LEARNING OBJECTIVES

AT THE CONCLUSION OF THIS SESSION PARTICIPANTS SHOULD BE ABLE TO:

1. Discuss the pharmacology of opioids used in the hospital setting.
2. Recognize the mechanism of opioid allergies and the cross reactivity between different classes.
3. Distinguish between opioids used in the pre-operative, peri-operative, and post-operative settings.
4. Discuss common errors made in the prescribing of opioids.

DISCLOSURE

I have no actual or potential conflict of interest in relation to this program/presentation.

THE OPIATES

- Opiate: Substance extracted from opium
  - Opium: a mixture of alkaloids from *Papaver somniferum*
  - Only the L-Isomer is analgesic
  - 2 types of alkaloids
    - Phenanthrene
      - Morphine: 10% in opium
      - Codeine: 0.5% in opium
      - Thebaine: 0.2% in opium (non-analgesic)
    - Benzoisoquinoline
      - Papaverine: 1% in opium (non-analgesic)
      - Noscapine: 6% in opium (non-analgesic)

BASIC PHARMACOLOGY

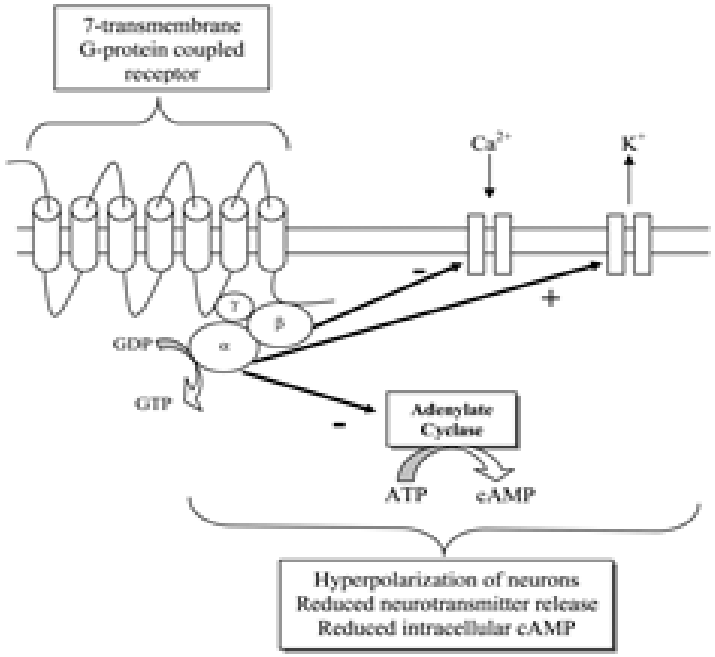
- Mu (MOP) μ: morphine
  - Analgesia, dependence, euphoria, respiratory depression miosis, constipation
- Kappa (KOP) κ: ketocyclazocine (the first ligand to act at this receptor)
  - Analgesia, diuresis, dysphoria
- Delta (DOP) δ: vas deferens (the tissue within which it was first isolated)
  - Analgesia, constipation
- Nociceptin/orphanin (NOP): not affected by naloxone
  - Analgesia, hyperalgesia

CLINICAL EFFECT

	MOP	KOP	DOP	NOP
SUPRASPINAL ANALGESIA	+++	-	-	-
SPINAL ANALGESIA	++	+	++	++
RESPIRATORY DEPRESSION	+++	-	+	-
EUPHORIA	+++	-	-	-

G-PROTEIN COUPLED RECEPTORS

Fig 1 The seven transmembrane structure of opioid G-protein–coupled receptors. Activation by opioid receptor ...



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1. Inhibit activation of nociceptors
2. Inhibit cells that release inflammatory mediators
3. Inhibit terminals of C fibers in the spinal cord
4. Prevent ascending transmission of pain signal
5. Turn on descending inhibitory systems

ACTIVATION OF MOP RECEPTOR

AFFINITY/EFFICACY

- Affinity is a measure of the strength of interaction between a compound binding to its receptor
- Efficacy is a measure of the strength of activity from this binding
- Potency is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity
    - A highly potent drug (e.g. fentanyl) evokes a given response at low concentrations, while a drug of lower potency (e.g. meperidine) evokes the same response only at higher concentrations. Higher potency does not necessarily mean more side effects.

