

Pain Management



Leveraging the Opioid
Crisis:

Reviewing Various Opioids

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Learning Objectives

- Elucidation of the current state of the opioid epidemic and how it will affect you as a clinician
- Ability to readily describe and treat the systemic adverse affects related to opioids
- Fundamental competence with pragmatic opioid utilization



Paingry

A STATE OF

ANGER CAUSED BY

LONG TERM PAIN.



Opioids

Which is a greater cause of death in the United States?

A) Traffic Related Deaths

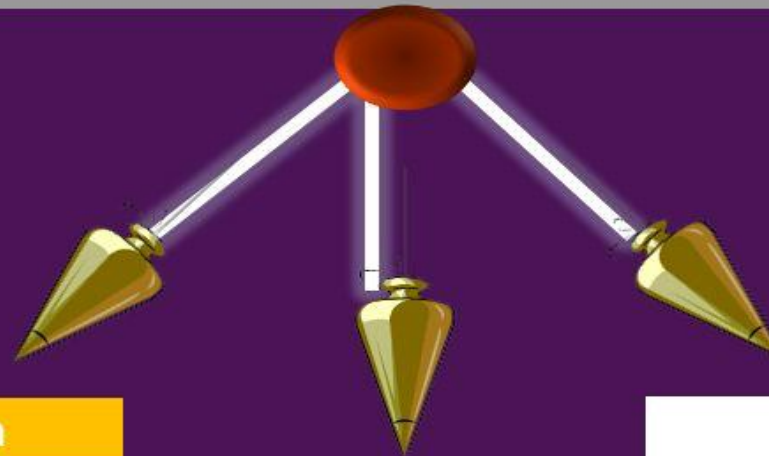
B) Opioids

Which is a greater cause of death in the United States?

A) Traffic Related Deaths

B) Opioids

The Opioid Pendulum



Opiophobia

Opiophilia

*Balance of
Addiction Medicine
and Pain Management
Principles*

DEA MISSION

- To prevent, detect, and investigate the diversion of controlled substances from legitimate sources
 - while
- ensuring an adequate and uninterrupted supply for legitimate medical and scientific purposes.



O.C. doctor gets 11 years in federal prison for selling prescriptions

Alvin Ming-Czech Yee of Mission Viejo often met with patients at Starbucks coffeehouses. He pleaded guilty in April.

October 17, 2013 | By Hailey Branson-Potts



An Orange County doctor who often saw patients at Starbucks coffeehouses was sentenced Thursday to 11 years in federal prison for selling prescriptions for highly abused medications to patients with no legitimate need for them.

"You abused the position," U.S. District Judge Andrew J. Guilford told Alvin Ming-Czech Yee before sentencing him. "People came to you for healing, and they came away worse for the experience."

Yee, 44, of Mission Viejo, pleaded guilty in April to seven counts of illegal distribution of a controlled substance by a practitioner.

Although Yee had reached a plea agreement with prosecutors and agreed to serve eight to 10 years in prison, the judge sentenced him to a longer term, saying Yee took advantage of a "position of trust and authority" and that the sentence needed to send a message to other doctors.



Authorities said Orange County doctor Alvin Ming-Czech Yee, center, brazenly... (Liz O. Baylen / Los Angeles...)

MEDICAL NECESSITY

Medical necessity is a United States legal doctrine, related to activities which may be justified as reasonable, necessary, and/or appropriate, based on evidence-based clinical standards of care.

An Rx must be issued “in accordance with a standard of medical practice generally recognized and accepted in the United States.”

What is the clinicians responsibility?

- There is a responsibility to:
 - Assure patients are using medications properly.
 - If aberrant behavior is observed, noted in testing, or received via a complaint...
 - Do NOT ignore it!

Common Characteristics

Unusual behavior in the waiting room

- Assertive personality
 - Often demanding immediate action

Unusual appearance

- Both Extremes, Overdressed or Untidy

Unusual knowledge of controlled substances

Ability to recite medical history with textbook symptoms

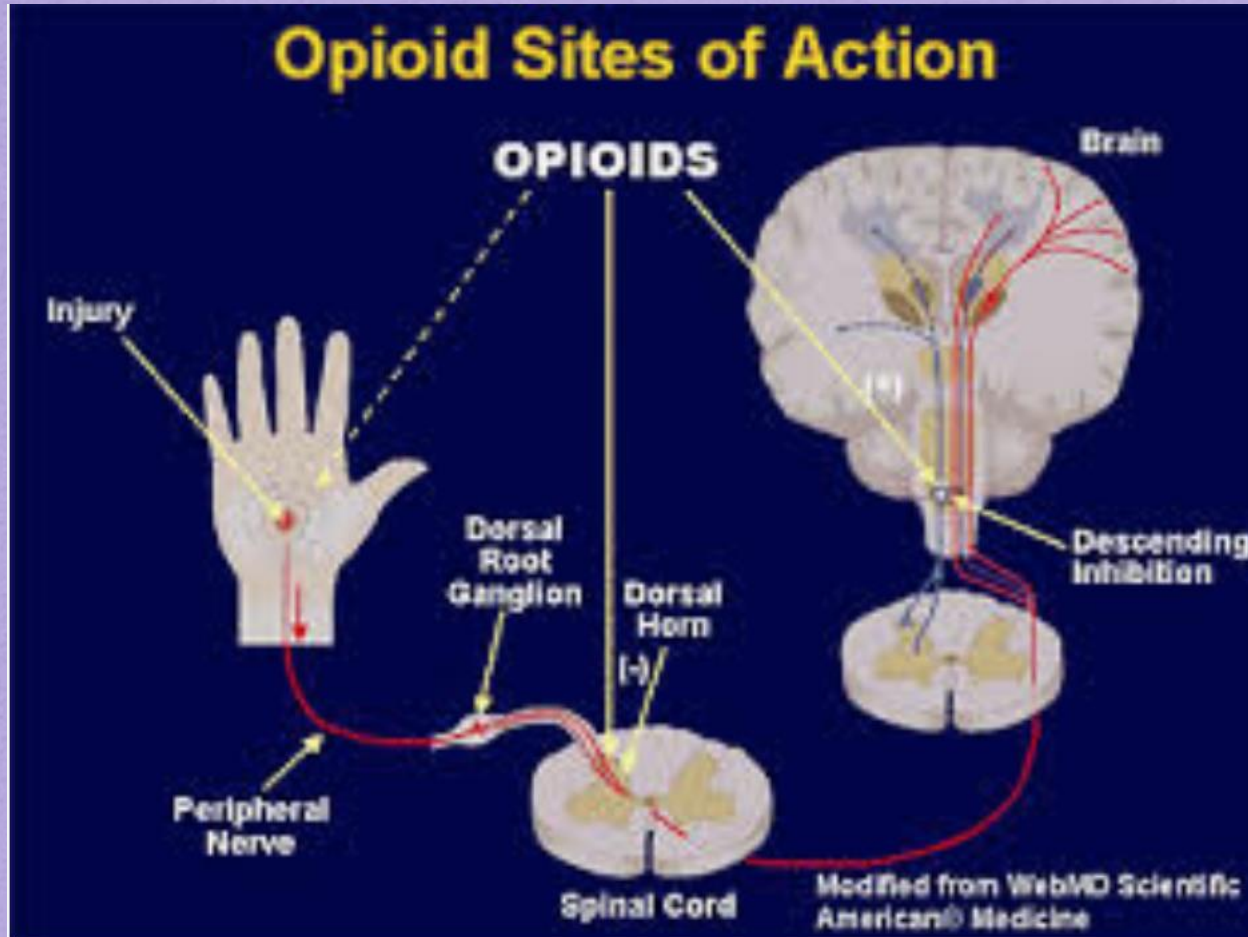
Evasive or vague answers to questions regarding medical history

