"Pharmacology of Opioids: What practitioners need to know"

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Objectives

- Describe actions of opioid receptors leading to:
  - Therapeutic effects
  - Side effects
- Contrast opioid agonists, antagonists and partial agonists
- Describe key pharmacokinetic and formulation differences amongst commonly used opioids
- Manage clinically significant drug interactions associated with opioids

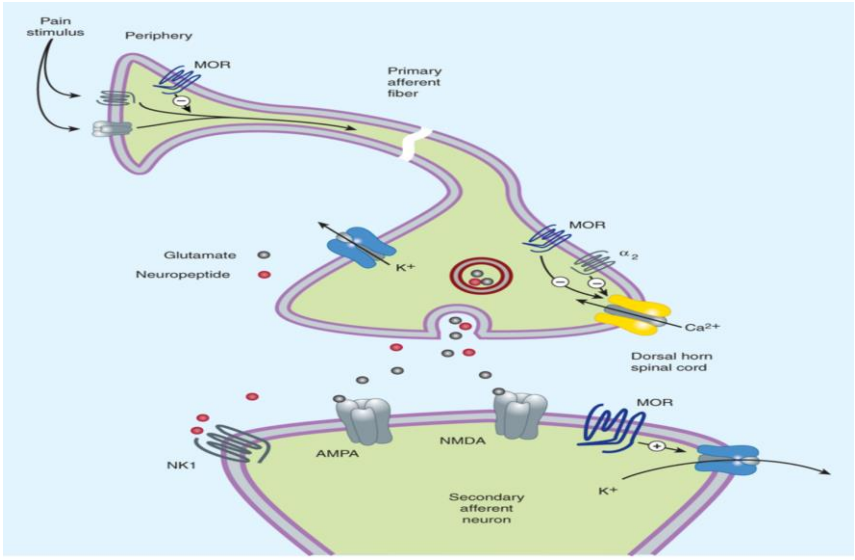
Opioids

- Opiate analgesics have been used and abused since the 3rd century B.C.
  - Derived from the Asian opium poppy plant (*Papaver somniferum* and *P album)*
    - After incision, the poppy seed pod exudes a white substance that turns into a brown gum that is crude opium.
    - Opium contains many alkaloids, the principal one being morphine, which is present in a concentration of about 10%
  - Opiate = naturally occurring alkaloid (ex. Morphine, codeine)
  - Opioid = any compound that works at opioid receptors
  - Medicinal uses: pain, cough suppression

Opioid receptor activities

Receptor Subtype	Functions
μ (Mu)	Supraspinal and spinal analgesia; sedation; respiratory depression; slowed gastrointestinal transit; euphoria; physical dependence
δ (Delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release
κ (Kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit

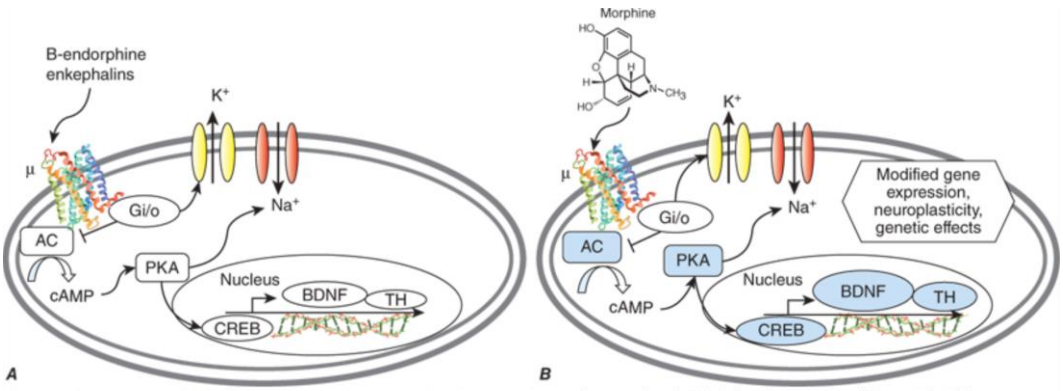
Modified from Basic & Clinical Pharmacology, 13e Bertram G. Katzung, Anthony J. Trevor, eds.