Pure agonist: affinity for binding plus efficacy

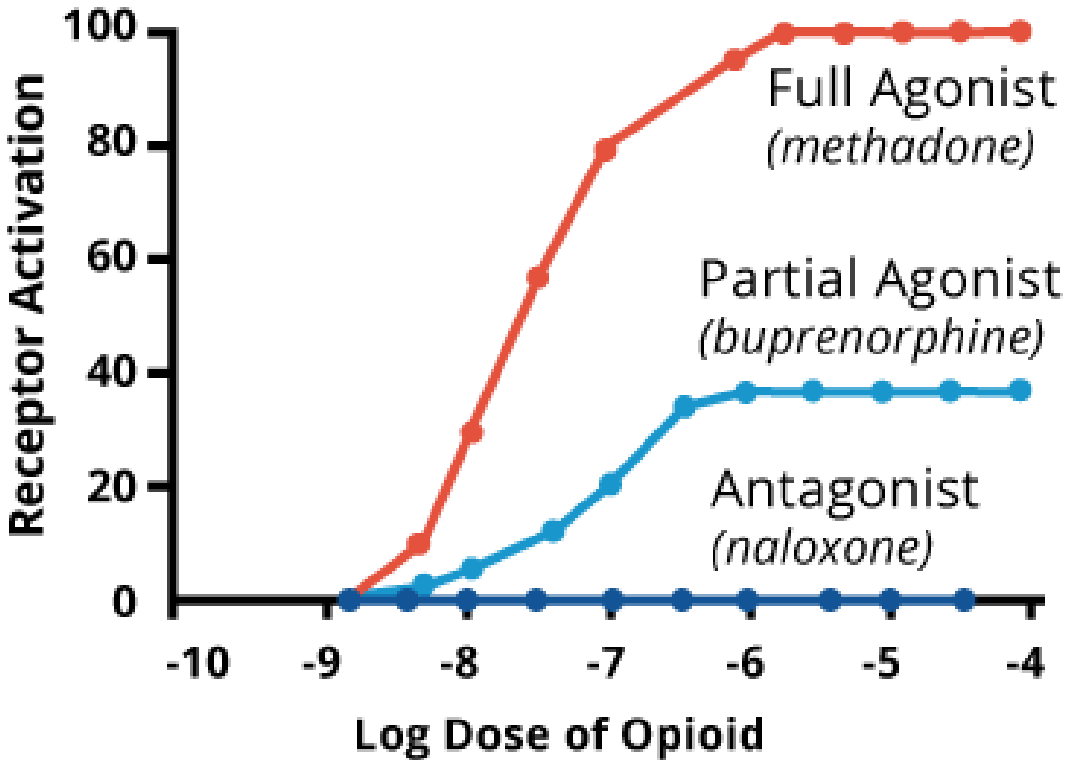
Pure antagonist: affinity for binding no efficacy

