The Pharmacology of Opioids: Risks, Side Effects, and Benefits

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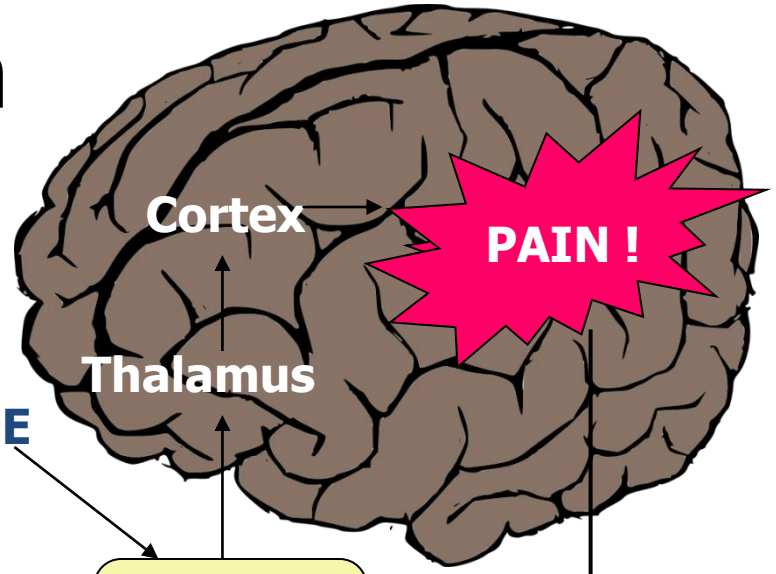
Objectives

- Discuss differences in the pharmacology of commonly prescribed opioids that contribute to pain control, misuse, and risk.

Pain Pathway: Nociception



Glutamate, 5-HT, substance P, ACh, NE

Release of Neurotransmitters (Prostaglandins, bradykinin, substance P, 5-HT, histamine)