Source: Bertram G. Katzung:
Basic & Clinical Pharmacology, Fourteenth Edition

ACCESS Pharmacy
Current Practices. Patient-focused Care.

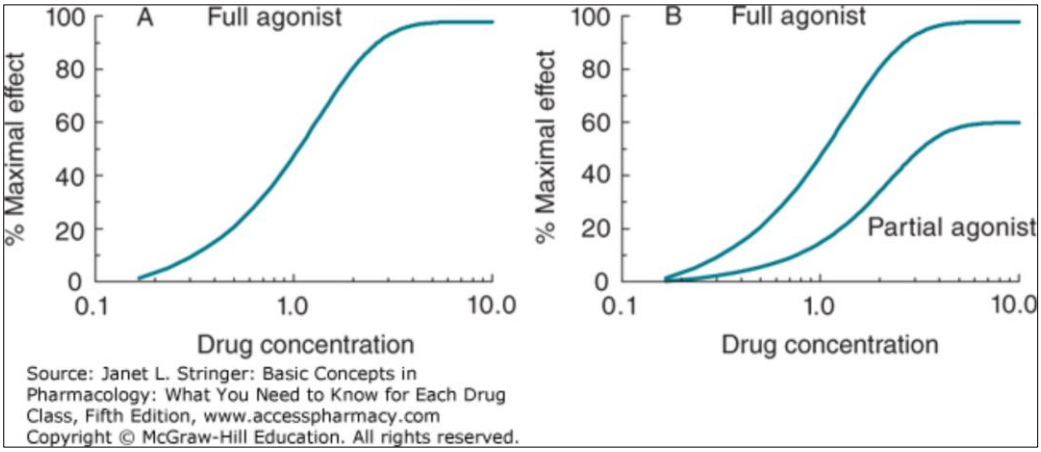
From: Opioid-Related Disorders
Harrison's Principles of Internal Medicine, 19e, 2015



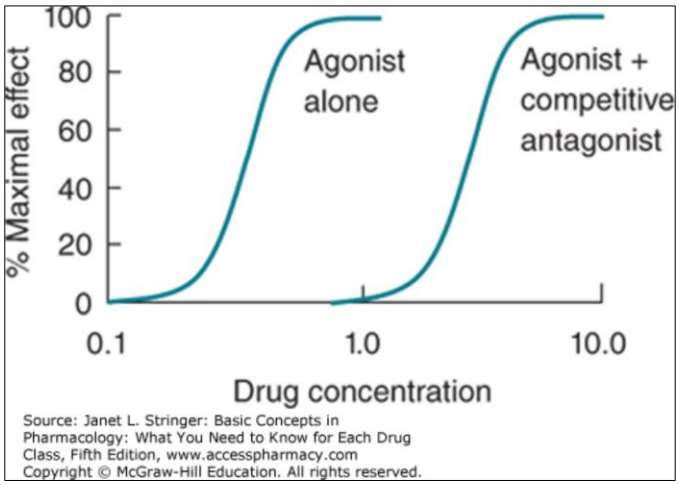
Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Opioid action at receptors

- **Full Agonists**: Compounds that are able to elicit a maximal response following receptor occupation and activation.
- **Partial Agonists:** Compounds that can activate receptors but are unable to elicit the maximal response of the receptor system.
- **Antagonist** Compounds that exert no biological effect when binding to a receptor. Antagonists cause a downward shift of the overall action of the receptor system.