Mixed: agonist at one receptor, antagonist effect at another

Partial agonist: affinity for binding but low efficacy

Receptor Activation

Full Agonist, Partial Agonist, Antagonist



Source: SAMHSA, 2001

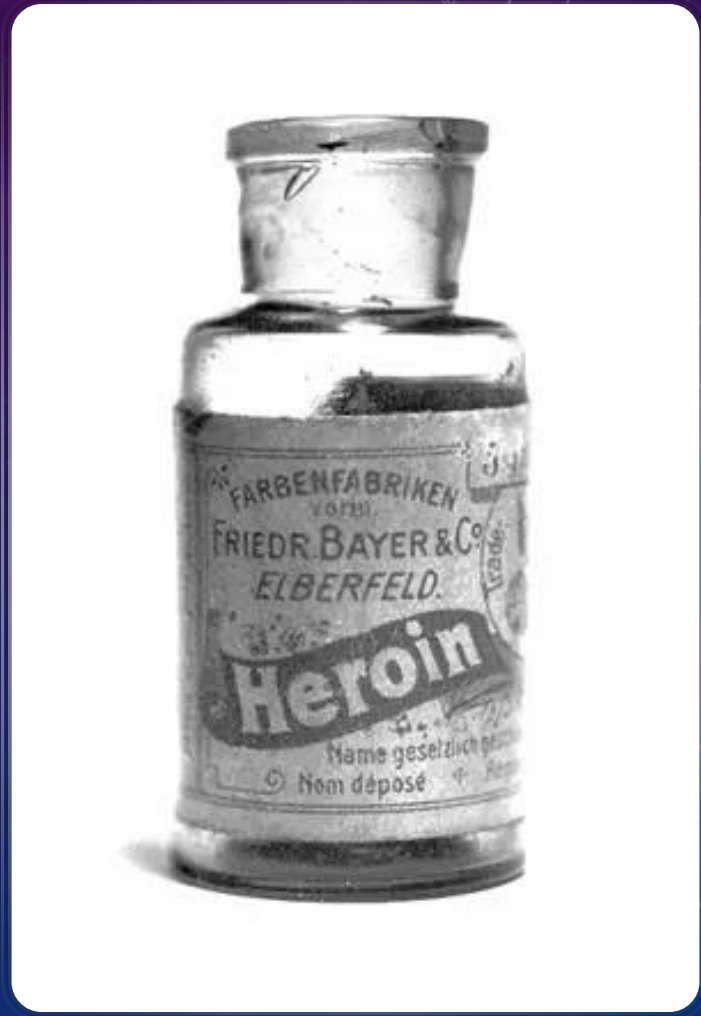
QUESTION #1

Which of the following actions is ascribed to the KOP (kappa) type of opioid receptors?

