Opiate Use Disorder: Opioid Withdrawal Treatment

Dawn Miller, PharmD, BCPS, BCCCP

Clinical Pharmacy Coordinator, Mount Carmel Grove City Hospital

OBJECTIVES

- Review the pathophysiology and mechanisms of opioid use disorder (OUD) and opioid withdrawal
- Recognize the signs and symptoms of opioid withdrawal and utilize a validated scoring tool to grade severity (Clinical Opiate Withdrawal Scale = COWS)
- Design a pharmacotherapeutic plan to treat opioid withdrawal including patient preference, timing of initiation, choice of agent, specific dose, route, and dosing interval
- Compare buprenorphine, methadone, and naltrexone in the treatment of OUD

Historical Misconceptions About Addiction

- "*For much of the past century, scientists studying drug abuse labored in the shadows of powerful myths and misconceptions about the nature of addiction. People addicted to drugs were thought to be morally flawed and lacking willpower. Those views shaped society's response to drug abuse, treating it as a moral failing rather than a health problem, which led to emphasis on punishment rather than prevention and treatment*."

https://nida.nih.gov/sites/default/files/soa_2014.pdf

Dispelling Misconceptions About Addiction

- "*Today, thanks to science, our views and our response to addiction has changed dramatically. Groundbreaking discoveries about the brain have revolutionized our understanding of compulsive drug use, enabling us to respond effectively to the problem. As a result of scientific research, we know addiction is a disease that affects both the brain and behavior. Increased understanding of the basics of addiction will empower people to make informed choices in their own lives and adopt science-based policies and programs that reduce drug abuse and addiction in their communities*."

  - Nora D Volkow, MD (Director National Institute on Drug Abuse)

Background: Opioid Mechanism of Action

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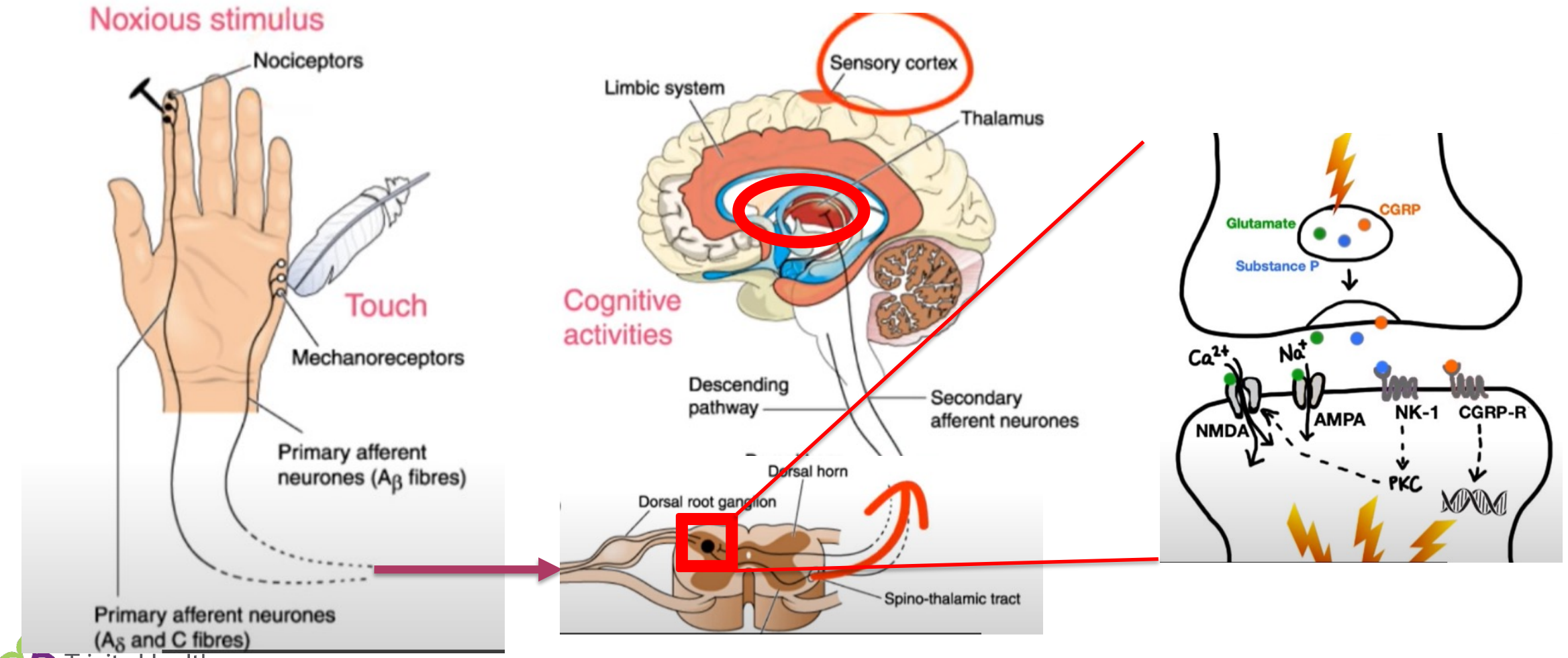
Background: Transmission of Pain



