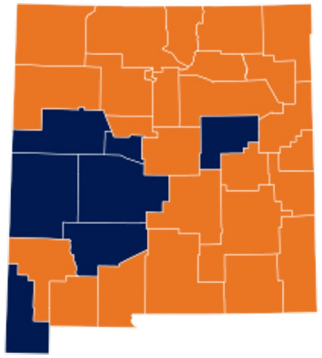
Opioid Remediation Collaborative (ORC)

of New Mexico



7 COUNTY STRATEGIES

orcnm.com

Pharmacology of Opioids

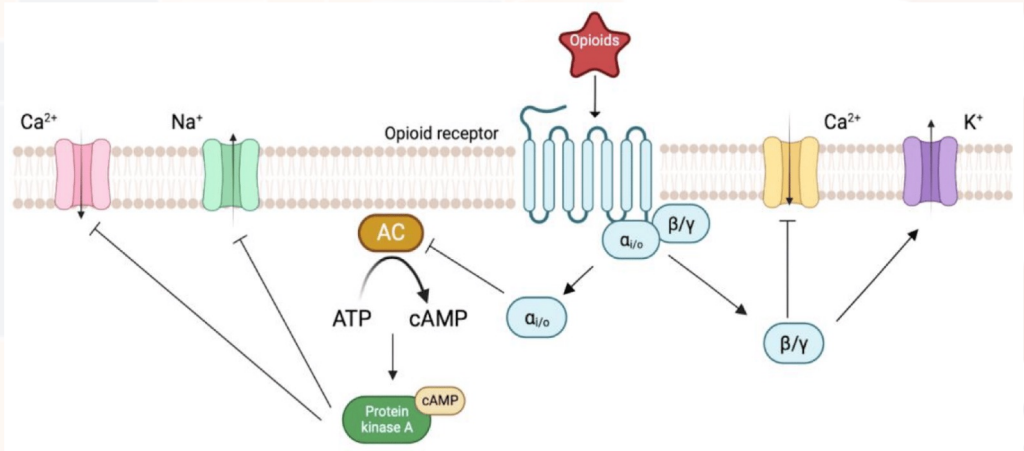
Disclosures

I I have no conflicts of interest to disclose.

Objectives

- Discuss the various classifications of opioids and their clinical implications.
- Discuss the metabolism, unique pharmacokinetics and pharmacodynamics of specific commonly prescribed opioids.
- Discuss the indications, contraindications and adverse effects of opioid therapy.

Definitions



- Opiates – naturally occurring derived from the opium poppy
- Opioid – synthetic or semisynthetic compounds created in the lab.
- All exert their clinical effect on the Mu receptors.
- Generally, ”opioid” refers to both opiates and opioids.

Classification of opioids

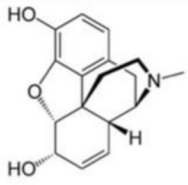
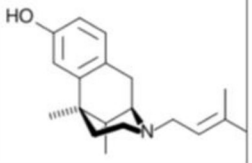
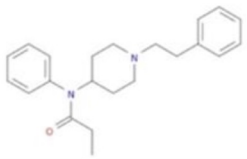
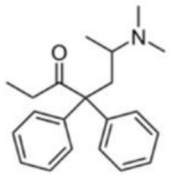
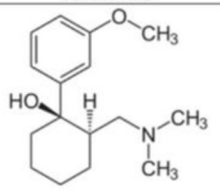
- Naturally occurring vs synthetic/semi-synthetic
- Chemical classification - specifically related to ring structures
- Action at the receptors:
  - intrinsic activity – potency
  - receptor binding
  - receptor dissociation
- Metabolism and drug interactions

Natural vs Synthetic vs Semi-synthetic

Table 12.1. Types of Opioid Drugs

	NATURAL	SEMISYNTHETIC	SYNTHETIC
Source	Naturally occurring	Derived from natural opioids	Synthesized independently
Chemical Structure	Typical	Similar	Dissimilar
Examples	Morphine Codeine	Hydromorphone Oxymorphone Hydrocodone Oxycodone Heroin	Methadone Fentanyl Meperidine Tramadol