A. Euphoria
B. Proconvulsant
C. Dysphoria
D. Muscular Rigidity

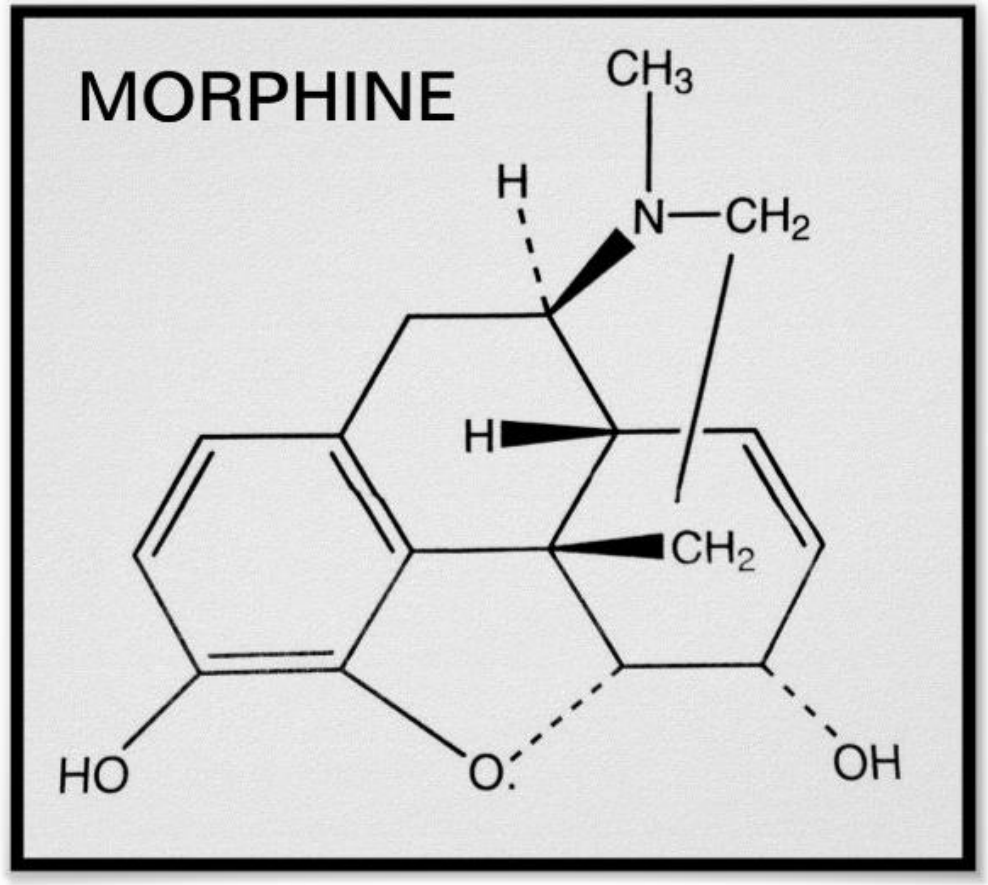
THE OPIOIDS

- Opioid: Compound with morphine like activity
- Opioid Agonists
  - Natural: morphine & codeine
  - Semisynthetic: oxymorphone, hydromorphone, oxycodone, hydrocodone
  - Synthetic: fentanyl, alfentanil, sufentanil, remifentanil, methadone, tramadol, meperidine



MORPHINE[NATURAL]

- The archetypal opioid
- MOP, KOP, DOP agonist
- Respiratory acidosis increases brain concentrations
- Metabolized to codeine and hydromorphone in very small amounts
- Inhibits the release of glutamate from primary afferent fibers in the spinal cord
- Hydrophilic
- Onset: 5 minutes (IV, Peak: 20 minutes) to 30 minutes (PO, Peak: 60 minutes)
- Duration: 3 - 7 hours
- Bioavailability: 17% - 33%
- $T_{½}$ = 2 - 4 hours



CODEINE [NATURAL]

- Oral only available in the US
- 50% the potency of morphine
  - Weak affinity at MOR receptor
- 10% will metabolize to morphine
  - 5-10% of the population lack the ability to metabolize to morphine
- Many more drug interactions (CYP2D6)
- Low doses are more emetic than higher doses
- Should not be given to nursing mothers or children
  - Potential of rapid metabolism resulting in overdose
- Onset: 30 - 60 minutes (Peak 120 minutes)
- Duration: 4 - 6 hours
- Bioavailability: 53%
- $T_{½}$ = 2.5 - 3 hours

MEPERIDINE [SYNTHETIC]

- Structurally related to atropine
  - May cause tachycardia
- Negative inotrope
- Hepatic biotransformation (48-56% first pass metabolism)
  - Toxic metabolite: normeperidine
  - Accumulation may cause seizures
- Anticholinergic
- Causes tachycardia
- Onset: 5 - 7 minutes (IV, Peak: 30 minutes) 2 hours (PO, Peak: 1 hour)
- Duration: 2 - 4 hours
- Bioavailability: 50% - 60%
  - Increased in liver disease
- $T_{½}$ = 3 hours
  - $T_{½}$ of normeperidine is 8 - 16 hours

TRAMADOL[SYNTHETIC]

- Racemic Drug
  - R-Isomer: MOP selective, inhibits serotonin reuptake
  - L-isomer: inhibits norepinephrine reuptake
- Less respiratory depression and gastrointestinal side effects
- Onset: 1 hour (Peak: 2 - 4 hours}
- Duration: 3 - 6 hours
- Bioavailability: 75%
- $T_{½}$: 6 hours

METHADONE [SYNTHETIC]

- Racemic Drug
  - L- isomer: MOR agonist
  - R- isomer: NMDA antagonist
- Long duration of action
- QT prolongation
- Limited 1st pass metabolism
  - No active metabolites
- Lipophilic
- Limited euphoria
- Inhibits reuptake of norepinephrine and serotonin
- Onset: 30 – 60 minutes
- Duration: 4-8 hours (up to 48 hours with repeated doses)
- Bioavailability: 40 to 100%
- T ½ = 12 to 150 hours

OLICERIDINE[SYNTHETIC] (OLINVYK)

- MOP partial agonist
  - Selectively binds to the G-protein section of MOP
- Reduced activation of the Beta-arrestin pathway
- IV only
- Poor 2D6 metabolizers with have 2 x systemic exposure
- QT prolongation
- Onset: < 5 minutes
- Duration: 1 – 3 hours
- Bioavailability: none
- $T_{½}$: 1.3 - 3 hours