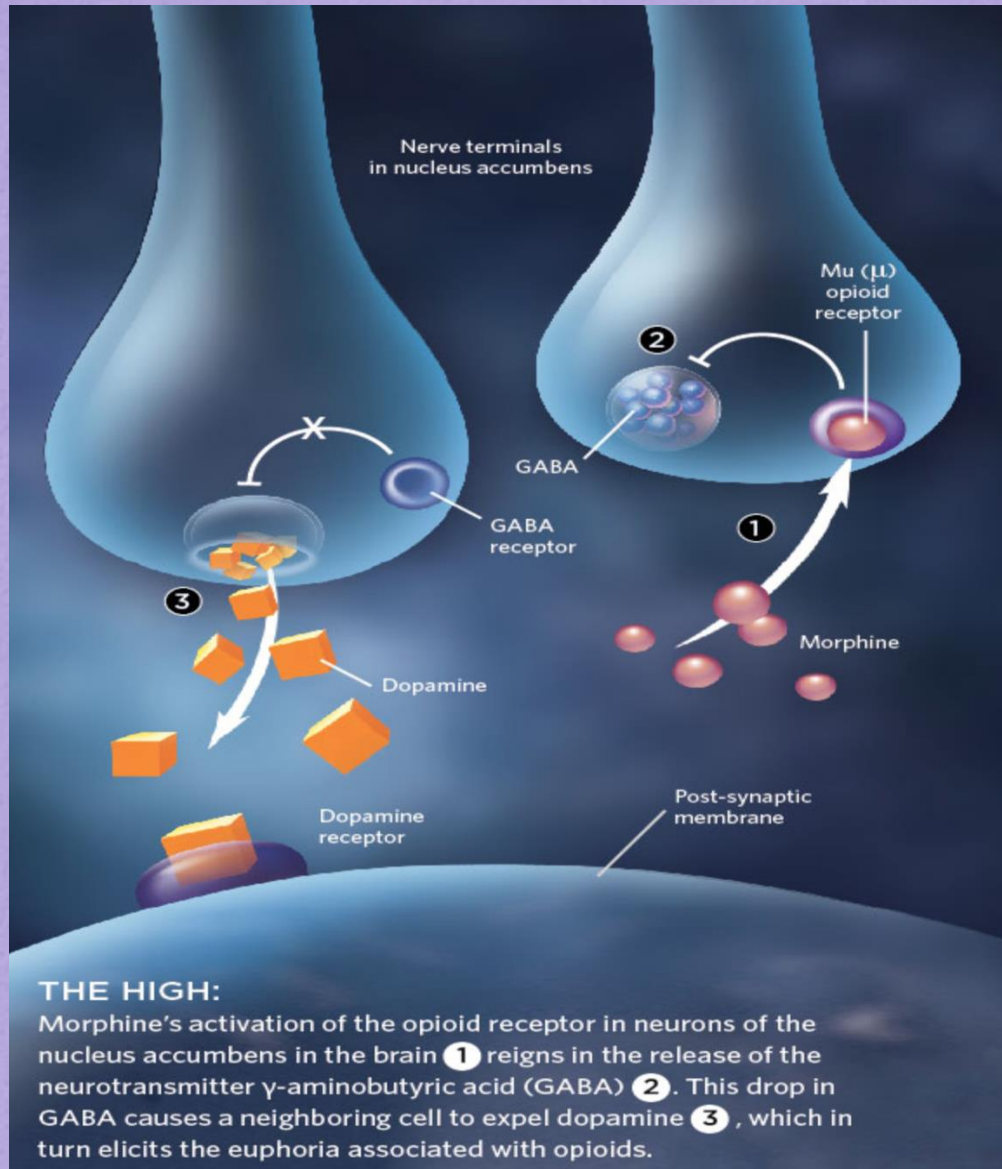
Reluctant to try different regimens, drugs, or to see other specialists

How Do Opioids Work?



Opioid Sites of Action



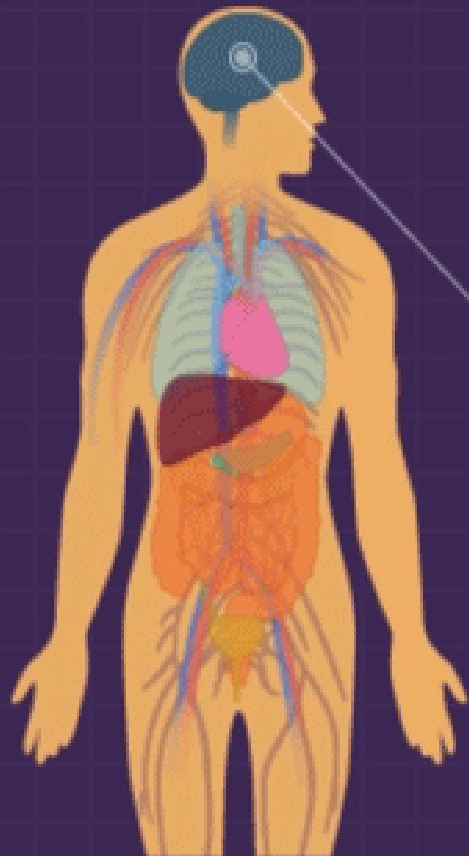


Opioid Pharmacodynamics

- Neurologic
- Respiratory
- Cardiovascular
- Gastrointestinal



The Effects of Opiates on the Brain



• Opiate painkillers can cause daytime sedation or sleepiness.