Chemical Classification

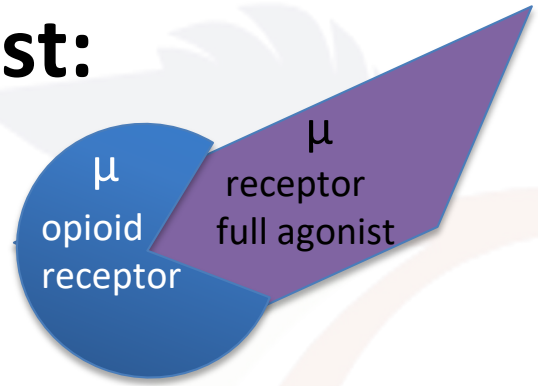
PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanil Sufentanil **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil	Methadone Propoxyphene	Tapentadol Tramadol

Fudin, Jeffrey & Levasseur, Deborah & Passik, Steven & Kirsh, Kenneth & Coleman, John. (2003). Chronic Pain Management with Opioids in Patients with Past or Current Substance Abuse Problems. Journal of Pharmacy Practice. 16. 10.1177/0897190003258507

Action at the Mu Receptor

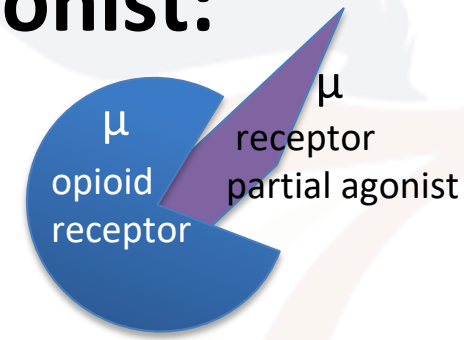
- Describes intrinsic activity and potency
  - Full Agonist
  - Partial Agonist
  - Antagonist
- Receptor Binding/Affinity
- Opioid-Receptor Dissociation

Full opioid agonist:



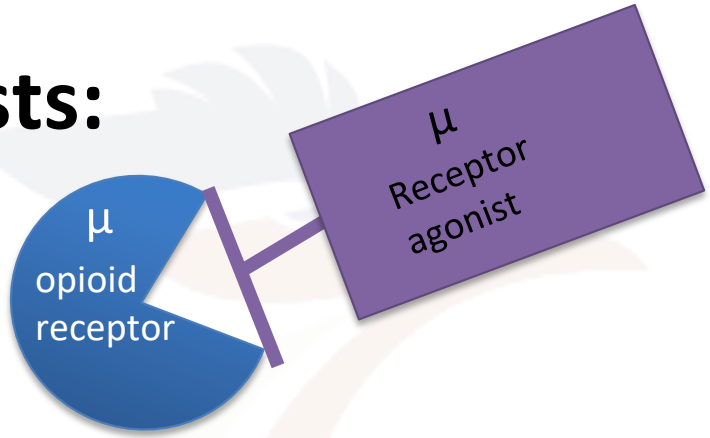
- Full agonist binding activates the μ opioid receptor
- Additive effect when combined with other full agonists
- Is highly reinforcing and has higher potential for abuse
- Abrupt discontinuation will result in withdrawal
- Hydrocodone, hydromorphone, morphine, heroin, methadone

Partial opioid agonist:

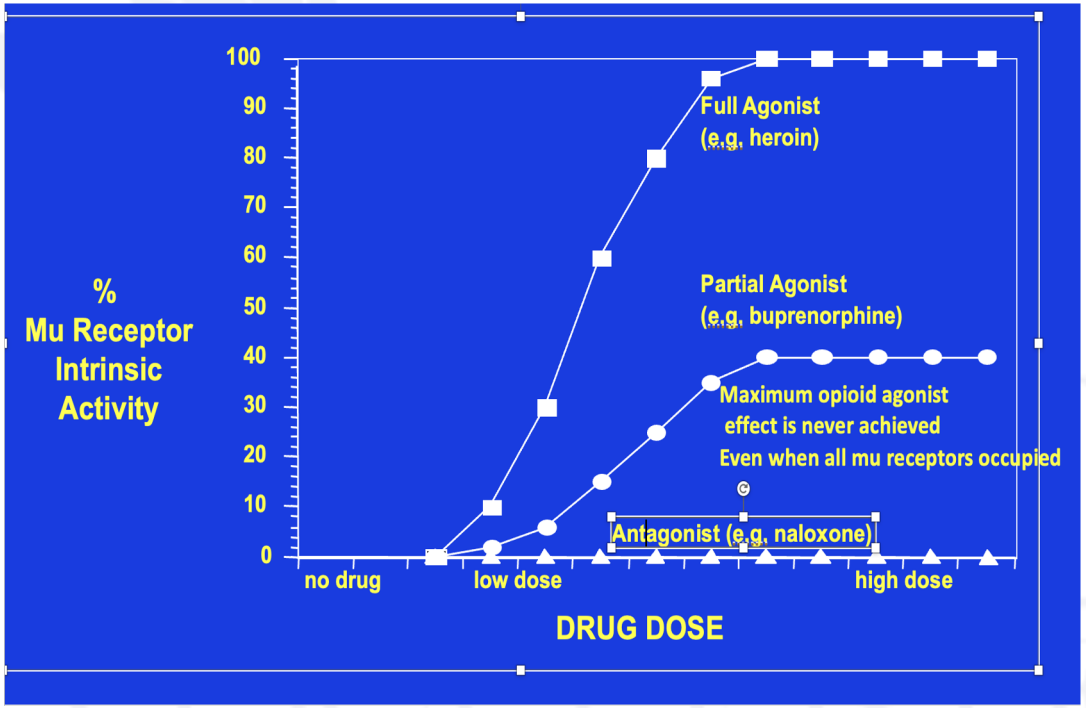


- Partial agonist binding activates the μ opioid receptor – less intrinsic activity
- Is less reinforcing than full agonists (lower risk for abuse)
- Abrupt discontinuation will result in withdrawal
- Example is Buprenorphine

Opioid antagonists:



- Antagonist binding to the μ opioid receptor occupies without activating- no intrinsic activity
- Is not reinforcing
- Blocks opioid agonist binding
- Examples are naloxone, naltrexone, nalmefene



Pharmacology of Opioids

Potency

- Doesn’t equate to intrinsic activity.
- Refers to drug concentration needed to achieve effect.
- It also can relate to receptor affinity.

CDC OPIOID CONVERSION GUIDE

Drug Name	Morphine Ratio
CODEINE	0.15
FENTANYL TRANSDERMAL (in mcg/hr)	2.4
HYDROCODONE	1
HYDROMORPHONE	5
METHADONE	4.7
MORPHINE	1
OXYCODONE	1.5
OXYMORPHONE	3
TAPENTADOL	0.4
TRAMADOL	0.2

Source: CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

Affinity for the receptor

- Affinity is the readiness to bind to the receptor.
- With low intrinsic activity but high affinity, the opioid can be more potent.
- High affinity opioids will displace lower affinity opioids.
- If a high affinity opioid has lower intrinsic activity this can lead to withdrawal.

Opioid affinities for mu receptor

Opioids	Range of Ki Value
Levorphanol	0.19 to .23[32]
Buprenorphine	0.21 to 1.5
Naltrexone	0.4 to 0.6 (antagonist effects)[20]
Fentanyl	0.7 to 1.9
Methadone	0.72 to 5.6
Naloxone	1 to 3 (antagonist effects)[20]
Morphine	1.02 to 4
Pentazocine	3.9 to 6.9
Codeine	65 to 135

Fudin, J, Opioid Agonist, Partial Agonist, Antagonists: Oh My, Pharmacy Times, Jan 6, 2018

Opioid Choice – Old thinking

- Duration and onset of action
- "Rate hypothesis" - fast on, fast off – most rewarding – addicting
- Short-acting opioids increase risk of opioid-withdrawal mediated pain
- Patient's prior experience
- Mu polymorphisms – differences in opioid responsiveness
- **Spoiler: Currently there are NO abuse resistant opioids or opioid formulations!!**

