

AAP BRS Podcast: Opioid Pharmacology

Opioid Mechanism of Action: bind to inhibitory G-protein-coupled receptors

Receptor	Effect
Mu1	Analgesia
Mu2	Respiratory depression, sedation, euphoria, dependence, emesis
Delta	Analgesia, spinal analgesia
Kappa	Analgesia, sedation, respiratory depression, euphoria

Natural	
Morphine	High mu, low kappa and delta agonist
Codeine	Weak mu and delta agonist
Semi-Synthetic	
Hydromorphone, hydrocodone, oxycodone, oxymorphone	Mu agonist
Buprenorphine	Partial mu agonist and full kappa antagonist
Synthetic	
Fentanyl	High mu, low kappa, no delta sensitivity
Tramadol	Weak mu agonist, weak NE/5HT reuptake inhibitor
Methadone	High mu, high delta, low kappa selectivity, NE/5HT reuptake inhibitor, NMBA antagonist

Chemical Classes of Opioids: *Low risk of cross-reactivity between classes*

- **Phenanthrenes:** codeine, hydromorphone, levorphanol, morphine, oxycodone, hydrocodone, and pentazocine.
- **Phenylpiperidine:** meperidine and fentanyl.
- **Phenylheptane:** methadone and propoxyphene.

Opioid Chemical Characteristics

- **pKa:** pH at which the ionized and unionized forms exist in equal concentrations.
 - Opioids are weak bases (pH 6.5-9)
 - Poorly absorbed in acidic environment of stomach and rapidly absorbed in alkaline small intestine → low bioavailability
- **Octanol/water partition coefficient:** indicates lipid solubility
 - Increased coefficient = more lipophilic = less spread = faster onset of action.
 - Fentanyl has the highest coefficient and oxycodone has the lowest

Opioid Conversations

- **DOMED = daily oral morphine equivalent dose** (ideally less than 50; doses over 50 daily MME increase risk of OD >2x)
- Oral morphine has a conversion factor of 1.5
- Hydrocodone has a conversion factor of 1
- IV to PO:
 - Morphine: conversion factor of 3
 - Hydromorphone: conversion factor of 5

Excellent conversion calculators available online or on mobile apps!

Key Opioid Side Effects

- **Respiratory depression:** due to decreased PCO₂ sensitivity in the respiratory centers of brainstem.
- **Depressed cough reflex:** codeine historically used as cough suppressant
- **Constipation:** activation of opioid receptors throughout enteric system → inhibition of gastric emptying, increased sphincter tone, and peristalsis.
 - Treatment: Laxatives, opioid-receptor antagonists w/ limited absorption (ex. oral prolonged-release naloxone), or opioid receptor antagonists that do not penetrate the BBB (ex. methylnaltrexone)

Opioid-Induced Hyperalgesia (OIH): long-term use of opioids causes hyperalgesia or allodynia

- Pathology: neuroplastic changes in PNS and CNS causing nociceptive sensitization
- New, more diffuse, unrelated, or worsened pain compared to their original pain in the setting of dose escalation.

Opioid Overdose

- Often seen following drug holidays or those who have been tapered off medications and subsequently restart previous drug doses.
- **Treatment: Naloxone** (opioid antagonist)
 - Caution: may put patient in opioid withdrawal

Opioid Withdrawal

- Symptoms: chills, agitation, insomnia, nausea, vomiting, diarrhea, abdominal pain, muscle aches, piloerection
- Treatment of withdrawal (*symptomatic*): loperamide for diarrhea, promethazine for nausea/vomiting, ibuprofen for pain, clonidine for hypertension.

Opioid Weaning

- **Methadone:** full mu agonist
 - Tends to be used for severe dependence
- **Buprenorphine:** partial mu agonist and full kappa antagonist
 - Advantage: less sedating and less respiratory depression
 - Ceiling effect: after a certain point, taking more will not increase the effects of the drug