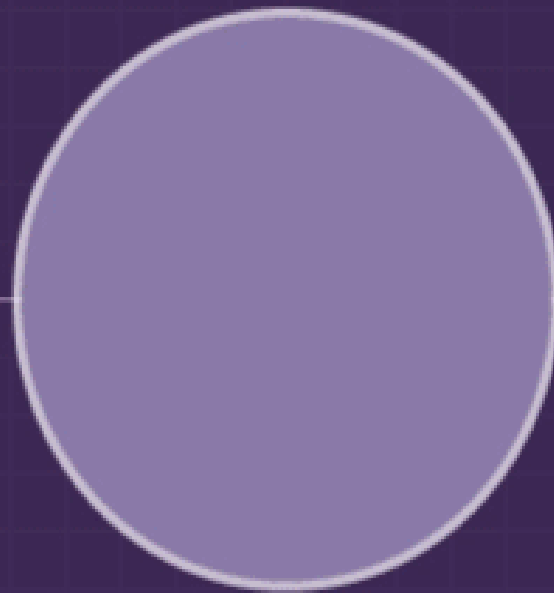
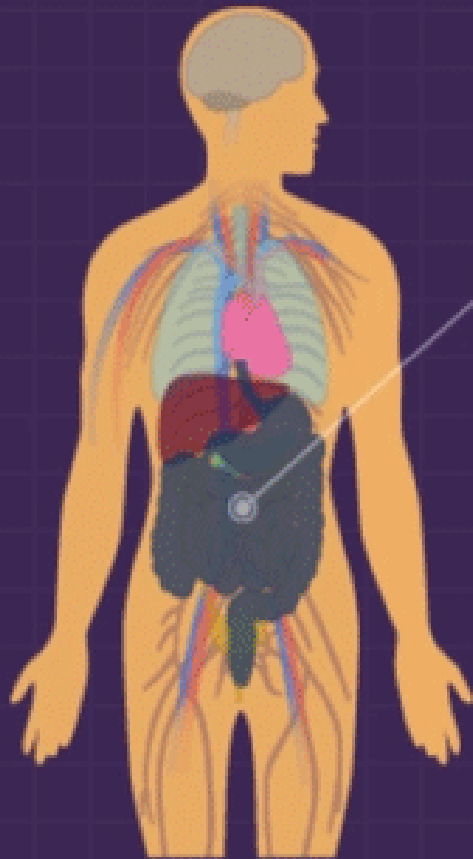
• Chronic painkiller use is associated with a higher risk of major depression.

Opioid Miosis

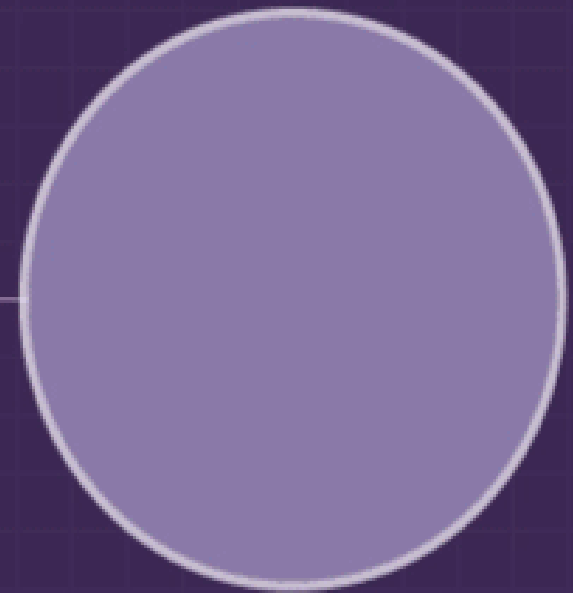
- Seen with all opioid agonists
- No tolerance develops
 - Hence useful in overdose dx
 - Even in tolerant addicts



The Effects of Opiates on the Digestive System



- Opiate-induced slow digestion can lead to constipation.



- Opioid painkiller abuse can lead to nausea and vomiting.

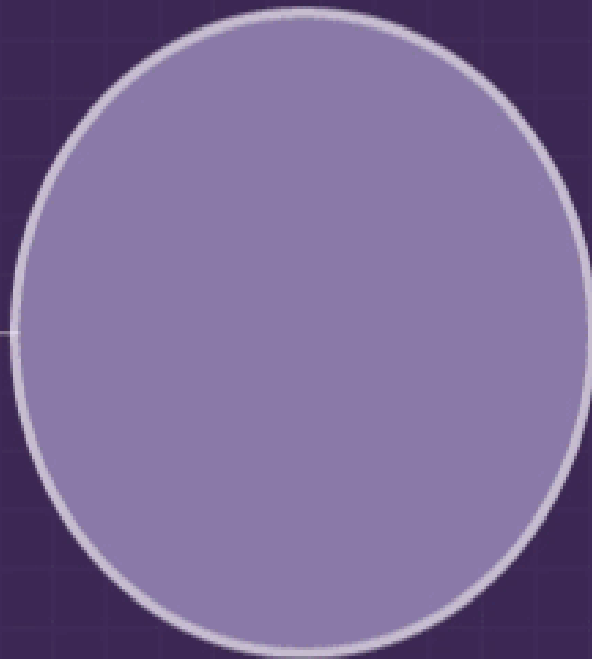
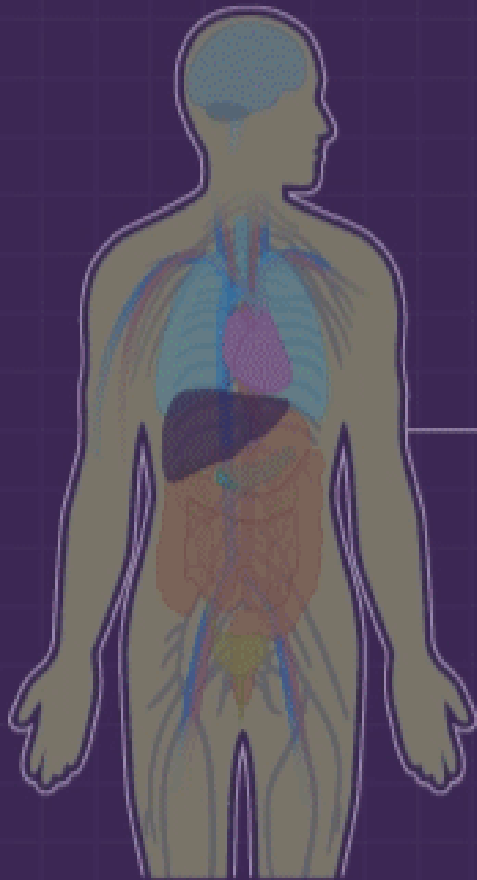
GI Effects

Opioid Pharmacodynamics

- Slowed peristalsis
 - Via enteric NS opioid receptors
- Nausea/Vomiting
 - Via chemoreceptor trigger zone



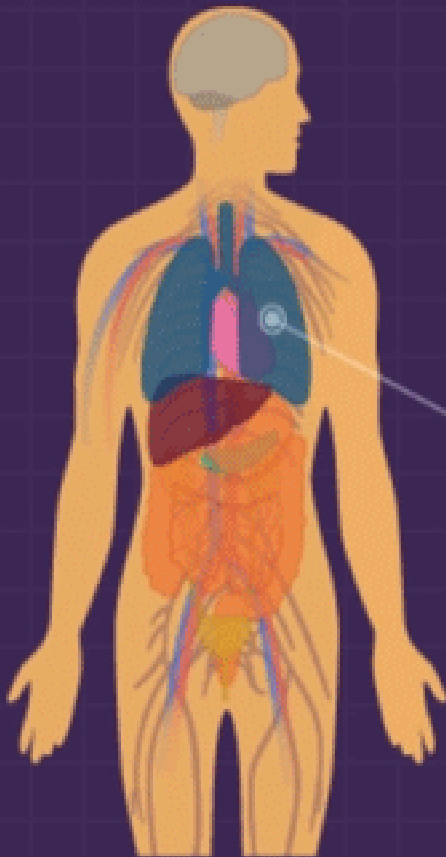
The Effects of Opiates on the Immune System



- Opioid painkillers can inhibit immune response, leading to increased susceptibility to infection.