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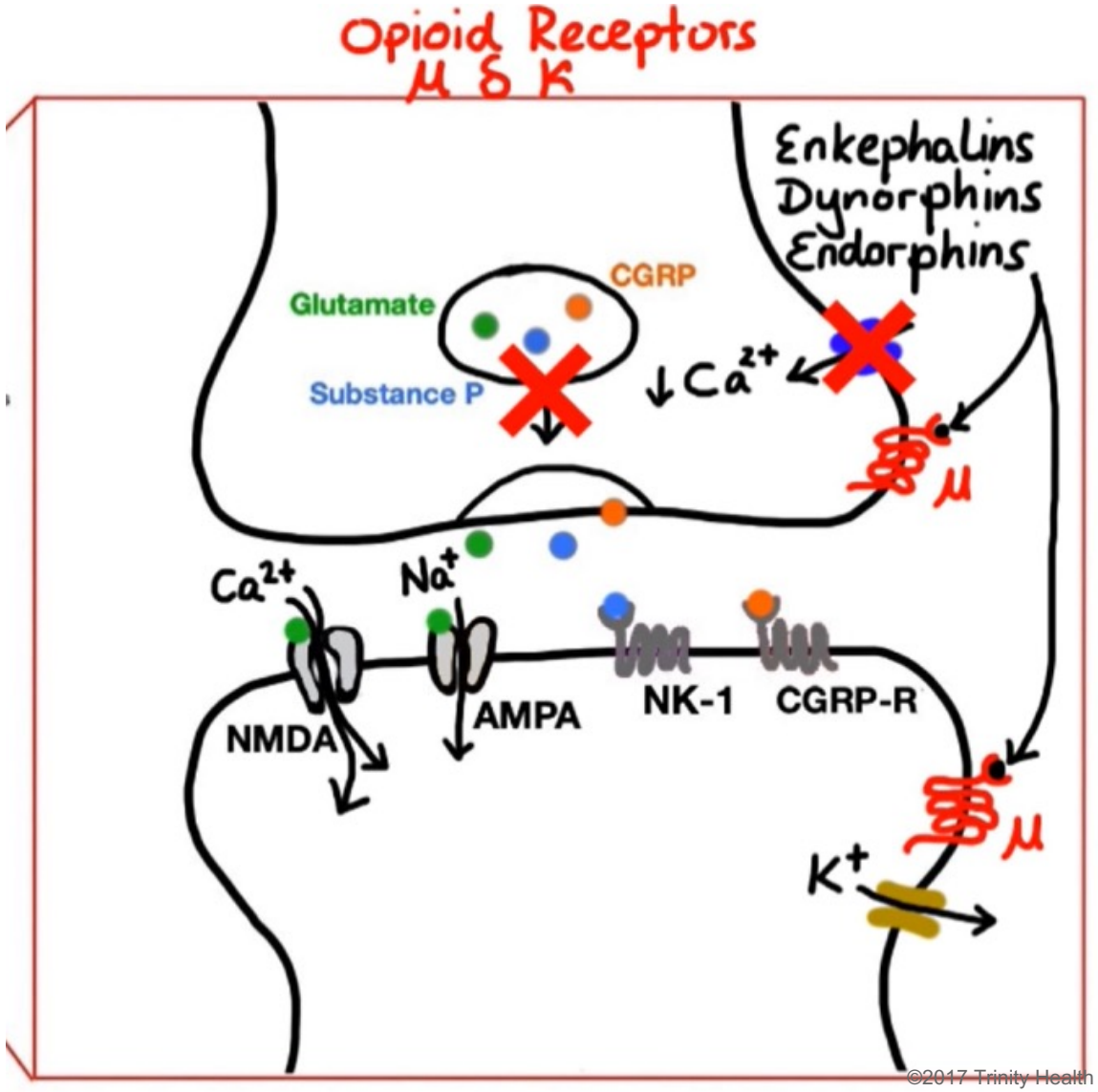
Background: Endogenous Opioid Mechanism

- To deal with pain the body releases endogenous opioid substances to counteract the pain transmission pathway
  - Enkephalins, dynorphins, and beta-endorphins
  - Chronic activation cause complex changes that lead to tolerance