THE LOST OPIOID

LEVORPHANOL

[SYNTHETIC]

- MOP, DOP, KOP agonist
- NDMA antagonist
- Optical Isomer of dextromethorphan
- Reuptake inhibitor for serotonin and norepinephrine
- Does not affect QT
- NO CYP450 interactions
- Onset: 10 - 60 minutes (Peak: 1 hour)
- Duration: 6 - 8 hours
- Bioavailability: unknown
- $T_{½}$: 11-16 hours

FENTANYL[SYNTHETIC]

- MOP selective
- Highly effective analgesic
- Highly lipophilic
- Prolonged administration as a result of sequestration of drug to fat stores
- Truncal rigidity
- Onset: immediate (IV), 6 hours (transdermal)
- Duration: 30 - 60 minutes (IV), 72 - 96 hours (transdermal)
- Bioavailability: 50% - 75% (formulation dependent)
- $T_{½}$: 2 - 4 hours (IV), 20 - 27 hours (transdermal)

PREOPERATIVE AND POSTOPERATIVE PAIN CONSIDERATIONS

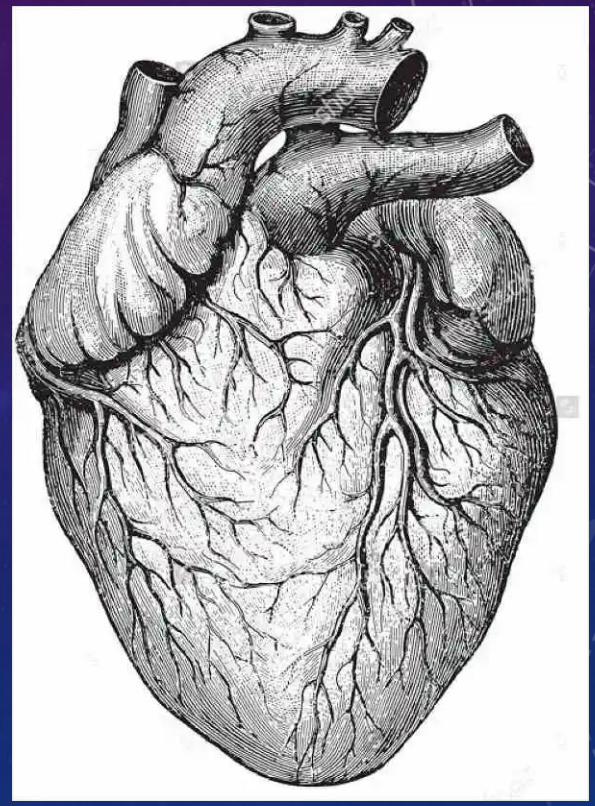
- Opioid Use Disorder
  - Goal to reduce overall amount of opioids administered during entirety of hospital stay
- Pre-operative options
  - Acetaminophen (oral v. IV)
  - Celebrex, Gabapentin, steroids
- Post-operative options
  - ATC Acetaminophen and/or ibuprofen
  - Muscle relaxants

OPERATIVE USES OF THE FENTANYL CLASS

- Remifentanil (2x fentanyl)
  - Most commonly used for TIVA
  - Fastest onset (1 minute), higher post-op shivering
  - Metabolized by plasma esterases in the plasma, RBC's and interstitial tissue
  - $T_{1/2}$ = 10 minutes
- Sufentanil (10x fentanyl)
  - Best used for operations shorter than 6-8 hours.
  - Longer distribution and elimination $T_{1/2}$
- Alfentanil (3x less fentanyl)
  - Best used for operations longer than 6-8 hours.

OPIOIDS NOT JUST FOR PAIN....