Action Potential

A Delta

C fibers

Na^+

Spinal cord

- ENDOGENOUS OPIOIDS RELEASED
- SEROTONIN & NOREPINEPHRINE REUPTAKE INHIBITED
- DECREASED PAIN PERCEPTION

INJURY

TRANSDUCTION **TRANSMISSION** **PERCEPTION** **MODULATION**

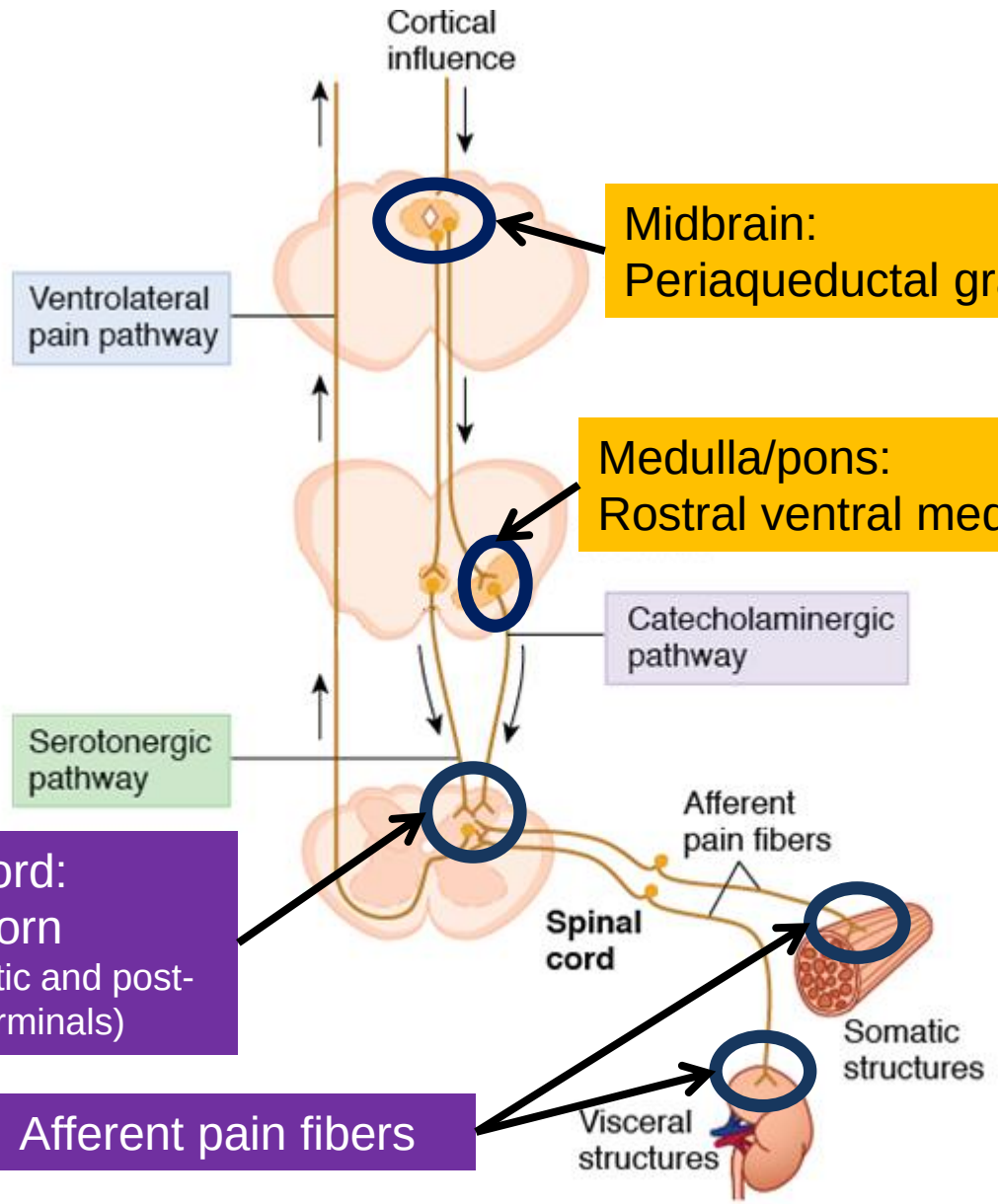
Descending pathway

Ascending pathway

5-HT: serotonin; Ach: acetylcholine; NE: norepinephrine

Adapted from Simpson MH. Treating Pain in the Hospitalized Patient. Powerpoint presentation.

Opioid Receptor Locations in Pain



Activates descending pathway

Inhibits ascending pathway

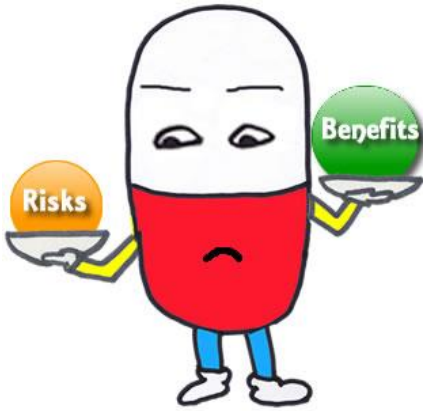
Opioids: Potent Analgesics

- Majority of analgesia due to agonism at mu receptor
  - Inhibition of ascending pain pathway (periphery and pre-synaptic/post-synaptic dorsal horn)
  - Activation of descending pain pathway

- Specific opioids with additional methods of analgesia/benefit
  - Inhibition of serotonin and norepinephrine reuptake
    - Ex. Tramadol, methadone
  - Antagonism of N-methyl-D-aspartate (NMDA) receptors may decrease neuropathic pain and prevent development of tolerance
    - Ex. Methadone

Clinical Benefits of Opioids

- Acute pain: Less pain perception and allow for healing
- Chronic pain: Less pain perception and ability to function!