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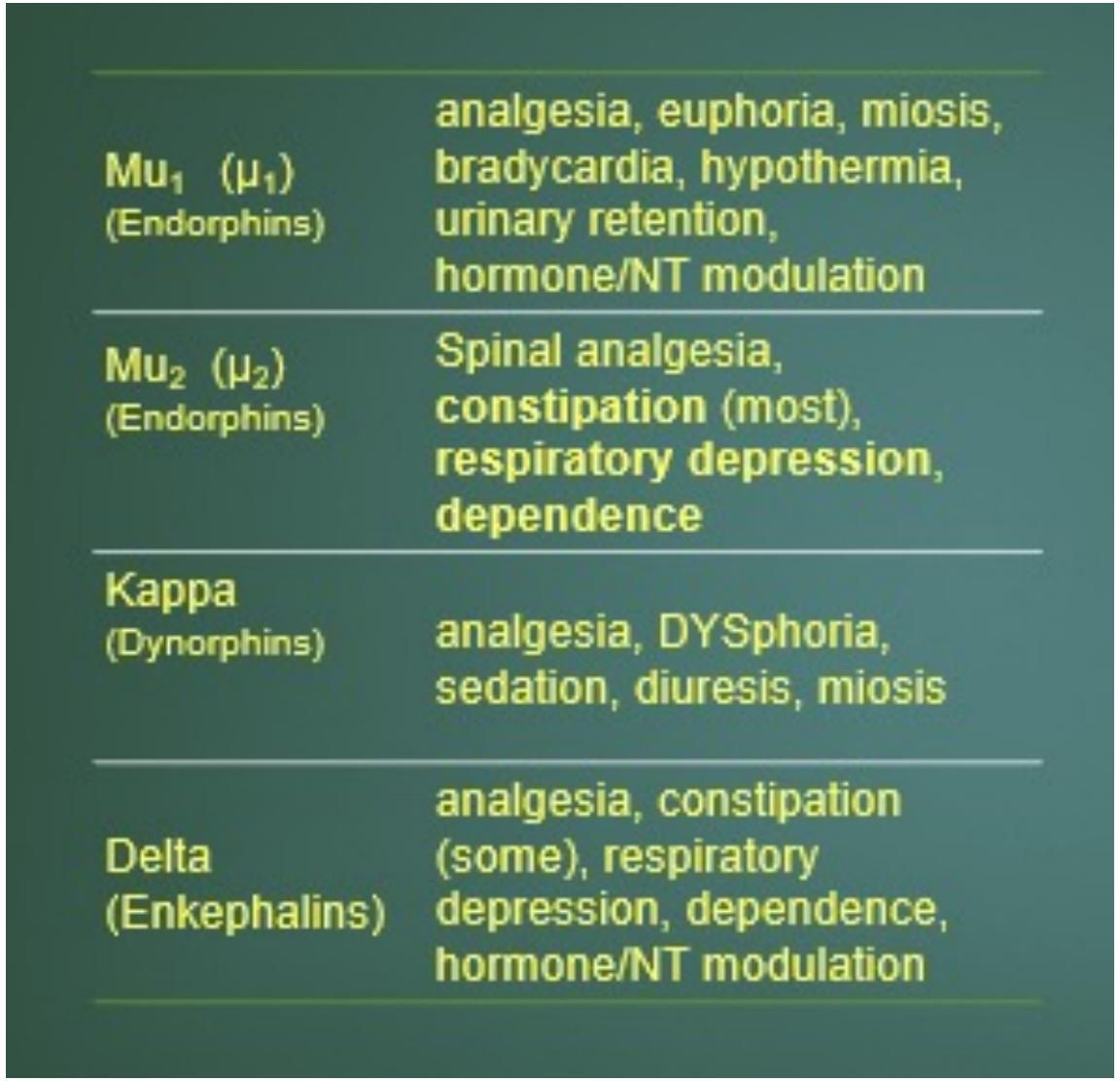
Review of Opioid Receptors

- The opioid class of medications act on specific opioid receptors in the nervous system to reduce perception to pain
  - Opioid receptors are located throughout both the central and peripheral nervous systems (CNS and PNS)

- Three classical types of opioid receptors
  - **Mu (μ) opioid receptor**
  - Delta (δ) opioid receptor
  - Kappa (κ) opioid receptor