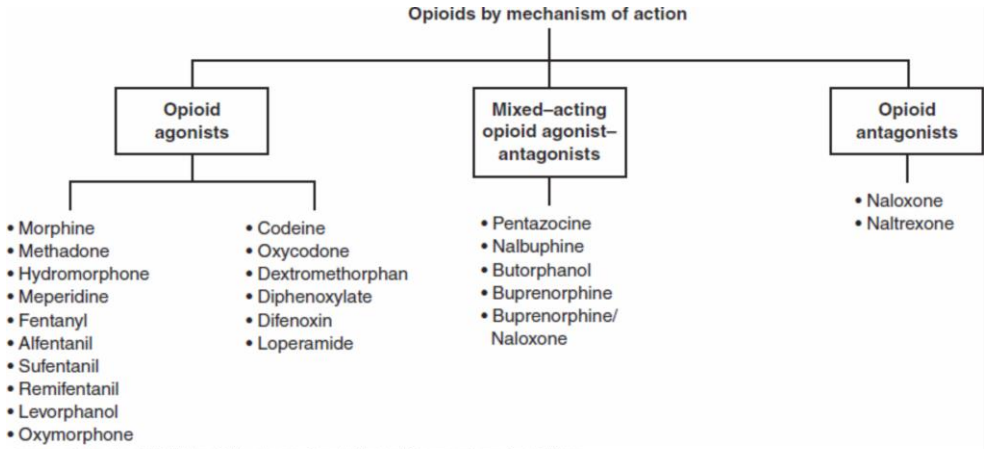


In A, the concentration-response curve for a full agonist is presented. The drug can produce a maximal effect. In B, the concentration-response curve for a partial agonist is also shown. In this case, the partial agonist is able to produce only 60% of the maximal response.

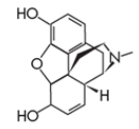
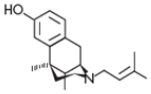
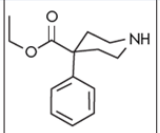
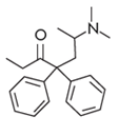
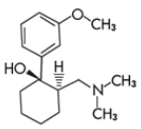


Source: Janet L. Stringer: Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, Fifth Edition, www.accesspharmacy.com

In this graph the concentration-response curve for an agonist alone is presented. When the effect of the agonist is tested in the presence of a fixed concentration of a competitive antagonist, the agonist appears less potent. The same maximal effect is achieved, but it takes higher doses to do so.



Source: Catherine E. Pelletier-Dattu: Lange Smart Charts: Pharmacology, 2nd Edition
www.accesspharmacy.com

	PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
					
	MORPHINE	PENTAZOCINE	MEPERIDINE	METHADONE	TRAMADOL
Strong Agonists	• Morphine • Hydromorphone • Oxymorphone		• Fentanyl • Meperidine	• Methadone	
Mild to Moderate Agonists	• Codeine • Oxycodone • Hydrocodone		• Diphenoxylate • Loperamide	• Propoxyphene	• Tramadol
Opioids with Mixed Receptor Actions	• Nalbuphine • **Buprenorphine**	• Pentazocine			
Antagonists	• Naloxone • Naltrexone • Methylnaltrexone • Naloxegol				

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Tramadol

- A centrally acting synthetic opioid analgesic, with a dual mechanism of action.
  - Tramadol and its metabolite, O-desmethyl-tramadol (M1), bind to mu-opioid receptors.
    - The metabolite, M1, has a 200-fold higher affinity to the mu-opioid receptor and is up to 6 times more potent than tramadol in producing analgesia.
  - Tramadol has also been shown to inhibit the uptake of norepinephrine and serotonin, suggesting that its anti-nociception activity is mediated by both opioid and nonopioid mechanisms
- Tramadol possesses a weak affinity for the mu-opioid receptor and even less for the kappa and delta receptors.
  - Its affinity is ~1/6000 that of morphine and 1/10 that of codeine.
  - It has been estimated that the analgesic potency of tramadol is 1/10 that of morphine
- Although tramadol is an opiate receptor agonist, it does not appear to produce significant respiratory depression or cardiovascular effects in most patients
- Addictive potential

Opioid Conversion

Table 4. Opioid Equianalgesic Dosing

Drug	Parental	Oral
Codeine	100 mg	200 mg
Fentanyl	0.1 mg	N/A
Hydrocodone	N/A	30 mg
Hydromorphone	1.5 mg	7.5 mg
Methadone	*	N/A*
Morphine	10 mg	30 mg
Oxycodone	10 mg	20 mg
Oxymorphone	1 mg	10 mg

* Methadone dosing is variable. Conversion between methadone and other opioids is not a linear relationship. Multiple strategies exist for the conversion of methadone, however the authors of this continuing education activity recommend the following: Fudin J, Marcoux MD, Fudin JA. Mathematical model for methadone conversion examined. *Pract Pain Manag.* 2012;12(8):46–51. Conversions to or from methadone may be used for approximating a target dose, but in all cases the transition should be made slowly and carefully. When converting to methadone, even in opioid-tolerant patients, the initial dose should not exceed 10 mg per day in divided doses.