- Decreases HR & BP
- Vasodilation
  - Reduce preload
  - Reduction in myocardial oxygen demand

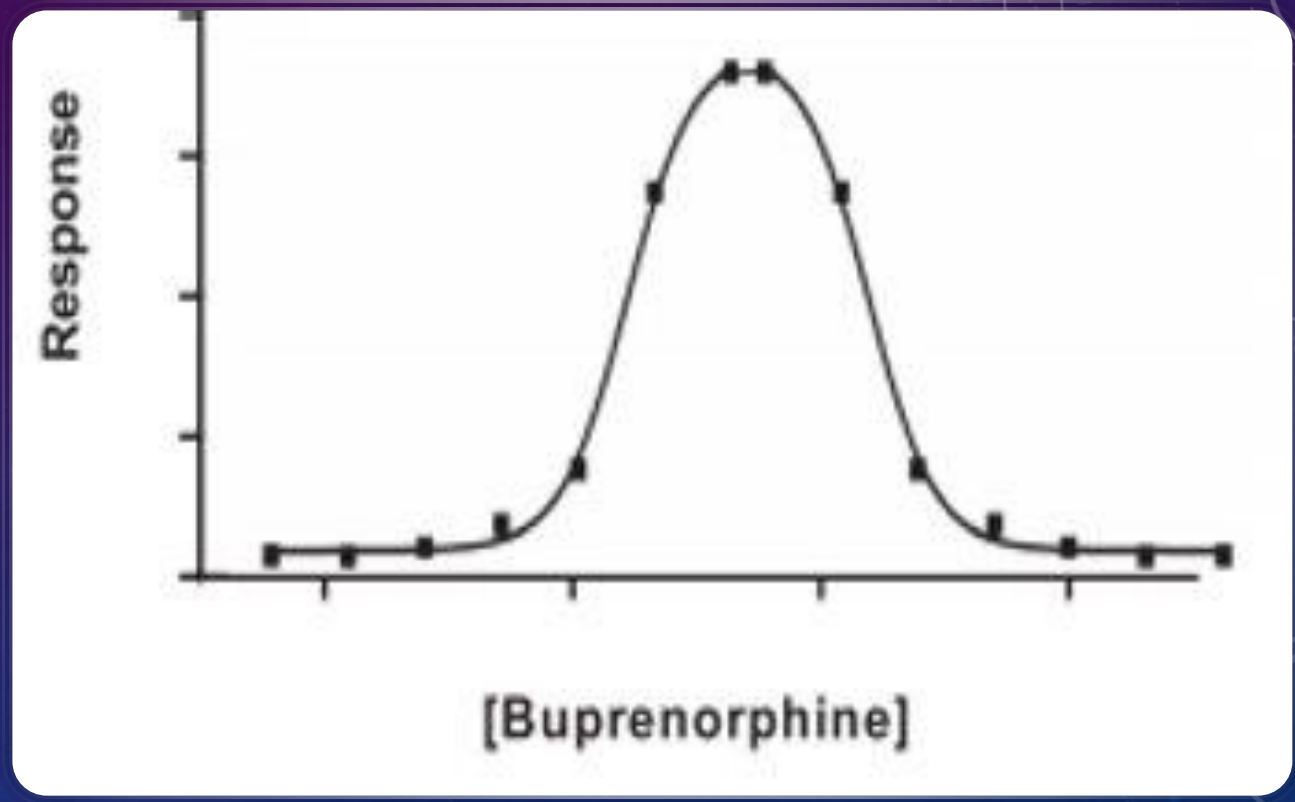


AGONIST-ANTAGONISTS

	MOP	KOP	DOP	NOP
buprenorphine	partial	x	x	x
butorphanol	antagonist	agonist	agonist	x
nalbuphine	antagonist	partial	agonist	x
pentazocine	antagonist	agonist	agonist	x

BUPRENORPHINE

- Partial MOP agonist (ceiling effect)
- Weak KOP/DOP antagonist
- Semisynthetic derivative of thebaine
- Highly lipophilic
- Produces analgesic effects at lower plasma concentrations
- Lower potential for tolerance, respiratory depression and overdose
- QT prolongation
- Onset: 10 - 30 minutes (IV, Peak: 1 hour)
- Duration: 6 hours (IV)
- Bioavailability: 29% (SL), Variable
- $T_{½}$: 2.2 hours (IV), 37 hours (SL)



NALBUPHINE

- KOP partial agonist
- MOP partial antagonist
- Typically used in obstetrics
  - Often used to treat pruritis caused by other opiates
- Less respiratory depression
- Onset: 2 - 3 minutes (Peak 30 minutes)
- Duration: 3 - 6 hours
- Bioavailability: very poor (high 1st pass metabolism)
- $T_{½}$ = 5 hours