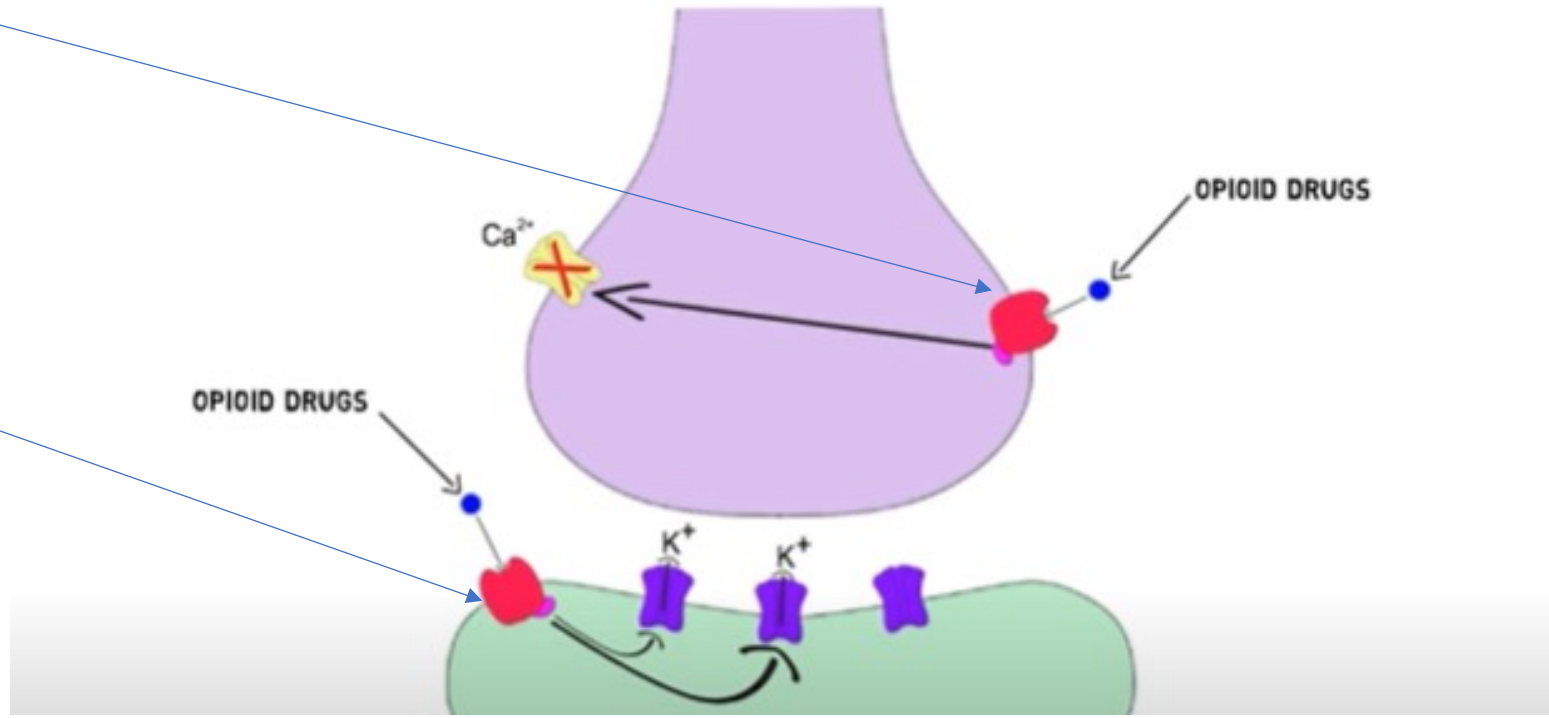


Mu_1 (μ_1) (Endorphins)	analgesia, euphoria, miosis, bradycardia, hypothermia, urinary retention, hormone/NT modulation
Mu_2 (μ_2) (Endorphins)	Spinal analgesia, **constipation** (most), **respiratory depression**, **dependence**
Kappa (Dynorphins)	analgesia, DYSphoria, sedation, diuresis, miosis
Delta (Enkephalins)	analgesia, constipation (some), respiratory depression, dependence, hormone/NT modulation

Mechanism of Action Opioids: Pain

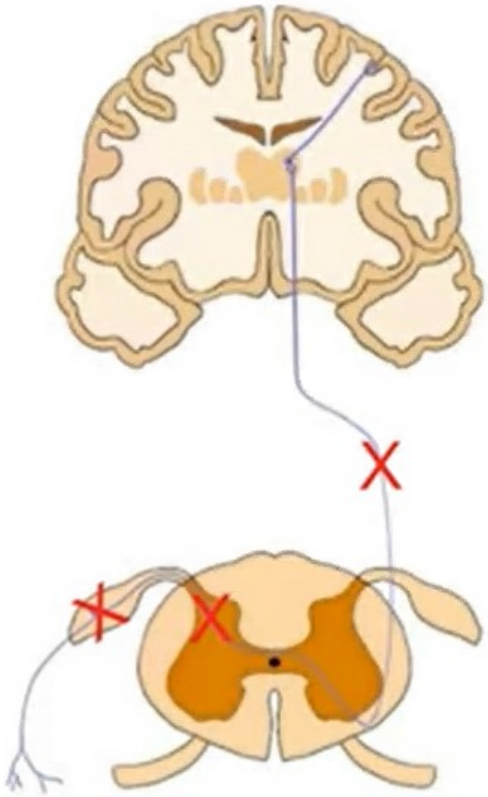
Opioid binds to pre-synaptic receptor and inhibit calcium conductance which makes the neuron less likely to release neurotransmitters

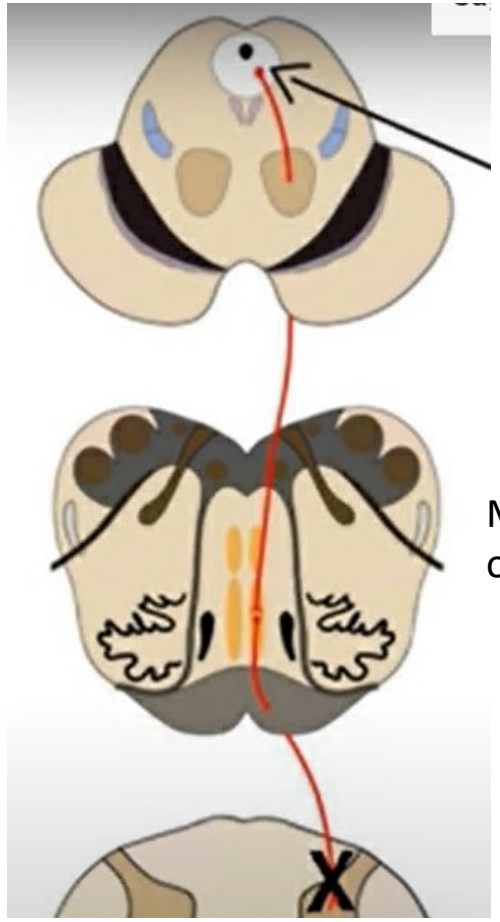
Opioid binds to post-synaptic receptor causing potassium to move through the channel which makes the neuron less likely to fire an action potential



Opioid Mechanism of Action

- The clinical effect (both desired and undesired) at the opioid receptor depends on where in the body the receptor is located
- Opioids can block the transmission of pain signals to the brain (both ascending and descending pathways)

