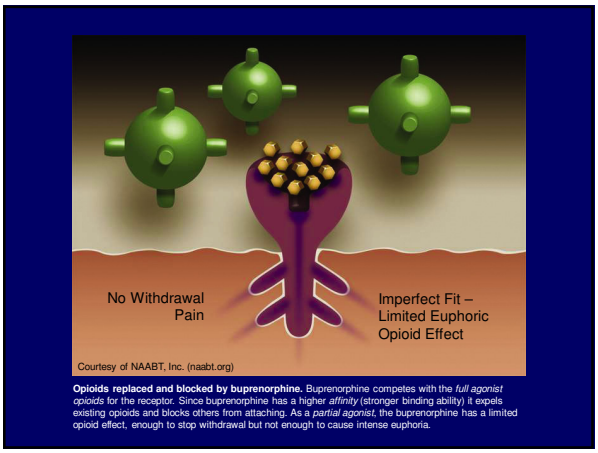
Therefore Full Agonists can't bind



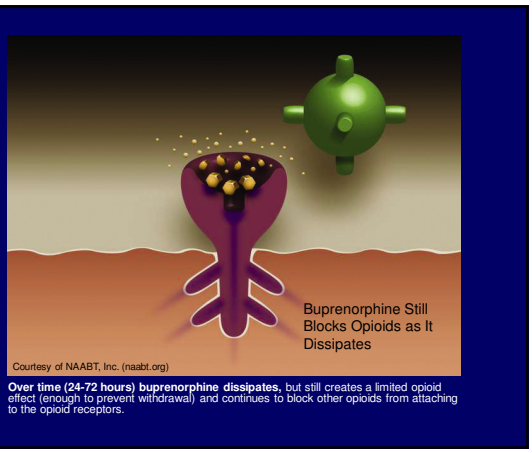
Opioid receptor unsatisfied – Withdrawal. As someone becomes "tolerant" to opioids their opioid receptors become less sensitive. More opioids are then required to produce the same effect. Once "physically dependent" the body can no longer manufacture enough natural opioids to keep up with this increased demand. Whenever there is an insufficient amount of opioid receptors activated, the body feels pain. This is withdrawal.



Opioid receptor satisfied with a full-agonist opioid. The strong opioid effect of heroin and painkillers stops the withdrawal for a period of time (4-24 hours). Initially, euphoric effects can be felt. However, after prolonged use, tolerance and physical dependence can develop. Now, instead of producing a euphoric effect, the opioids are primarily just preventing withdrawal symptoms.



Opioids replaced and blocked by buprenorphine. Buprenorphine competes with the *full agonist opioids* 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.



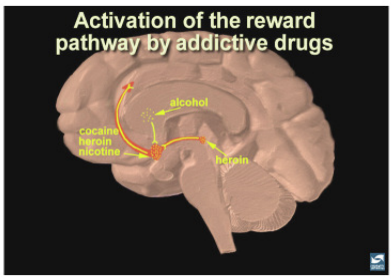
Over time (24-72 hours) buprenorphine dissipates, but still creates a limited opioid effect (enough to prevent withdrawal) and continues to block other opioids from attaching to the opioid receptors.

Opioid Responsiveness

- Degree of pain relief with maximum opioid dose in the absence of side effects ie. 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

Smith HS. Pain Physician 2008

Opioids and euphoria: the dopamine surge



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

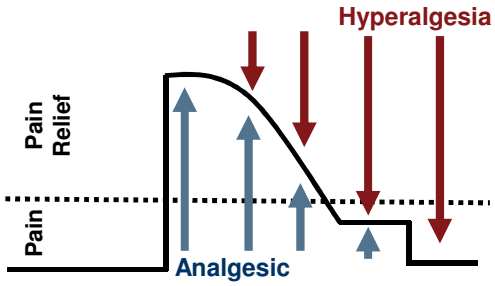
Physical dependence

- 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?
Ballantyne J, Sullivan M, Kolodny A, *Arch Intern Med*, 2012

"***Dependence on opioid pain treatment is not, as we once believed, easily reversible***; it is a **complex physical and psychological state** that may require therapy similar to addiction treatment, consisting of structure, monitoring, and counseling, and possibly continued prescription of opioid agonists …

Whether or not it is called addiction, complex persistent opioid dependence is a serious consequence of long term pain treatment that requires consideration when deciding whether to embark on long term opioid pain therapy as well as during the course of such therapy."

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 dta 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

Balantyne JC, Mao J. NEJM 2003 , Chou et al. JAMA 2009
Martell BA et al. Ann Intern Med 2007; Eisenberg E et al. JAMA. 2005

Opioid Efficacy in pain: Exploit Synergism with Adjuncts

- NSAIDs
  - Perez-Urizar J, et al. Pharmacol, biochem, behavior. 2003
  - 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	Long-acting
• Tramadol • Hydrocodone • Hydromorphone • Morphine • Oxycodone • Oxymorphone • Tapentadol • Etc. etc. etc.	• Slow-release delivery system – Transdermal fentanyl – Extended release morphine – Extended release oxycodone – Etc. etc. etc. • Intrinsic pharmokinetic property – Methadone – Buprenorphine – Levorphanol

Opioid Choice

- Strong vs weak (ceiling effect)
- Duration and onset of action
- Patient's prior experience
  - *Mu* polymorphisms – differences in individual patient's opioid responsiveness
- Route of administration
- Side effects and Cost
- "What is the lowest abuse potential opioid?

(There are **NO** abuse resistant opioids or opioid formulations!!)

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%***

Inturrisi CE. The Clinical J of Pain. 2002

Opioid Conversion Chart

ANALGESIC	ORAL	PARENTERAL
Morphine	30	10
Codeine	200	120
Hydromorphone	7.5	2
Oxycodone	20	-
Hydrocodone	30	-
Methadone	**20**	**10**
Fentanyl	100-200 mcg [TM] 50 mcg [TD]	100 mcg
Meperidine	300	100
Propoxyphene	65-130	-
Tramadol	100-150	-

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Morphine/Methadone Conversion Guidelines

Morphine (mg)

<30	**=**	**2-3:1** (2-3mg morphine:1 mg methadone)
31-99	**=**	**4:1**
100-299	**=**	**8:1**
300-499	**=**	**12:1**
500-999	**=**	**15:1**
>1000	**=**	**20:1**

Finsch and Cleeland. 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!