BUTORPHANOL

- MOP antagonist
- KOP partial agonist
- Typically use in obstetrics
- Less respiratory depression
- Useful in preventing and aborting the dry cough associated with MOP agonist use.
- Onset: 1 - 2 minutes (IV, Peak: 1 hour), 15 minutes (Nasal, Peak: 1 – 2 hours)
- Duration: 3 – 4 hours
- Bioavailability : 5% - 17% (high 1st pass metabolism)
- $T_{½}$: 2 - 9 hours, active metabolite hydroxybutorphanol: 18 hours

NALOXONE & NALTREXONE

- Pure, competitive antagonist at MOP, KOP and DOP
  - Highest affinity at MOP
  - Naloxone
    - low bioavailability
    - fast onset
    - short duration
  - Naltrexone: oral dosing

  - What happens if you give naloxone to a patient with no opioid agonist on board?

OPIOIDS IN RENAL IMPAIRMENT AND DIALYSIS

- Morphine clearance not affected by renal insufficiency
  - M3G & M6G will accumulate
- CrCl 10-50 mL/min
  - 50% - 75% of the original dose
- CrCl < 10 mL/min
  - Morphine is not recommended

OPIOIDS IN RENAL DYSFUNTION

SAFE

- **Fentanyl** considered relatively safe in renal failure
- **Methadone** is difficult to titrate and should be managed by an experienced provider (palliative or pain management)

CAUTION

- **Oxycodone** - use lower dose/longer time intervals and assess tolerance
- **Hydromorphone** - **active metabolite quickly accumulates** between HD treatments but is effectively removed during HD
  - With careful monitoring, it may be used safely in dialysis patients.
  - ***Use with caution*** in patients with a GFR < 30mL/min who have yet to start dialysis or who have stopped HD.

BEWARE

- **Morphine** - not recommended for chronic use in renal insufficiency (GFR <30 mL/min) - use only immediate release if no other options
- **Meperidine -** can cause seizures
- **Codeine –** can cause profound toxicity

OPIOIDS IN LIVER FAILURE

- Adverse Effects: Gastritis, Portal Hypertensive Gastropathy, and/or Ulcers
  - Often coupled with delayed gastric emptying
  - ***Do NOT prescribe ER formulations to Cirrhosis patients***
- Patients with Cirrhotic Liver & Ascites have increased volume of distribution
  - Secondary to third spacing
  - Increased risk of adverse effects with hydrophilic opioids
- Decreased production of Alpha-1-acid Glycoprotein and Albumin
  - Results in higher free-drug level of highly protein-bound opioids
- Start with lower initial doses and titrate to desired effect

OPIOIDS IN LIVER FAILURE

- SAFEST: Fentanyl (opioid of choice)
  - Requires little residual liver function
- CAUTION:
  - Morphine:
    - Low dose/Normal interval in early liver disease
    - Longer interval in advanced disease
  - Oxycodone:
    - Reduce dose to 30% - 50% of recommended starting dose

OPIOIDS IN LIVER FAILURE

- CAUTION:
  - Hydrocodone:
    - Only available as combination medication (w/acetaminophen)
    - Limits dosing
  - Methadone:
    - HCV infection can INCREASE drug clearance
    - Methadone needs to be monitored & titrated carefully, but is woefully underused

OPIOIDS **NOT** RECOMMENDED IN LIVER FAILURE

- Codeine and Tramadol
  - Avoid
- Meperidine
  - **Please avoid always**
- Hydromorphone
  - Glucuronide metabolites
    - NO analgesic properties
    - Can be **neurotoxic**

TOLERANCE

- Tolerance is a diminished physical response to a drug, typically due to the down regulation of receptors with prolonged use
  - Consequences of the lack of cross-tolerance
- Dependence is a function of withdrawal
  - The body requires a specific dose of a particular drug in order to prevent withdrawal.
- Addiction is a disease.
  - Can occur regardless of tolerance or dependence.