N/A = not applicable.

Source: Reference 22.

http://paindr.com/wp-content/uploads/2017/05/Opioid-Medications-DAEPE-CE-Monograph_APhA_12-2016.pdf

Table 5. Guidance for Changing Opioid Therapy

Step	Description
1	Determine the total 24-hour dose of the currently prescribed analgesic.
2	Convert the currently prescribed opioid to an equivalent morphine dose of the same route (oral vs. parenteral).
3	If the route is to remain the same, use the conversion table to convert the morphine dose to the equivalent new opioid use. If the route is to change, first convert the morphine dose to the desired route before converting from morphine to the new opioid. • Consider decreasing dose by 50% in elderly & in patients with renal failure.
4	If pain is controlled, start at 50% to 75% of the equivalent dose. If pain is uncontrolled, then start at 100% of the dose.
5	Determine the strength per dose by dividing the dose calculated in Step 4 by the dosing interval. • Choose a dosing interval consistent with the medication duration of action.
6	Provide an appropriate "rescue" dose for breakthrough pain. • Ten percent of the total opioid dose given every one to two hours as needed. • Elderly: Rescue dose= 5% of the total opioid dose administered every 4 hours as needed.
7	Titrate baseline and as needed dose to provide effective pain relief.
8	Use cathartic and stool-softening medications as constipation prophylaxis.

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Adverse Effects

Table 1. Most Common Opioid-Induced Adverse Effects

Category	Adverse Effect
Common	• Constipation • Dizziness • Dry mouth • Fatigue • Impaired cognition • Nausea and vomiting • Pruritus • Postural hypotension • Sexual dysfunction • Sedation • Testosterone abnormalities
Severe	• Opioid-induced respiratory depression • Addiction/dependence • Death
Other Risks	• Falls • Hyperalgesia • Neonatal abstinence syndrome (potentially life-threatening)

Degree of Tolerance to Opioid Adverse Effects

High	Moderate	Minimal or None
Analgesia	Bradycardia	Miosis
Euphoria, dysphoria		Constipation
Mental clouding		Convulsions
Sedation		
Respiratory depression		
Antidiuresis		
Nausea and vomiting		
Cough suppression		

http://paindr.com/wp-content/uploads/2017/05/Opioid-Medications-DAEPE-CE-Monograph_APhA_12-2016.pdf

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Drug interactions

- 2D6 inhibitors
  - Fluoxetine, paroxetine, bupropion, amiodarone
  - Significantly reduce the effect of codeine, tramadol, ?hydrocodone
- 3A4 inhibitors
  - Grapefruit juice, ciprofloxacin, antifungals
  - Significantly increase the serum concentration of oxycodone, buprenorphine
- Drugs that prolong QT interval – caution with methadone
- Any other medications that cause CNS depression:
  - **Benzodiazepines**, muscle relaxants, sedating antidepressants, sedating antihistamines

Formulation Clinical Pearls

- IR vs ER/LA
- Fentanyl patch
  - Peak effect not realized for 24-48 hours after application
- Buprenorphine formulations
  - All oral forms must be absorbed via the oral mucosa (NOT SWALLOWED)
- Abuse deterrent formulations
  - Create barriers in an attempt to hinder abuse and misuse.
  - Strategies include use of:
    - polyethylene oxide, gums, and carbomers = turn to gel when crushed
    - mixing with solvents = altered viscosity deterring injection or snorting
    - combining with an opioid antagonist, emetics, or mucous membrane irritant = make abuse unpleasant