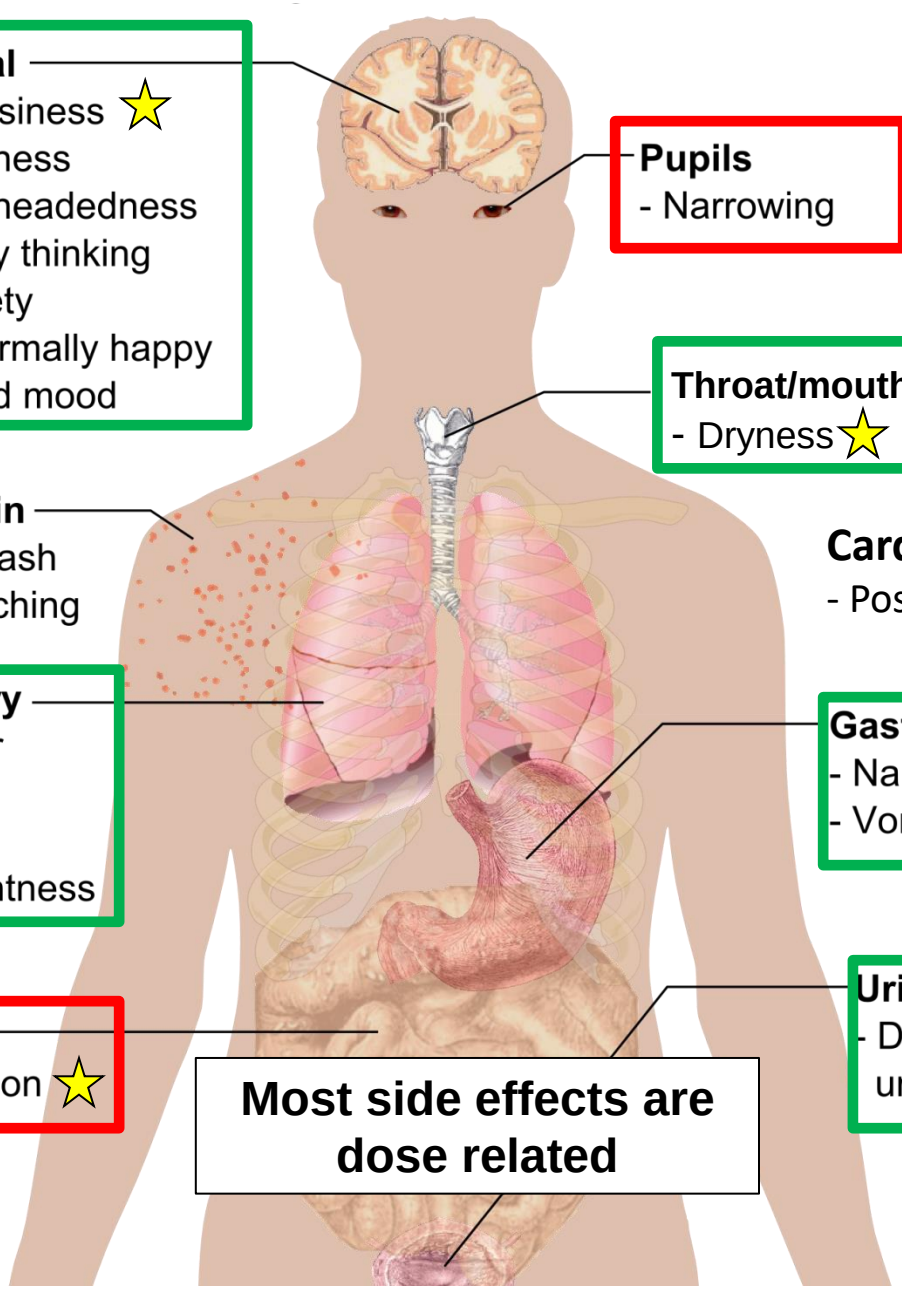
Opioids: Mechanism of Action

- Bind to opioid receptors in peripheral nervous system and the central nervous system
  - μ (mu), δ (delta), κ (kappa)
  - Agonist, antagonist, and mixed

μ (mu)	δ (delta)	κ (kappa)
• Analgesia (high) • Respiratory depression • Nausea/vomiting • Slowed GI transit • Euphoria • Modulate hormone and neurotransmitter release	• Analgesia • Dysphoria • Psychotomimetic effects • Modulate hormone and neurotransmitter release	• Analgesia • Respiratory depression • Dependence • Dysphoria • Psychotomimetic effects

Schumacher MA, Basbaum AI, Naidu RK. Opioid Agonists & Antagonists. In: Katzung BG. eds. Basic & Clinical Pharmacology, 14e New York, NY: McGraw-Hill; .
Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11:S133-S153.

Potential Side Effects of Opioids



Central
- Drowsiness ★
- Dizziness
- Lightheadedness
- Fuzzy thinking
- Anxiety
- Abnormally happy or sad mood

Pupils
- Narrowing

Throat/mouth
- Dryness ★

Histamine release

Skin
- Rash
- Ítching

Cardiac
- Postural hypotension

Respiratory
- Slowed or irregular breathing
- Chest tightness

Gastric
- Nausea ★
- Vomiting ★

Intestinal
- Constipation ★
- Biliary colic

Urinary
- Difficulty urinating

Most side effects are dose related

★ Most common side effects

Green – tolerance develops
Red = no tolerance

Opioid Endocrinopathy

Table 1 Effects of acute and chronic opioid use on the endocrine system in humans—modified from Vuong et al. [4]