Highest Morbidity Opioids

The Effects of Opiates on the Respiratory System



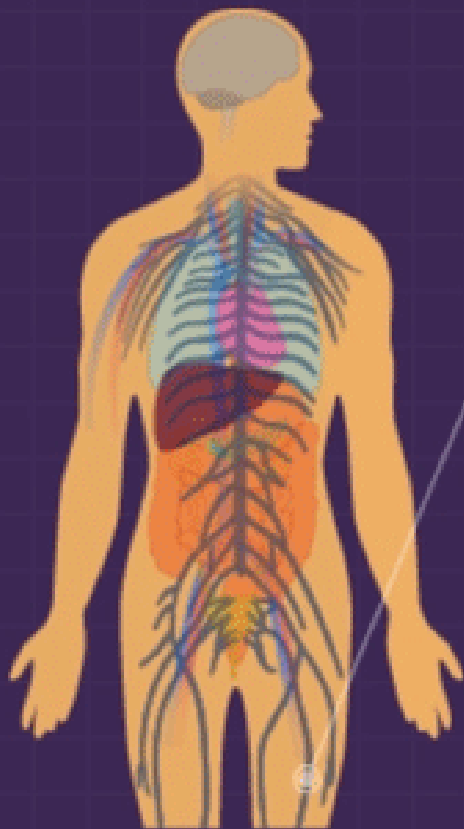
- Opiates can cause respiratory depression, which can slow breathing and result in death.

Respiratory Depression

- #1 way opioids kill
- Best way to avoid it?
- **HOLD IF SEDATED**
- **Avoid Polypharmacy**



The Effects of Opiates on the Nervous System



- Opioid-induced hyperalgesia can cause greater pain and sensitization.
- Opioids can cause psychomotor impairment, which is a slowing of physical movement.

Pharmacodynamics

Dependence

- Is this different from tolerance?
- When a patient is dependent, if the medication is abruptly stopped, they will have symptoms of withdrawal.
- Are those that are tolerant and/or dependent also addicted?
- Addiction is a complex condition, a brain disease that is manifested by compulsive substance use despite harmful consequence.

Pharmacodynamics

Tolerance

Tolerant to

- Euphoria
- Sedation
- Analgesia
- N/V
- Respiratory Depression

Not tolerant to

- Miosis
- Constipation



Pharmacodynamics Withdrawal

- Symptoms are of sympathetic overdrive
 - Anxiety, insomnia, diaphoresis, yawning, rhinorrhea, lacrimation
 - HTN, tachycardia
 - Hyperventilation
 - Mydriasis
- Except!: Diarrhea and abdominal cramping
- You don't die from it! (But it sure feels like it)

APPENDIX 1 Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____		Date and Time ____/____/____:_____	
Reason for this assessment: _____			
Resting Pulse Rate: _____beats/minute <i>Measured after patient is sitting or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120		GI Upset: over last 1/2 hour 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting	
Sweating: over past 1/2 hour not accounted for by room temperature or patient activity. 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face		Tremor observation of outstretched hands 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching	
Restlessness Observation during assessment 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds		Yawning Observation during assessment 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute	
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible		Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult	
Bone or Joint aches <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort		Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
Runny nose or tearing <i>Not accounted for by cold symptoms or allergies</i> 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks		Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____	

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Addiction

- Opioids are associated with high rate of addiction
- Use that results in physical, psychological, or social dysfunction (or a combination), as WELL AS continued use despite dysfunction



Pragmatic Use





Would you drive a car before you knew how to?

Quiz time!

- Which of the following drugs and dose combinations would deliver the highest dose of opioid to a patient?
 1. 2 mg PO Hydromorphone (Dilaudid) tablet
 2. 20 mg PO Oxycodone tablet
 3. 15 mg PO Morphine Immediate Release tablet
 4. 2 tabs of 10/325 Norco (Hydrocodone/Acetaminophen)

Quiz time!

- Which of the following drugs and dose combinations would deliver the highest dose of opioid to a patient?
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Equianalgesic Opioid Dosing

Drug	Equianalgesic Doses (mg)	
	Parenteral	Oral
Morphine	10	30
Buprenorphine	0.3	0.4 (sl)
Codeine	100	200
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Meperidine	100	300
Oxycodone	10*	20
Oxymorphone	1	10
Tramadol	100*	120

*Not available
in the US

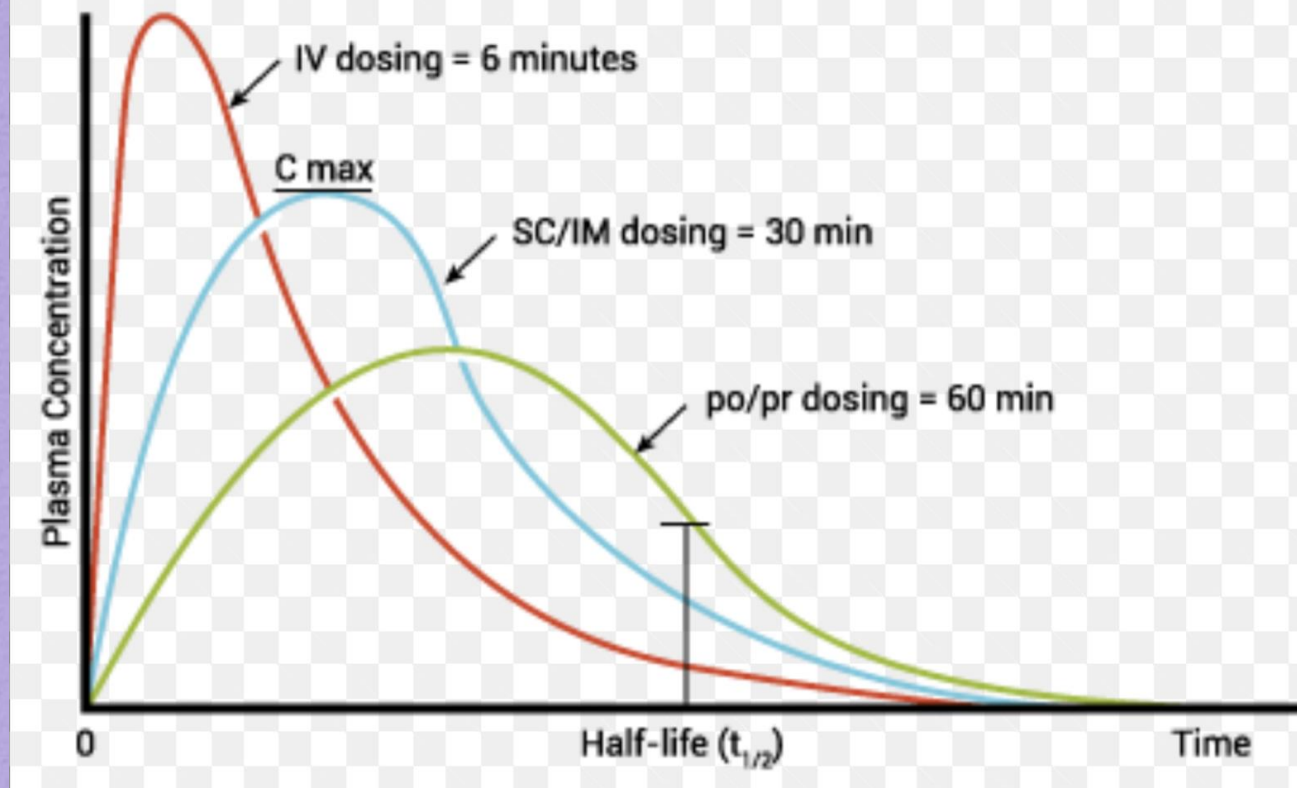
McPherson ML. *Demystifying Opioid Conversion Calculations: A Guide For Effective Dosing*. Amer Soc of Health-Systems Pharm, Bethesda, MD, 2010. Copyright ASHP, 2010. Used with permission.

NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

Incomplete Cross Tolerance

Time to maximal plasma concentration

Pharmacologic Dosing Curves After a Single Opioid Dose



Quiz time!

- Which of the following drugs is probably not the ideal choice in someone admitted with co-morbid end stage renal disease?
 1. IV fentanyl
 2. IV hydromorphone (dilaudid)
 3. IV morphine
 4. PO oxycodone

Quiz time!

- Which of the following drugs is probably not the ideal choice in someone in the hospital with end stage renal disease?
 1. IV fentanyl
 2. IV hydromorphone (dilaudid)
 3. **IV morphine**
 4. PO oxycodone

PRINCIPLE: START LOW AND GO SLOW

- **In using opioids to treat chronic non-cancer pain, emphasis is on SAFETY and SIDE EFFECT avoidance initially.**
- **Any medication should be given in its lowest doses, with slow increases over time to achieve maximal effect while reducing risks.**

Names to know

- **Agonists**

- Morphine
- Codeine
- Hydrocodone
- Oxycodone
- Meperidine
- Fentanyl
- Hydromorphone
- Methadone
- Tramadol

- **Antagonists**

- Naloxone
- Naltrexone

- **Agonist/Antagonist**

- Nalbuphine

- **Partial Agonist**

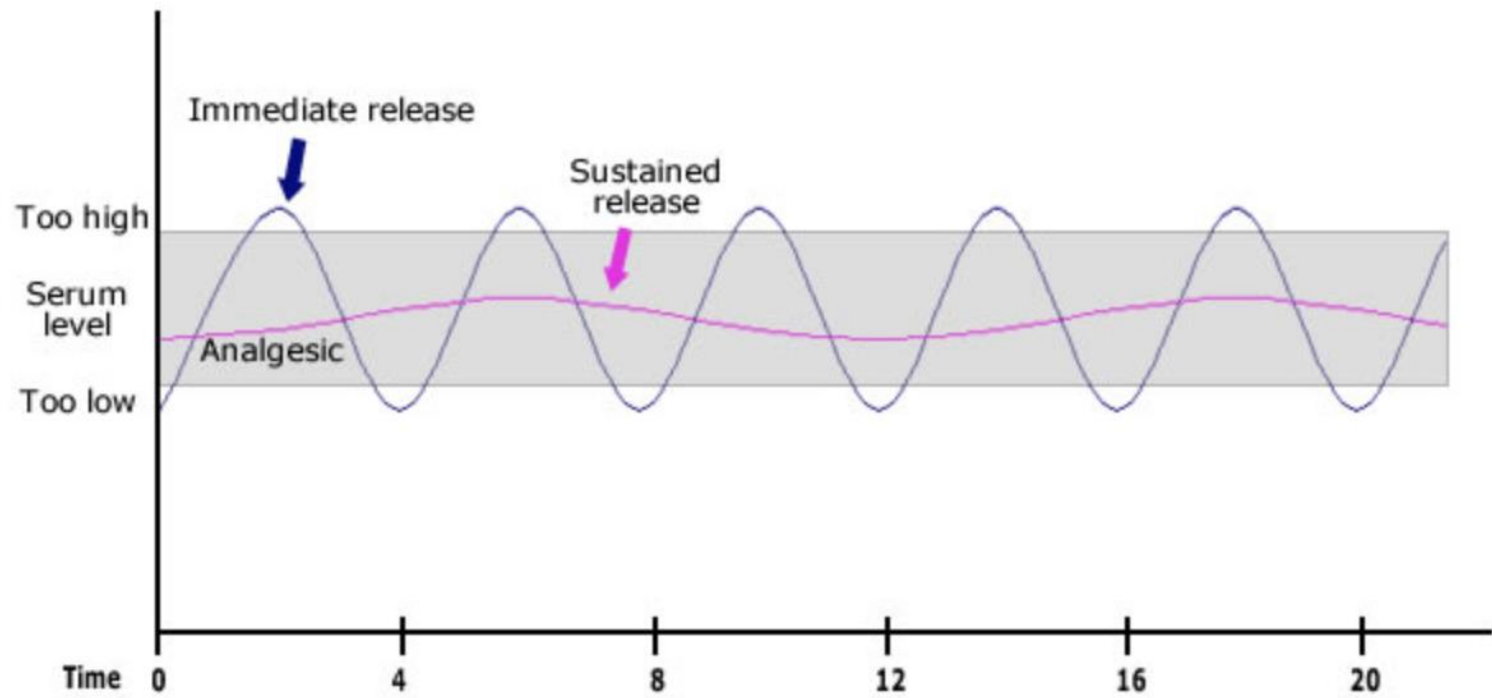
- Buprenorphine



Morphine

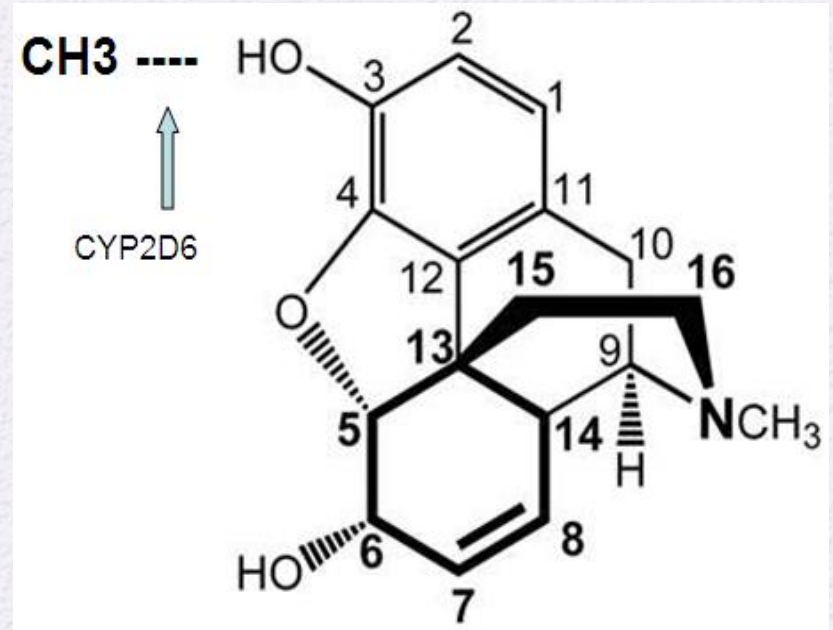
- Prototypical opioid
- Metabolic transformation in liver by conjugation with glucuronic acid
- 3-glucoronide morphine (90%, inactive) and 6-glucoronide morphine (10%, more potent agonist at u receptor, similar half life as morphine)
- Excreted by kidney, metabolites may accumulate in renal impairment
- Histamine release
 - Rash, Hypotension
- IV and PO forms. Tablets and liquid elixir
- Immediate release (MS IR) and sustained release form (MS Contin)

Advantages of sustained-release dosing



Codeine

- FDA Indications
 - Mild-mod pain,
 - cough,
 - diarrhea
- AKA methyldmorphine
- ‘Weak’ opioid
- Must be metabolized by CYP2D6



Codeine

- CYP2D6: 80 identified genetic variations, resulting in variable enzymatic activity ranging from 1% to 200%.
- Each individual can be classified:
 - Ultra-rapid metaboliser,
 - Extensive metaboliser
 - Intermediate metaboliser
 - Poor metabolise
- Ten percent of Caucasians are poor metabolizers and experience little analgesia.
- 3% of Caucasians are ultra-rapid metabolizers and have a higher incidence of codeine-related adverse reactions.

Oxycodone

- Oral tablets. Liquid elixir available
- Relative potency: oxycodone : morphine 2:3
- Sustained release formula: oxycontin
 - Xtampza ER
- Percocet (oxycodone/tylenol)