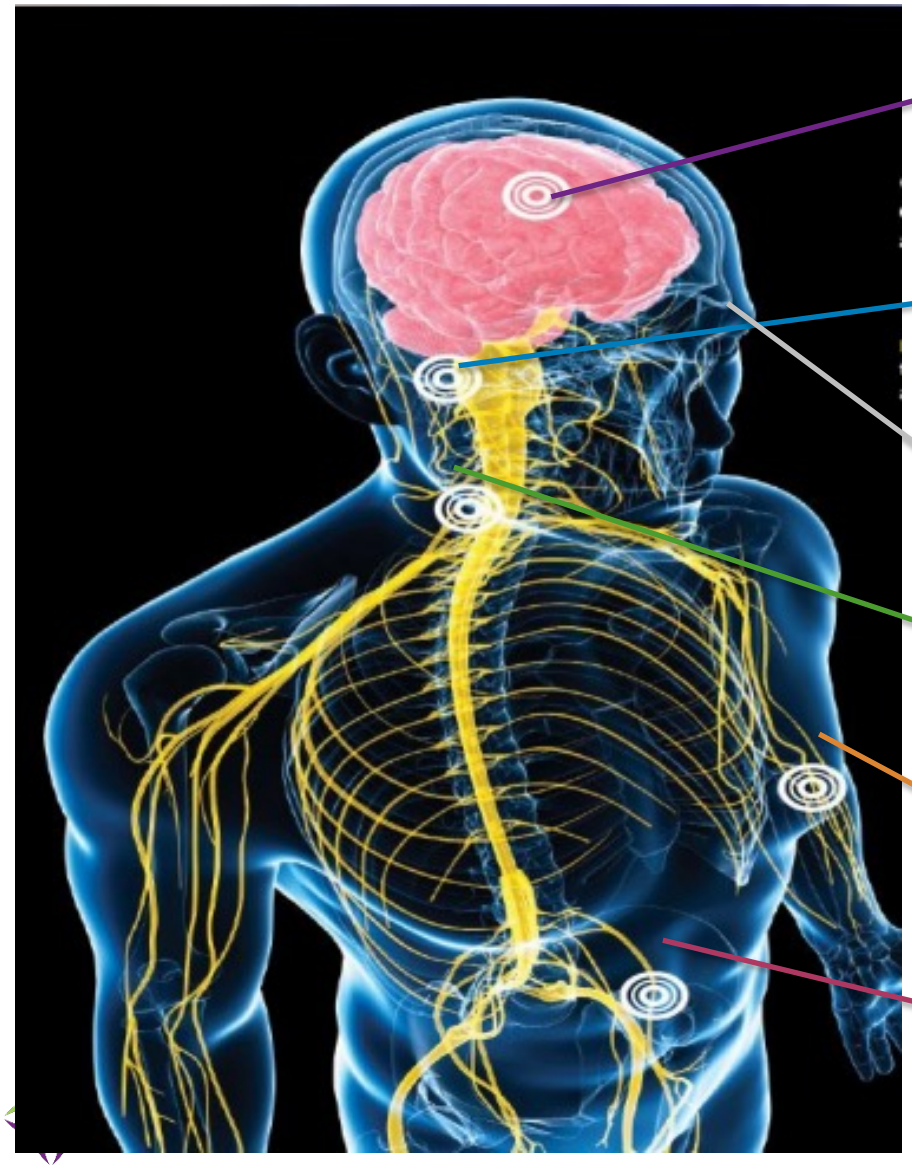




Peri-aquaductal grey (brain stem)

Medulla oblagata

Location/Distribution of Opioid Receptors



Brain → opioid receptors responsible for perception of pain, emotion, reward, and addiction → **analgesia, sedation, euphoria**

Brain stem → opioid receptors are abundant in respiratory control centers especially the pons and medulla. Opioids suppress respiratory inspiratory rhythm and decrease sensitivity to changes in pH that would normal stimulate breathing (such as rise in CO_2 and subsequent decrease in pH) → **respiratory depression (hypercarbia/hypoxia)**

Pupil → opioids activate pupillary sphincter muscle → **miosis**

Spinal cord → transmission of pain signals through region called the dorsal horn is dampened by opioids.

Peripheral: nociceptors that transmit pain signal centrally. Dilate cutaneous blood vessels through release of histamine → flushing, itching

Intestines → Opioids increase sphincter tone, delay gastric emptying, decrease gastric motility (block peristaltic reflex), inhibit submucosal plexus to suppress secretion and liquidity of intestinal contents → **constipation, nausea**