Hormone	Acute opioid administration	Chronic opioid administration
Growth hormone	↑	↓/↔
Prolactin	↑/(↑↔↓)[a]	↑/↔
Thyroid-stimulating hormone	↑/↓[b]	↔
Adrenocorticotropin hormone	↓	↓/↔/↑[c]
Luteinizing hormone	↓↓	↓↓
Follicle-stimulating hormone	↔	↔
Estradiol	↓↓	↓/↔
Testosterone	↓↓	↓↓
Arginine vasopressin	↑/↓	↑/↓

↑, stimulation; ↓, inhibition; ↔, no change

[a] Buprenorphine at low, medium, and high doses [17]

[b] Severely stressed patients [19]

[c] Methadone [30]

Table 2 Symptoms of hypogonadism [85]

Loss of libido
Erectile dysfunction
Infertility
Depression and anxiety
Decreased muscle mass and strength
Fatigue or tiredness
Hot flashes and night sweats
Amenorrhea, irregular menses, galactorrhea
Osteoporosis and fractures
Pain[a]
Decreased opioid effect[a]

[a] Potential symptoms of hypogonadism

Buss T, Leppert W. Opioid-induced endocrinopathy in cancer patients: an underestimated clinical problem. Adv Ther. 2014; 31:153-167.

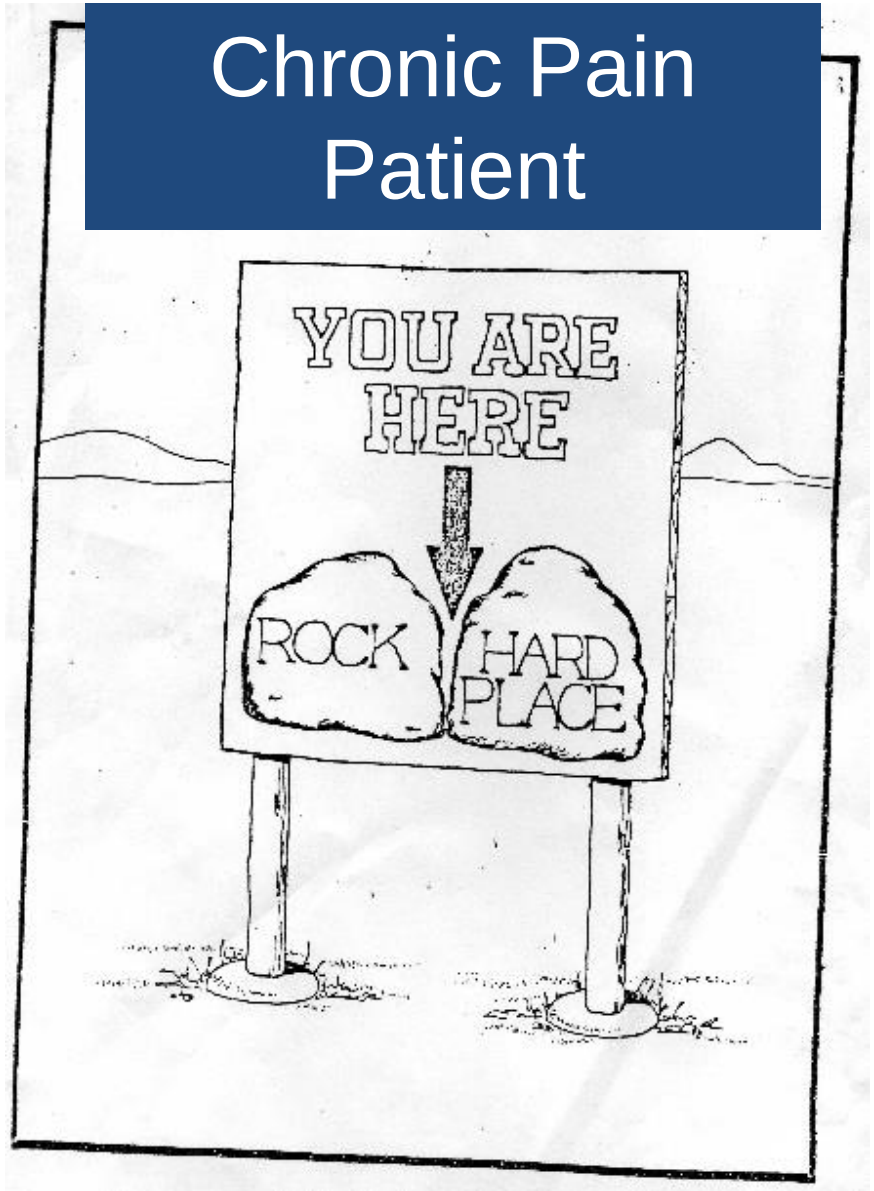
Long-Term Effects of Opioids

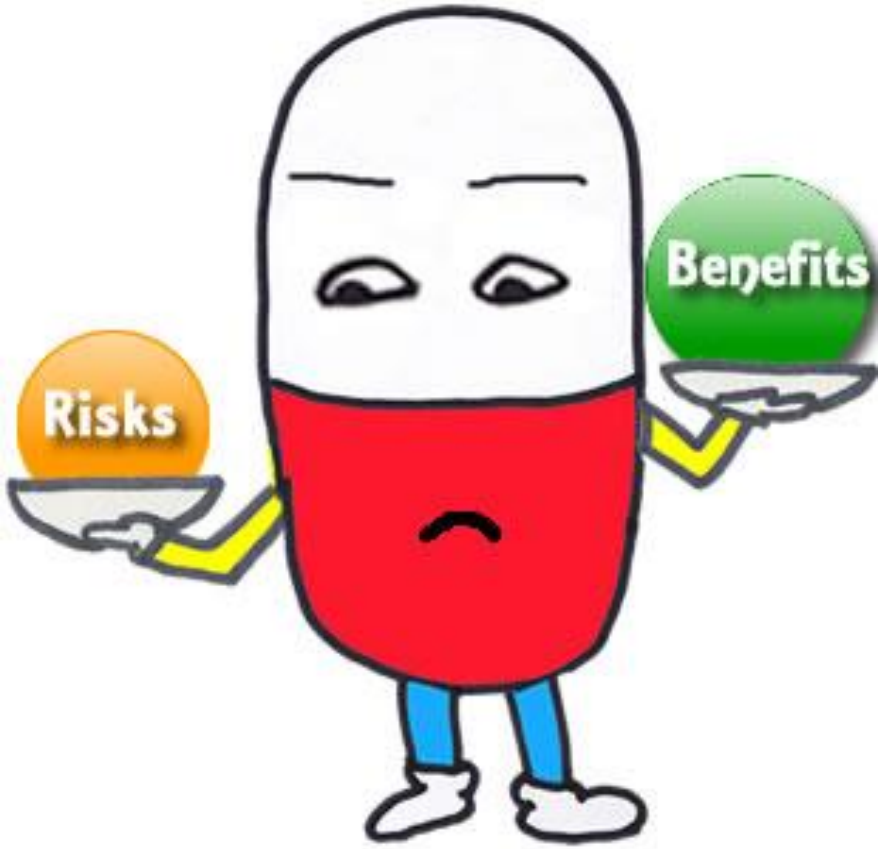
- Potential for harm persists
- Research is limited

Respiratory depression	Opioid overdose and breathing problems during sleep
Falls and fractures	Hip or pelvis fractures
Gastrointestinal effects	Chronic constipation and intestinal blockage
Cognitive and neurophysiologic effects	Sedation, disruption of sleep and hyperalgesia