Hydromorphone

- 5-7 times more potent than morphine
- Tolerance and physical dependence is more intense than morphine because of its high potency
- Respiratory depression same as morphine

Hydrocodone

- Component of Vicodin, Lortab, Lorcet
- FDA Indications: mod-sev pain, cough
- Active and prodrug (P450, CYP2D6)
 - Hydromorphone
- CYP2D6 polymorphism also affects hydrocodone pharmacological effect

Fentanyl

- Synthetic opioid, different structure than morphine
- High potency, 80 to 100 times more potent than morphine
- Rapidly acting drug when given IV.
- Short acting (30-45 min) due to redistribution when given IV in smaller dose.

Fentanyl



- Transdermal
 - Slow onset as it builds up subQ depot
 - Sustained release for chronic pain
 - Often used for pts with “GI” issues
 - Variable time achieving therapeutic levels with skin differences

Meperidine

- About 1/8th potency of morphine
- Accumulation of its metabolite, normeperidine, can cause neurotoxicity, a potentially severe adverse effect, especially in renally impaired patients.
- Inhibit reuptake of monoamine neurotransmitters -- Potential to cause life-threatening serotonin syndrome when used concurrently with monoamine oxidase inhibitors (within 2 to 3 weeks) or other agents with serotonin reuptake inhibiting properties

Meperidine

- One of the most efficacious agents available for treatment of post-operative shivering
- Not opioid receptor mediated, primarily related to a change in shivering threshold.
- High potential for abuse

Tramadol

- An oral scheduled analgesic
- Works by two mechanisms:
 - Mu receptor agonism
 - Blocks the reuptake of 5-HT and NE
- Used for mild to moderate pain



Commonly prescribed withdrawal medications

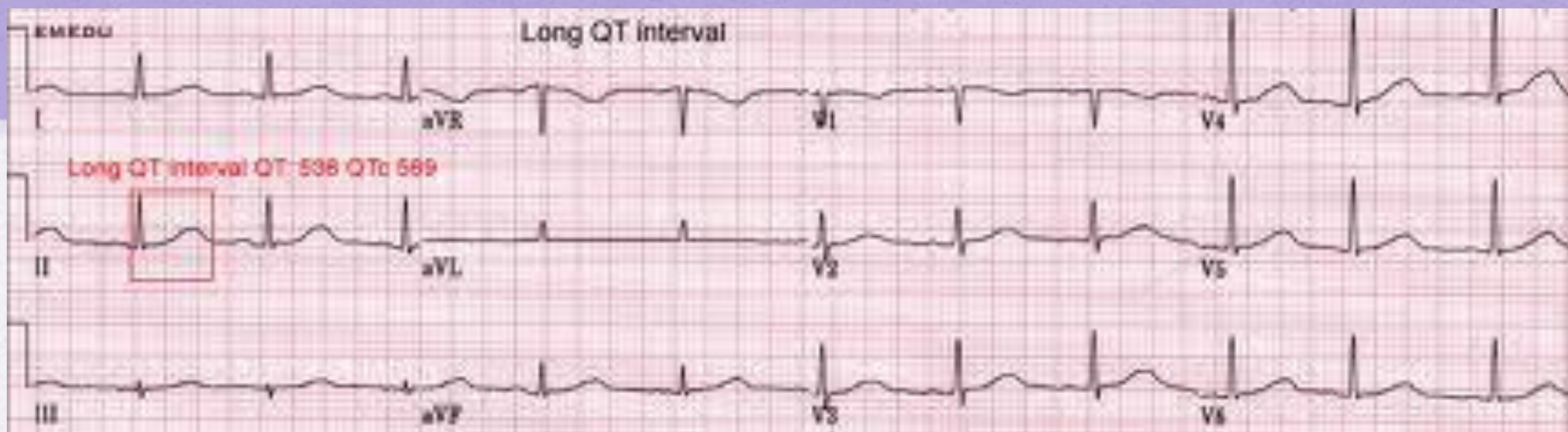
- Methadone
- Buprenorphine

Methadone

- Pharmokinetics
 - Oral Peak concentration is 1-7 hours
 - Elimination half life is 7-59 hours
 - Variable bioavailability with resultant different duration of action and dosing regimens
- Used for drug detoxification (need a license), opioid abuse, neuropathic pain, and somatic pain

Methadone

- The usual dose for pain treatment in an opioid naïve patient can range from 2.5 to 10 mg PO every 3-6 hours
- The usual maintenance dose for abuse is 80 – 120 mg/day orally
- Renal and hepatic impairment may increase the accumulation of methadone and therefore dosing should be adjusted
- Black box warning: can cause QT prolongation and serious arrhythmia (torsades de pointes)
 - Baseline EKG!