Addiction to Opioids

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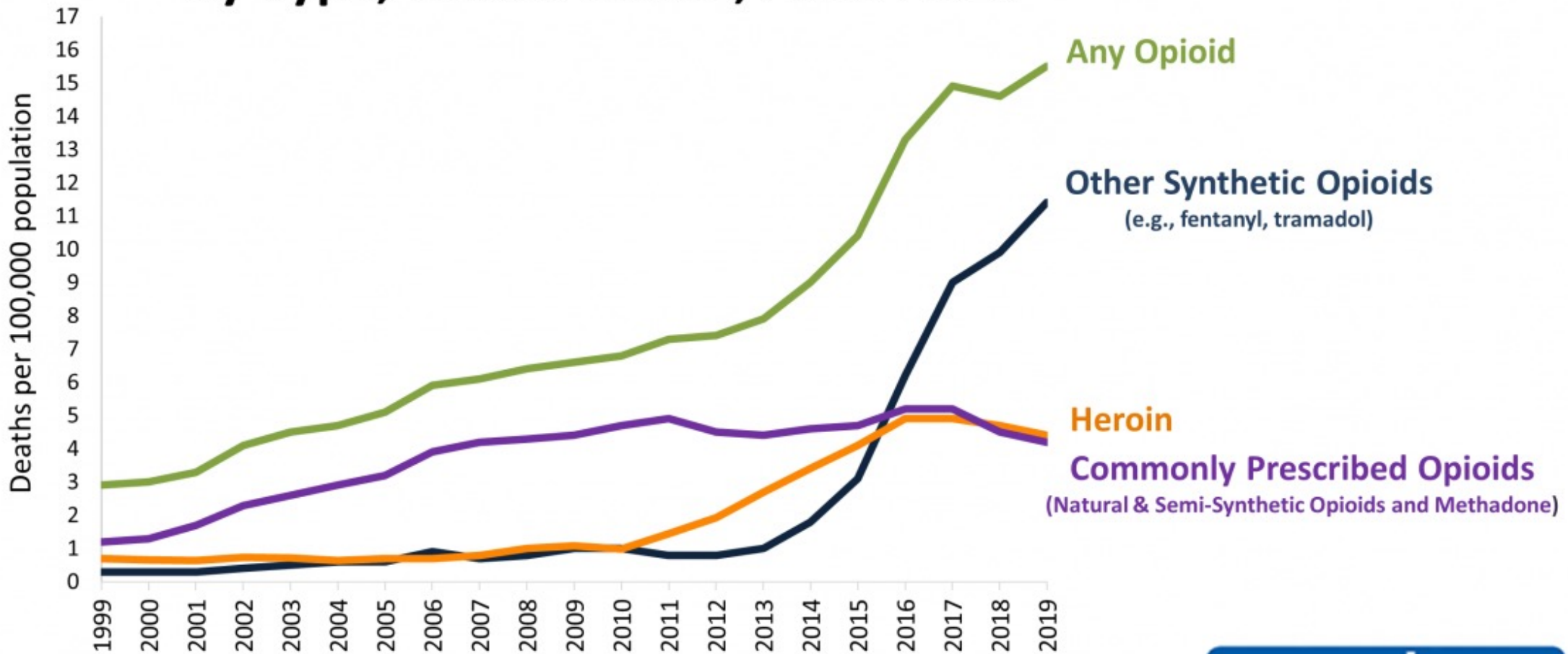
Epidemiology

- In the United States, 5.7 million people (2.1% of people older than 12 years) were estimated to have used heroin and over 3 million people reported misuse of prescription opioids such as taking non-prescribed opioids
- Between 2002 and 2018, prevalence of heroin use nearly doubled, with nearly 31,335 deaths reported in 2018 and then continued
- Synthetic opioids are responsible for most opioid overdoses (i.e. fentanyl), estimated 73% of overdose deaths in 2020
- Risks for opioid-overdose:
  - Concurrent use of other sedatives such as alcohol, benzodiazepines
  - Recent abstinence with relapse due to a lowering of patient's previous tolerance

Wilson N, et al. Drug and Opioid Involved Overdose Deaths – United States, 2017-2018. MMWR Morb Mortal Wkly Rep. 2020;69(11):290.

Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

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Opioid Use Disorder DSM-5

TABLE 1 Summarized DSM-5 diagnostic categories and criteria for opioid use disorder

Category	Criteria
Impaired control	• Opioids used in larger amounts or for longer than intended • Unsuccessful efforts or desire to cut back or control opioid use • Excessive amount of time spent obtaining, using, or recovering from opioids • Craving to use opioids
Social impairment	• Failure to fulfill major role obligations at work, school, or home as a result of recurrent opioid use • Persistent or recurrent social or interpersonal problems that are exacerbated by opioids or continued use of opioids despite these problems • Reduced or given up important social, occupational, or recreational activities because of opioid use
Risky use	• Opioid use in physically hazardous situations • Continued opioid use despite knowledge of persistent physical or psychological problem that is likely caused by opioid use
Pharmacological properties	• Tolerance as demonstrated by increased amounts of opioids needed to achieve desired effect; diminished effect with continued use of the same amount • Withdrawal as demonstrated by symptoms of opioid withdrawal syndrome; opioids taken to relieve or avoid withdrawal

Background: Brain Anatomy

- When analyzing the acute and chronic changes associated with substances of abuse and the development of dependence and addiction, much of the focus has been on the ventral tegmental area (VTA) where dopamine is released in response to addictive substances
- VTA is one of the components of an interconnected brain region known as the mesolimbic dopamine system and is thought to drive pleasure and subsequent craving
- Chronic activation (release of dopamine) promotes neuroplasticity and altered gene expression that may be associated with the development of tolerance and addiction

Limbic System = responsible for perception of emotion and functions as the brain's reward circuit