Psychosocial effects	Depression, anxiety, deactivation and apathy
Addiction	Drug addiction or misuse
Hormonal effects	Hypogonadism, impotence, infertility and osteoporosis
Other effects	Dry mouth that may lead to tooth decay; immunosuppression

Baldini A, Von Korff M, Lin EH. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. Prim Care Companion CNS Disord. 2012;14(3):PCC.11m01326. doi:10.4088/PCC.11m01326

Chronic Pain Patient





Considerations Between Opioids

Potency of Opioids Vary: Calculating MMEs (Milligrams Morphine equivalent)

Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors[i,ii]

Type of Opioid (strength units)	MME Conversion Factor
Buprenorphine film/tablet[iii] (mg)	
Buprenorphine patch[iii] (mcg/hr)	
Buprenorphine film [iii] (mcg)	
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[iv] (mcg)	0.13
Fentanyl film or oral spray[v] (mcg)	0.18
Fentanyl nasal spray[vi] (mcg)	0.16
Fentanyl patch[vii] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[viii] (mg)	3
>0, <= 20	4
>20, <=40	8
>40, <=60	10
>60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol[ix] (mg)	0.4
Tramadol (mg)	0.1

Total daily dose of current opioid (non-MME) **X** MME Conversion factor of current opioid **=** Total daily MME of current opioid

Morphine = 1, hydrocodone = 1 , oxycodone = 1.5

Ex: Percocet (oxycodone/APAP) 5/325mg tab, 2 tabs po q6h prn. What is the max allowed MME per day?