Opioid Conversion

Convert to daily methadone

Daily Oral Morphine Equivalents	Oral morphine: oral methadone conversion ratio
< 100 mg	3:1
100 – 300 mg	5:1
300 – 600 mg	10:1
600 – 800 mg	12:1
800 – 1000 mg	15:1
> 1000 mg	20:1

Buprenorphine

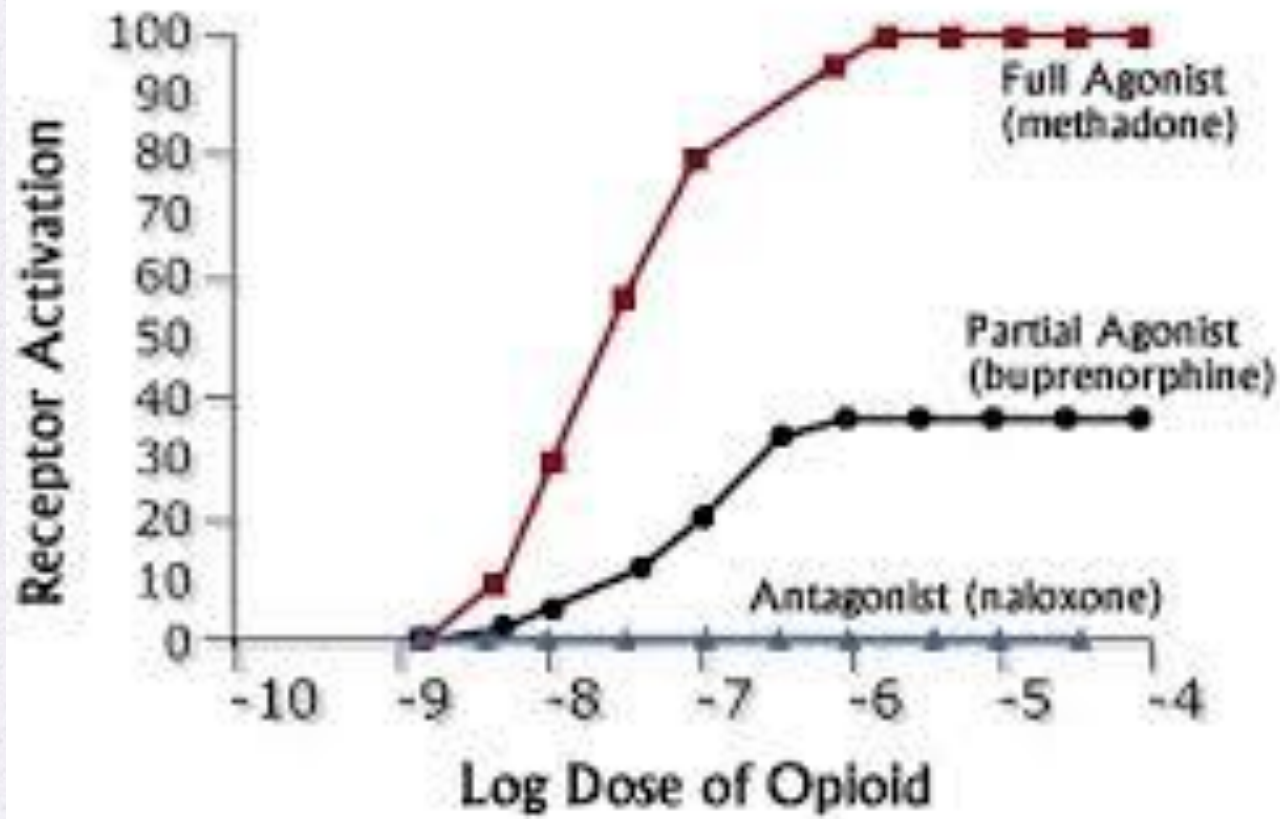
- Subutex = Buprenorphine
- Suboxone = Buprenorphine + naloxone
- Used for detoxication and long term replacement therapy for opioid dependence
- Buprenorphine: partial agonist at mu-opioid receptor and antagonist at k receptor. T_{1/2} 24 to 42 hours
- Ceiling effect
- high-affinity blockade significantly limits the effect of subsequently administered opioid agonists