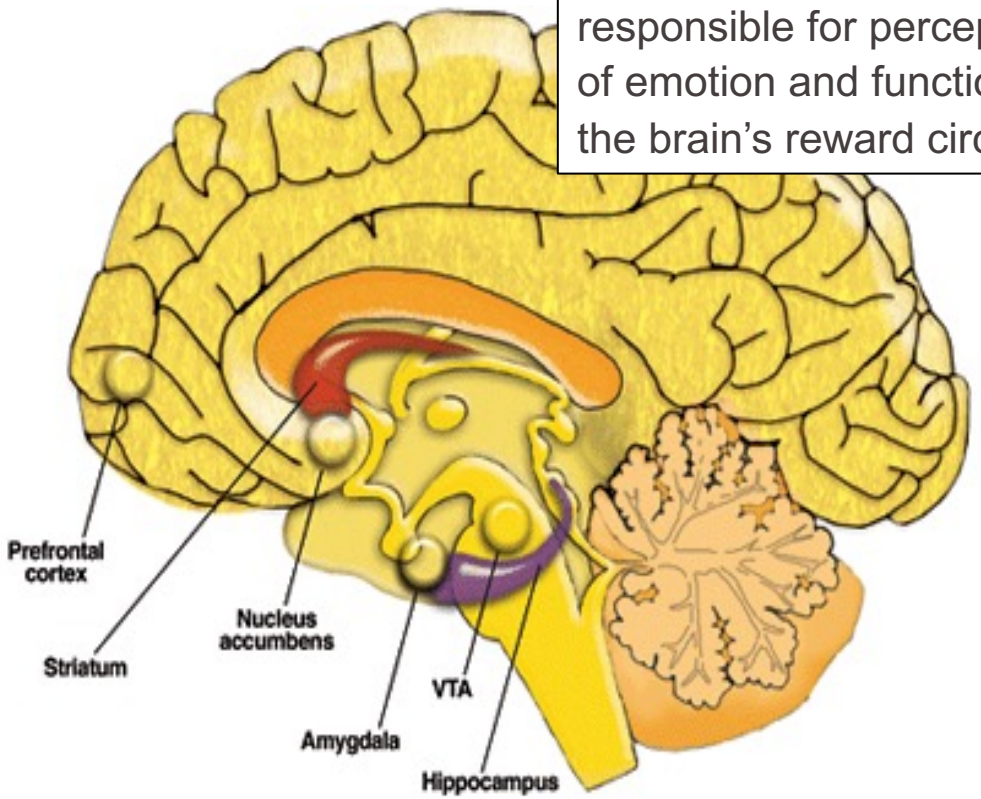
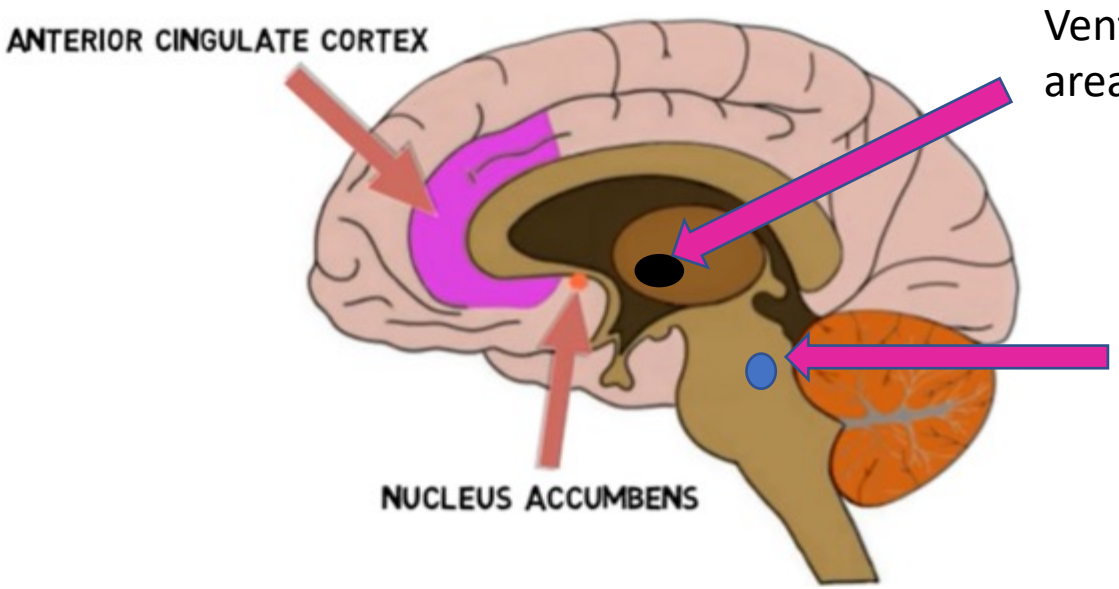
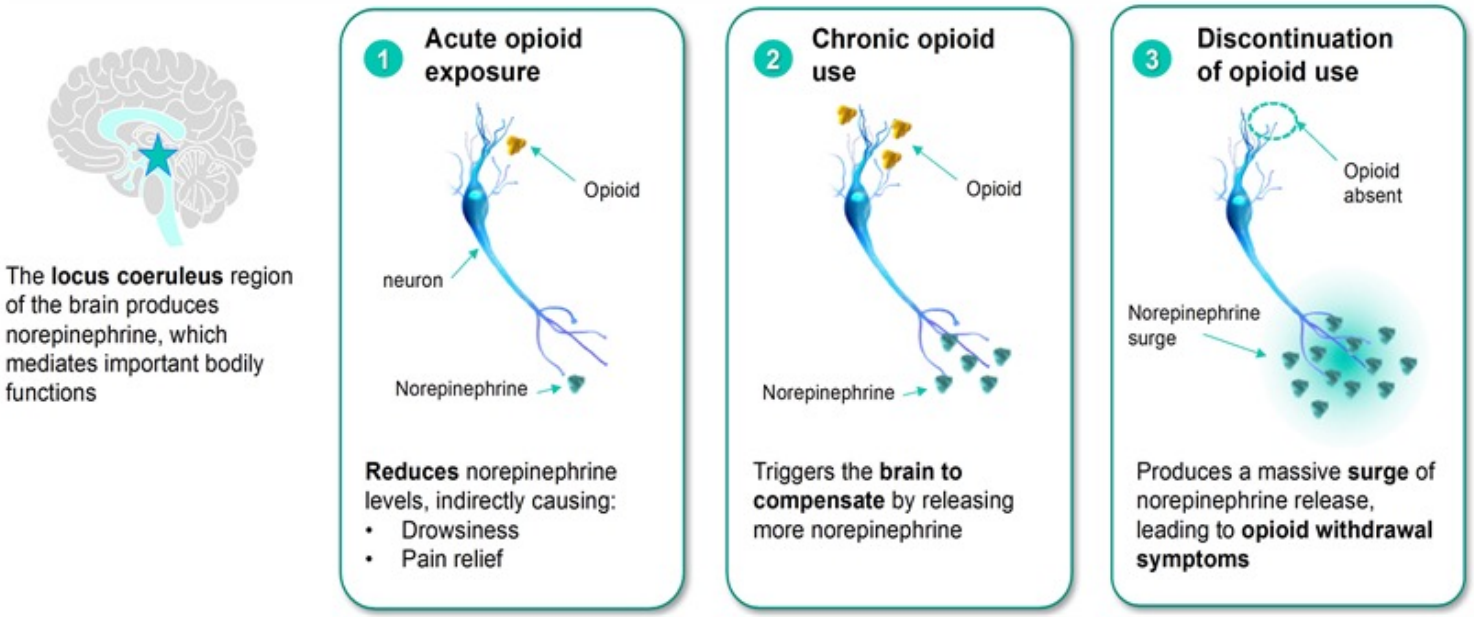