40mg oxycodone **X** *1.5* **=** *60 MME*

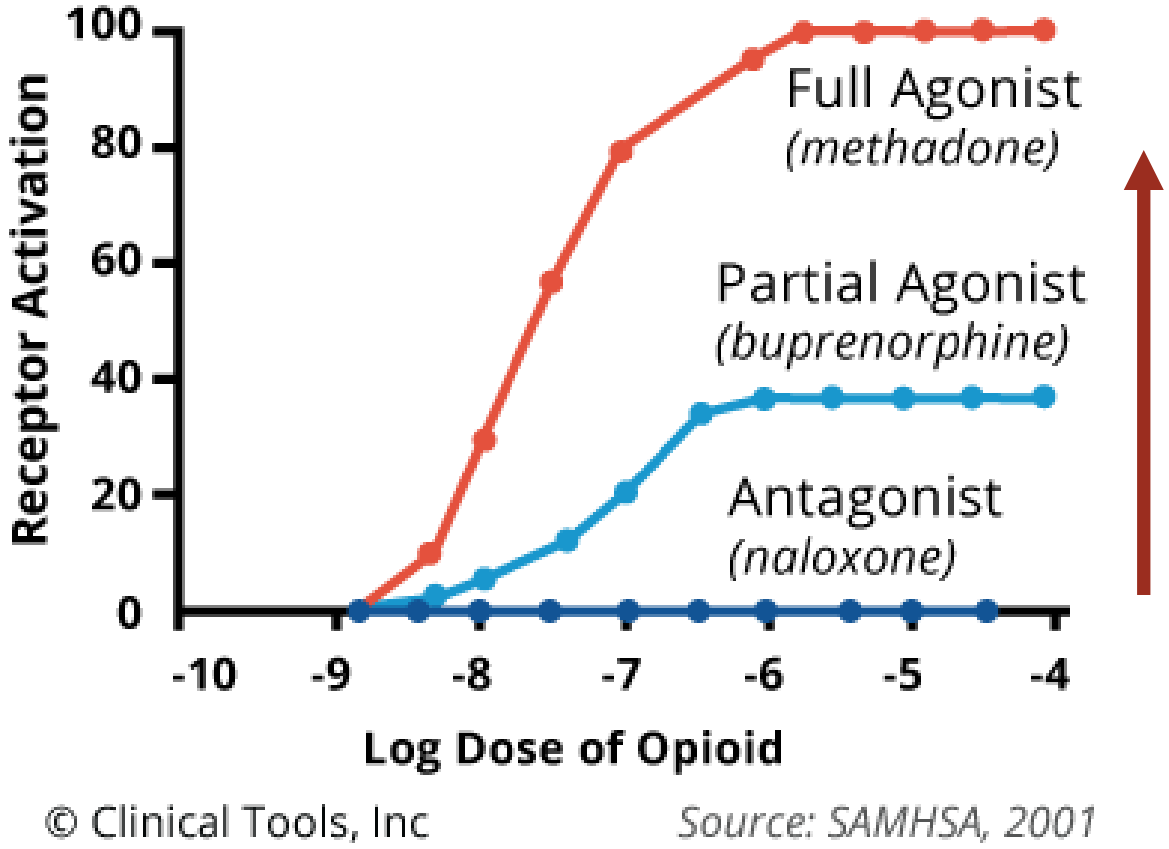
Compared to <20 MME/day

↑ Overdose Risk on ≥ 50 MME/day

↑ ↑ Overdose Risk on ≥ 90 MME/day

https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/Opioid%20Morphine%20EQ%20Conversion%20Factors%20%28vFeb%202018%29.pdf

Types of Receptor Activation

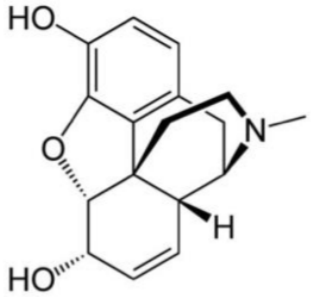
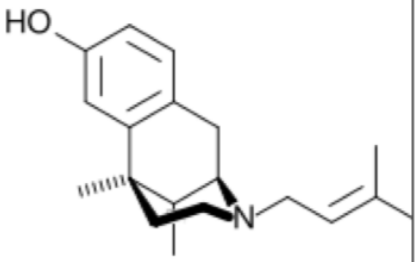
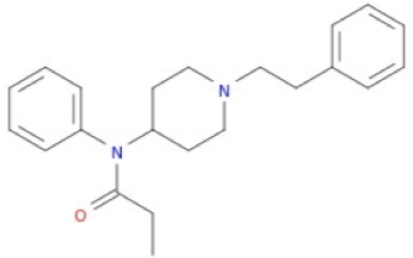
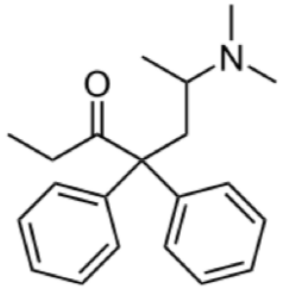
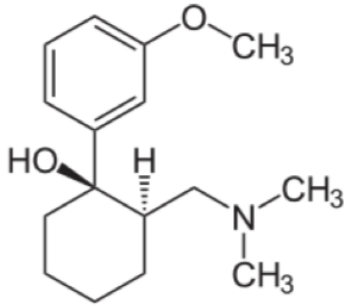