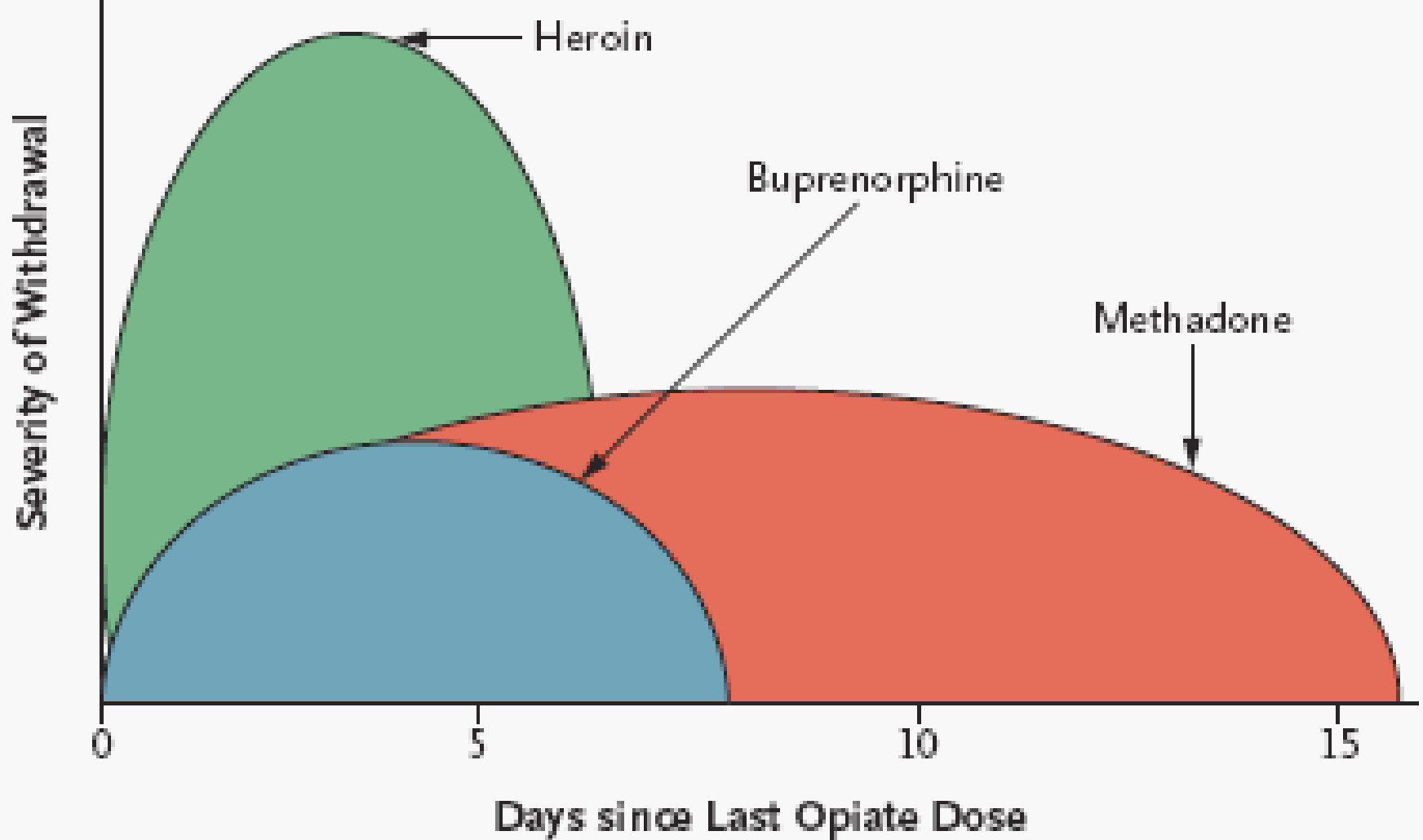
Management of Patients

Maintained on Suboxone/Subutex

- For elective surgery: titrate buprenorphine dose down and transfer the patient to a full opioid agonist prior to surgery.
- Emergent situation: higher doses of a full agonist opioid may overcome the blockade, with close monitoring by trained staff. Avoid long acting opioid to minimize the duration of respiratory depression
- Consider non opioid drugs (Ketorolac, etc)
- Consider regional techniques (epidural, peripheral nerve block etc)

Receptor Activation: Full Agonist, Partial Agonist, Antagonist



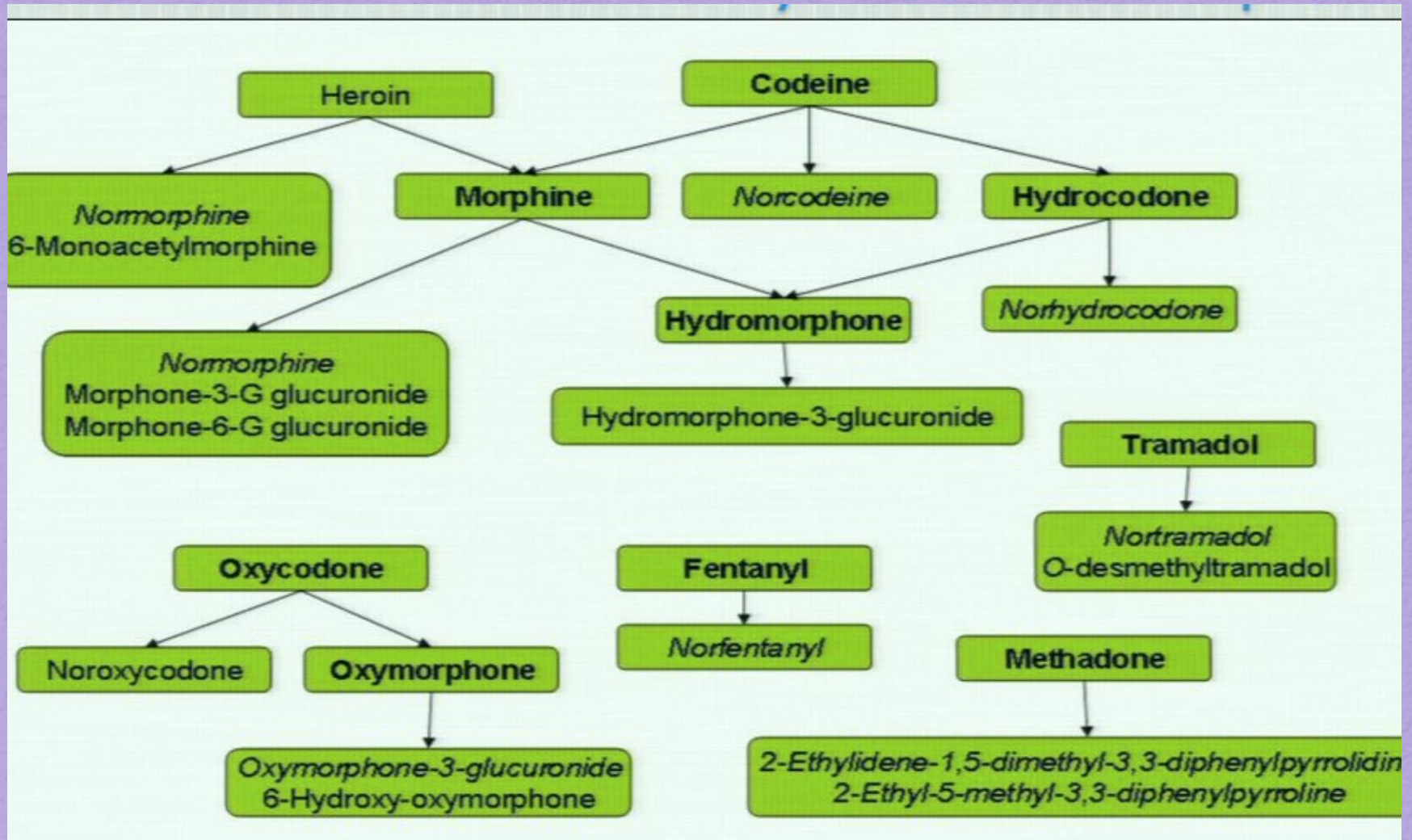


- **Blinded abrupt d/c buprenorphine 8mg/day:**
 - Less intense vs heroin, methadone withdrawal
 - Briefer duration of withdrawal sx vs methadone

Urine Drug Screen

Drug	Time
Alcohol	7-12 hours
Amphetamine	48 hour
Benzodiazepine	3 days (short acting) 30 days (long acting)
Cocaine	2-4 days
THC	3 days (single use) 10-15 days (daily use) > 30 days (long term use)
Codeine	48 hours
Heroin	48 hours
Methadone	3 days
Oxycodone	2-4 days
Hydromorphone	2-4 days
PCP	8 days

UDS Interpretation



Overdose

- Clinical Signs
 - Respiratory depression/arrest
 - Sedation or unresponsive
 - Miosis
- ABCs!! : Support ventilation
- Antagonist: Naloxone



Naloxone

- Opioid Antagonist
- Short half life of 1 hour, duration is 15 min to 4 hours
- CAUTION: Reversal is short-lived
- VERY poor bioavailability
 - Combine in opioid pills to prevent IV abuse
- Is a competitive antagonist