QUESTION #2

OPIOID EFFECT LEAST LIKELY TO EXHIBIT TOLERANCE FOLLOWING PROLONGED OPIOID ADMINISTRATION.

- A. Analgesia
- B. Bradycardia
- C. Respiratory Depression
- D. Miosis
- E. Euporia

OPIOID SIDE EFFECTS

Central

- Respiratory Depression
- Euphoria: Dopamine release in the nucleus accumbens
- Dysphoria: KOP agonist
- Nausea/vomiting: stimulation of CTZ
- Miosis: stimulation of Edinger Westphal nucleus of the third cranial nerve
- Bradycardia and vasodilation: vagal center

Peripheral

- Constipation: high density of receptors in the gastrointestinal tract
- Urinary Retention
- Pruritus/urticaria: mast cell degranulation and histamine release

SIDE EFFECTS OF OPIOIDS

- Are not allergies
- Side effects should be anticipated and managed
  - Ondansetron, diphenhydramine, bowel regimen
- Change class if the side effects are not tolerated

SUGGESTED BOWEL REGIMENS

Medication	Dose
Polyethylene glycol (Miralax)	17 g powder dissolved in 4 – 8 ounces of liquid daily or bid
Bisacodyl (Dulcolax)	5 – 15 mg po 10 mg pr in NPO or dysphagia
Sennosides (Senna)	8.6 mg tablets, 2 tablets po daily or bid
Docusate (Colace)	50 – 500 mg per day divided daily to qid

OPIOID ALLERGY/FACT OR FICTION?

True allergies are rare!

- Pseudoallergy is the result of histamine release: flushing, itching, sweating, mild hypotension.
- Premedicate with an H1 or H2 blocker.

Uticaria, pruritis, sneezing are common

Risk of cross-sensitivity is extremely low

- Switch from natural/semi-synthetic to a synthetic and vice versa if a true allergy is suspected.

ON THE HORIZON (MIXED AND BIASED OPIOIDS)

- Targinact: oxycodone + naloxone
- Difelikefalin: selective KOP agonist
- MOP agonist + DOP antagonist (UFP-505)
- Mixed opioid – NOP agonist (cebranopadol)

MISCELLANEOUS

- Diphenoxylate: opioid agonist
  - Lomotil: a subtherapeutic dose of atropine added as an abuse deterrent (CV)
- Loperamide: opioid agonist (OTC)
- Methylnaltexone: MOR opioid antagonist
- Alvimopan: MOR opioid antagonist

PRESCRIPTION PEARLS

- Use electronic system
  - Federal SUPPORT Act
    - If exempt: one medication per prescription.
- No more than three days supply for acute pain
- No benzodiazepine + opioid combination
- Include diagnosis or indication
- No codeine for children
- Watch the MME (Morphine Milligram Equivalents)
- Prescription Drug Monitoring Programs (all 50 states as of 8/28/21)
- Hospice and Long Term Care Patients

OPIOID SAFETY

- Opioid use disorder
  - Chronic brain disease in which people continue to use opioids in spite of harms caused by their use
  - 2.1 million in the US (2021)
- Institute for Safe Medication Practices (ISMP) www.ismp.org
  - Free resources
  - Best Practices for Hospitals
    - Know patient's opioid status (naïve v. tolerant)
- Naloxone nasal spray for home use

CASE STUDY

- CM is a cancer patient who weight 89 kg, is currently taking MS Contin 60 mg tid and oxycodone 10 mg q6h prn for breakthrough pain. She has come to the ED complaining of abdominal pain and not having a BM for at least 3 days. Her labs consist of SCr 2.1, AST 31, ALT 27, WBC 9.17, PLT 329, BUN 28, NA 146
  - Does morphine 6-glucuronide likely play a role in the analgesic effect in the patient's pain relief?
  - What would be the recommended take home bowel regimen?

TAKE HOME POINTS

- Avoid opioids in head injury or when increased ICP is suspected.
- All opioids cross the placenta
- Avoid "cookbook" dosing.
- Fentanyl is the safest option in renal and hepatic dysfunction.
- Meperidine is not your friend.
- Avoid Codeine in children and in pregnancy.

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QUESTIONS?

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