More receptor activation = more analgesia, side effects, overdose risk*

**degree of effect at a given % receptor activation is dependent on patient-specific opioid tolerance level*

Chemical Classes of Opioids

https://www.pharmacytimes.com/view/opioid-allergy-pseudo-allergy-or-adverse-effect

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
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

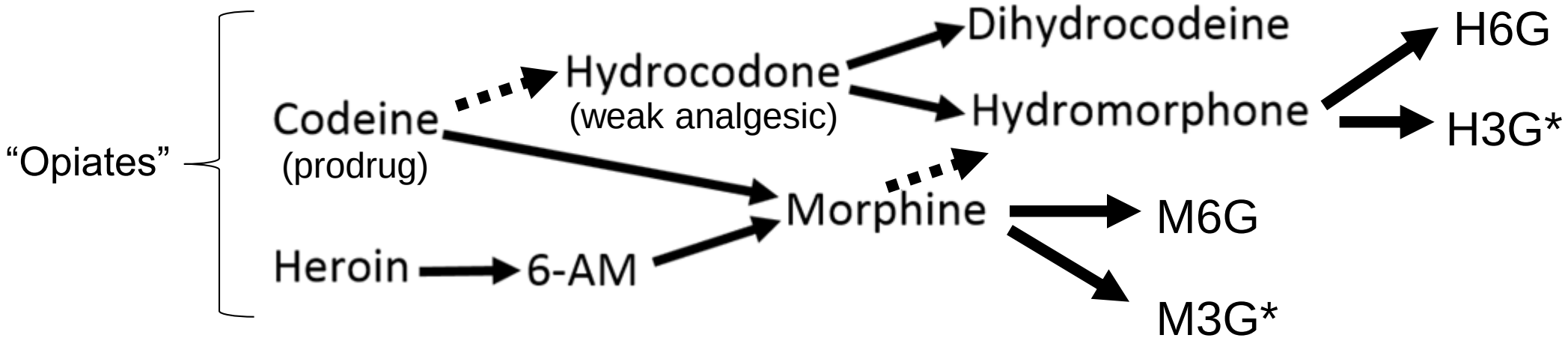
*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

True allergy: Avoid opioids; change chemical class of opioids w close monitoring

Pseudoallergy:
- Highest risk: morphine, codeine, meperidine
- Less risk: hydrocodone, oxycodone, hydromorphone
- Lowest risk: tramadol, fentanyl

Antihistamine and dose reduction may reduce sx

Opioid Metabolism



Oxycodone → Noroxycodone, Oxymorphone

Meperidine → Normeperidine*

Tramadol (prodrug) → O-desmethyl-tramadol

Methadone → EDDP (inactive)

Fentanyl → Norfentanyl (inactive)

Buprenorphine → Norbuprenorphine

⋯▶ Minor pathway (at high doses)

*neurotoxic metabolite

Drug	μ	δ	κ	Metabolic pathway*	Active metabolites
Morphine	+++		+	Phase II glucuronidation and 2D6 (minor)	M3G (neurotoxic), M6G (strong), hydromorphone
Hydromorphone	+++			Phase II glucuronidation	H3G (neurotoxic)
Oxymorphone	+++			Phase II glucuronidation	O6G
Oxycodone	++			3A4 (major to noroxycodone) 2D6 (minor to oxymorphone)	Noroxycodone (weak opioid); oxymorphone (does not cross BBB as readily as oxycodone)
Hydrocodone (prodrug-like)	+			2D6 (to AM), 3A4 *(to norhydrocodone – inactive)*	***Hydromorphone***
Codeine (prodrug)	+	+		2D6 (to AM), 3A4	**Morphine**, hydrocodone
Methadone	+++			3A4, 2B6 (major) 2C9, 2C19, 2D6 (minor)	
Levorphanol	+++			Hepatic	
Meperidine	+++	++		2B6, 2C19, 3A4	Normeperidine (neurotoxic)
Fentanyl	+++			3A4	
Tramadol (prodrug)	+			2D6 (to AM), 3A4, glucuronidation	**O-desmethyl-tramadol**
Buprenorphine	±	-	-	3A4	