Specific opioids

- Codeine
  - ceiling effect at 60mg per dose
  - converts to morphine by liver
  - very weak analgesia effect
  - 6-10% of Caucasians lack enzyme CYP 2D6 and have diminished ability to convert codeine to morphine
  - smaller percent are rapid metabolizers and reach higher levels of morphine quicker.
  - drugs such as bupropion, celecoxib, cimetidine, cocaine inhibit CYP 2D6
  - lower doses cause more nausea than higher doses
  - don't use in severe liver or renal disease.

Shorter D and Kosten, T, The Pharmacology of Opioids, Chapter 11, ASAM Principles of Addiction Medicine, 6th Edition, 2019, pp136-149

Specific opioids

- Hydrocodone
  - 5-10 mg q 4-6 hrs.
  - not available without acetaminophen or ibuprofen (max doses limited by additives)
  - most commonly used/abused opioid
  - hydrocodone weak activity, metabolizes by CYP 2D6 to hydromorphone which is active.
  - deficiency of CYP 2D6 like codeine will render less effective.

Specific opioids

- Oxycodone
  - schedule II drug
  - activity at multiple receptors
  - starting @ 5mg q 6hrs
  - ½ life 2.5 – 3 hrs
  - not a prodrug – oxycodone is active, but does metabolize to oxymorphone (CYP 26D) which is also active
  - use with caution in liver and renal disease.

Specific opioids

- Hydromorphone
  - schedule II semi-synthetic
  - 2mg q 6hrs starting dose
  - 7-11 times the potency of morphine
  - metabolized by the liver to hydromorphone 3 glucuronide which has no analgesic activity and can cause hyperalgesia, myoclonus, and possibly seizures.

Specific opioids

- Tramadol
  - atypical opioid
  - metabolized by CYP 2D6 to a metabolite with 6 times the affinity for the Mu receptor as the parent compound
  - racemic mixture of two enantiomers
    1. one form is Mu agonist + serotonin reuptake inhibitor
    2. the other is NE reuptake inhibitor.
  - toxicity – excitation and seizures.

Specific opioids

- Morphine
  - IR – onset of action in 30 min
  - SR – onset of action in 90 min
  - morphine has 2 metabolites
    - morphine 6 glucuronide (additional analgesic effect, can accumulate with renal failure)
    - morphine 3 glucuronide (hyperalgesia)
  - more apt than others to cause histamine release
  - venous pooling – orthostatic hypotension
  - spasm of sphincter of Oddi
  - increased incidence of urinary retention
  - high dose >100mg per day can show hydromorphone metabolite in urine.

Indications for Opioid therapy in pain patients

- Moderate to severe pain that has failed to respond to indicated non-opioid and non-drug interventions
- Potential benefits will outweigh the risks
- **Pain has significant impact on function and on quality of life**
- Patient has been fully informed and consents to therapy
- Clear and measurable goals are established
- **Patient agreeable to…**
  - **take opioid as prescribed (e.g. no dose escalation)**
  - **close monitoring (e.g. pill counts, urine drug testing)**

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

Contraindications to opioid therapy

- Severe respiratory instability
- Acute psychiatric instability – uncontrolled suicidal risk
- Active Substance Use Disorder not in remission and not in treatment
- True allergy to opioids
- Qtc > 500 msec for methadone
- Active diversion
- Serious adverse events to prior trials.

Adverse effects of opioids

- Sedation, mental clouding, euphoria, rebound headaches
- Sleep disturbance, sleep apnea worsened or even caused by opioids
- Respiratory depression, bronchoconstrction, orthostasis, bradycardia
- Qtc interval prolongation with methadone
- Constipation, nausea, biliary spasm
- Urinary retention
- Decreased testosterone, fsh, lh, estrogen.
- Altered Hypothalmic-pituitary-adrenal axis
- Osteopenia and osteoporosis
- Dental decay
- Immunosuppressive effects