Buprenorphine + Naloxone Formulations

Brand name	Dosage Form	Ingredient(s)	Pearls
Zubsolv (and various generics)	Sublingual tablet: 0.7mg/0.18mg 1.4mg/0.36mg 2.9mg/0.71mg 5.7mg/1.4mg 8.6mg/2.1mg 11.4mg/2.9mg	Buprenorphine + naloxone	• Tablet should be placed under the tongue until dissolved. • Do not cut, chew, or swallow tablets. • If multiple tablets are required, administer all at once if possible OR administer 2 tablets at a time
Suboxone	Sublingual film: 2mg/0.5mg 4mg/1mg 8mg/2mg 12mg/3mg	Buprenorphine + naloxone	• Drug concentration reduced 23% to 37% by co-ingestion of liquids • Place film under the tongue, close to the base on the left or right side. • Must be kept under tongue until completely dissolved.
Bunavail	Buccal film: 2.1mg/0.3mg 4.2mg/0.7mg 6.3mg/1mg	Buprenorphine + naloxone	• Half a normal dose can achieve same result as other products, due to twice the bioavailability • Drug concentration reduced 23% to 37% by co-ingestion of liquids • Wet the inside of the cheek. Hold the film with the text (BN2, BN4, or BN6) facing up and place that side with the text against the inside of the cheek. Press and hold the film in place for 5 seconds.

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Buprenorphine-only Formulations

Brand Name	Dosage Form	Ingredient(s)	Pearls
Subutex (and various generics)	Sublingual tablet: 2mg 8mg	Buprenorphine	• Tablet should be placed under the tongue until dissolved. • Do not cut, chew, or swallow tablets. • If multiple tablets are required, administer all at once if possible OR administer 2 tablets at a time
Probuphine	Subdermal implant: 74.2mg	Buprenorphine	• Insert 4 rods, remove after 6 months • For patients who have achieved stability with transmucosal buprenorphine equivalent doses of ≤ 8 mg/day
Sublocade	Subcutaneous injection 100mg/5mL	Buprenorphine extended release	• Administered monthly; given in abdominal region
Belbuca	Buccal Film: 75mcg up to 900mcg	Buprenorphine	• NOT FDA approved for MAT (pain only)
Butrans	Transdermal Patch: 5mcg/hour up to 20mcg/hour	Buprenorphine	• NOT FDA approved for MAT (pain only)

https://www.buppractice.com/node/12096

Opioid Products with Food and Drug Administration (FDA)–Approved Abuse-Deterrent Labeling.*

Brand Name	Type of Opioid	Year of Approval	Reported Abuse-Deterrence Mechanism	Commercially Available
OxyContin (reformulated)	Oxycodone	2010	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.	Yes
Targiniq ER	Oxycodone	2014	Combination pill containing extended-release (ER) oxycodone and naloxone; if the formulation is crushed and administered intravenously or intranasally, high naloxone concentrations block opiate-induced euphoria and can induce withdrawal symptoms.	No
Embeda	Morphine	2010	Capsules of ER morphine pellets that contain a sequestered core of naltrexone; if the pellets are swallowed, the morphine is gradually released and absorbed, while the naltrexone core passes through the gut intact. If the pellets are crushed, chewed, or dissolved, the naltrexone is released, blocking morphine-induced euphoria.	Yes
Hysingla ER	Hydrocodone	2015	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.	Yes
MorphaBond	Morphine	2015	Formulated with inactive ingredients that make the tablet harder to adulterate while maintaining ER characteristics if the tablet is subjected to physical manipulation or chemical extraction.	No
Xtampza ER	Oxycodone	2016	Capsules containing microspheres formulated with oxycodone base and inactive ingredients that make the formulation harder to manipulate.	Yes
Troxyca ER	Oxycodone	2016	Contains pellets that consist of oxycodone that surround sequestered naltrexone. When taken orally, the naltrexone is intended to remain sequestered and patients receive ER oxycodone. When the pellets are crushed, the naltrexone is released and counteracts the effects of oxycodone.	No
Arymo ER	Morphine	2017	A polymer matrix tablet technology with controlled-release properties as well as physical and chemical barriers that resist manipulation. The technology results in a viscous hydrogel on contact with liquid, making the product very difficult to draw into a syringe.	Yes
Vantrela ER	Hydrocodone	2017	Incorporates abuse-deterrent technology designed to resist drug extraction through the most common routes: oral, intranasal, and intravenous.	No
RoxyBond	Oxycodone	2017	Includes inactive ingredients that make the tablets harder to misuse by physical manipulation, chemical extraction, or both; in vitro data suggest physicochemical properties that are expected to make abuse through injection difficult.	No

* There are no currently approved generic versions of opioids with approved abuse-deterrent labeling. Information is from the FDA.

Becker & Fiellin. NEJM 2017; 376:2103-2105

Questions?