Strong agonist: +++,++ weak agonist: + partial agonist: ± antagonist: -

Bold and underlined = major active compound

*CYP metabolism to inactive metabolites unless indicated otherwise
AM = active metabolite

Schumacher MA, Basbaum AI, Naidu RK. Opioid Agonists & Antagonists. In: Katzung BG. eds. Basic & Clinical Pharmacology, 14e New York, NY: McGraw-Hill; . ;
https://www.pharmgkb.org/pathway/PA166170927
Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11:S133-S153.

Drug Interactions and Other Considerations

- CYP450 Interactions
  - Not significant for morphine, hydromorphone, or oxymorphone
  - Many opioids metabolized to active or inactive metabolites
    - CYP2D6 = to active metabolites (codeine, tramadol, hydrocodone)
    - CYP3A4 = to inactive metabolites (oxycodone, fentanyl, hydrocodone)
    - Methadone has a lot of CYP interactions
- CYP450 polymorphisms may alter effect(s)
  - Higher variability with codeine, tramadol, and methadone
- Additive CNS depressant effects for ALL opioids (esp. with alcohol, benzodiazepines)
- Renal and/or hepatic impairment
  - All opioids affected to some extent
  - Caution with neurotoxic metabolites, active metabolites, and extended-release products

Caution with ER/LA (Extended Release/Long-Acting) Opioids

- Higher risk of unintentional overdose with ER/LA opioids compared to short-acting opioids
- No evidence that use of ER/LA opioids are more effective for chronic non-cancer pain compared to short-acting opioids
- Abuse of both short-acting and ER/LA opioids are a serious problem
- For select patients, ER/LA opioids may allow more consistent and prolonged analgesia with less frequent dosing.

Dowell D, et al. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep. 2022;71(3):1-95.

Opioids with Unique Properties

	Unique Benefits	Unique Risks	Comments
Tramadol	• Efficacy for neuropathic pain	• CYP2D6 substrate • Serotonin syndrome • Seizure risk	• Pro-drug (CYP genetic polymorphism considerations) • Max dose 400mg/day • Weak opioid

Methadone	• Less euphoria and abuse potential
	• Less tolerance development
	• Efficacy for neuropathic pain
	• MAT indication
		• QT prolongation
		• CYP interactions
		  • Substrate of 3A4, 2B6, 2C19, 2D6)
		  • Inhibitor of CYP3A4
		• Serotonin syndrome
		• Complex equivalency ratio to other opioids
		• Highly variable half-life between patients
			• Inherently long-duration of action

Buprenorphine	• Less euphoria and abuse potential • Less overdose risk • MAT indication	• Can induce withdrawal if on strong opioid	• Mixed agonist-antagonist • Inherent ceiling effect

MAT: Medication Assisted Therapy

Many Differences Between Opioids

- Receptor activation (agonist, antagonist, or mixed)
- Opioid receptor subtypes
- Chemical class of opioids
- Relative potency
- Pharmacokinetics
  - Metabolism (glucuronidation vs CYP450; renal clearance)
  - Active metabolites
  - Toxic metabolites
  - Drug interactions
- Unique MOA and side effect profiles
  - e.g. tramadol; methadone; buprenorphine
- Pseudoallergy risk (histamine release)
- Ceiling dose/max recommended doses
- Combination with non-opioid
  - e.g. acetaminophen
- Duration of action (IR vs. ER/LA)
- Available routes of administration
- Cost

Choice of opioid based on patient specific factors

Patient Factors Impacting Benefits and Risks of Opioids

- Patient's Medication Regimen
  - Choice of opioid
  - Opioid dose/frequency
  - Other drugs in regimen (e.g. drug interactions)
- Patient Characteristics
  - Age
  - Pain type
  - Pain severity
  - Renal/hepatic function
  - Comorbidities
  - Health literacy/adherence
  - Opioid tolerance

Benefits:

Pain control/Function

Risks:

Short-term side effects

Long-term side effects

Misuse/addiction

RIOSORD Tool: Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression

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