Figure 1. Location of some of the regions in the human brain that are affected by alcohol, including the mesolimbic dopamine system (which includes the ventral tegmental area [VTA], nucleus accumbens, and prefrontal cortex), amygdala, striatum, and hippocampus.

- Opioids act directly on neurons in the nucleus accumbens to increase dopamine and produce reward
  - Nucleus accumbens is in the basal forebrain and considered the neural interface between motivation and action (pleasure, reward, and addiction)
- Opioids also affect the release of norepinephrine in the locus coeruleus
  - Locus coeruleus, located in the pons of the brain stem, a component of the reticular activating system, has widespread projections and known to be involved in depression, anxiety, and opioid withdrawal





Prescription and Illicit Opioids

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Opioid Types

- Opioid Agonist
- Weak agonist/reuptake inhibitors
- Partial agonist/mixed agonist-antagonist
- Antagonist

Opioid Types

AGONISTS
Codeine
Fentanyl
Heroin
Hydrocodone
Hydromorphone (Dilaudid)
Meperidine (Demerol)
Methadone
Morphine
Oxycodone
Oxymorphone (Opana)
Remifentanil
Sufentanil

WEAK AGONISTS/ REUPTAKE INHIBITORS (OPIOID-LIKE)
Tapentadol (Nucynta)
Tramadol (Ultram)

PARTIAL AGONIST
Buprenorphine (Subutex)
Butorphanol
Nalbuphine (Nubain)

ANTAGONISTS
Naloxone (Narcan)
Naltrexone (Vivitrol)

Peripherally acting:
Alvimopan (Entereg)
Methylnaltrexone (Relistor)
Naloxegol (Movantik)

Comparison of Common Opioids

Opioid	Equivalent IV Dose	Equivalent PO Dose	PK
Morphine	10 mg IV	30 mg PO	Onset: IV = 5 – 10 min, PO ~ 30 min Duration: IV/ PO IR = 3 – 5 hr, XR = 8 – 24 hr Half-life: IV/PO IR = 2 – 4 hr, Kadian XR 11 – 13 hr
Hydromorphone (Dilaudid)	1.5 mg IV	7.5 mg	Onset: IV = 5 min, PO = 15 – 30 min Duration: IV/PO = 3 – 4 hr, XR ~ 13 hr Half-life: IV/IR = 2 – 3 hr, XR 8 – 15 hr
Fentanyl	0.1 mg (100 mcg) IV	--	Onset IV = immediate Duration: IV = 0.5 – 1 hr Half-life: 2 -4 hours
Oxycodone	--	20 mg PO	Onset: 0.5 – 1 hr Duration: IR = 3 – 6 hours, Oxycontin XR = 12 hr Half-life: IR 3- 4 hr, XR 4 – 5 hr
Hydrocodone		30 mg PO	Onset: 1 hr Half-life: 4 hr

Opioid Withdrawal

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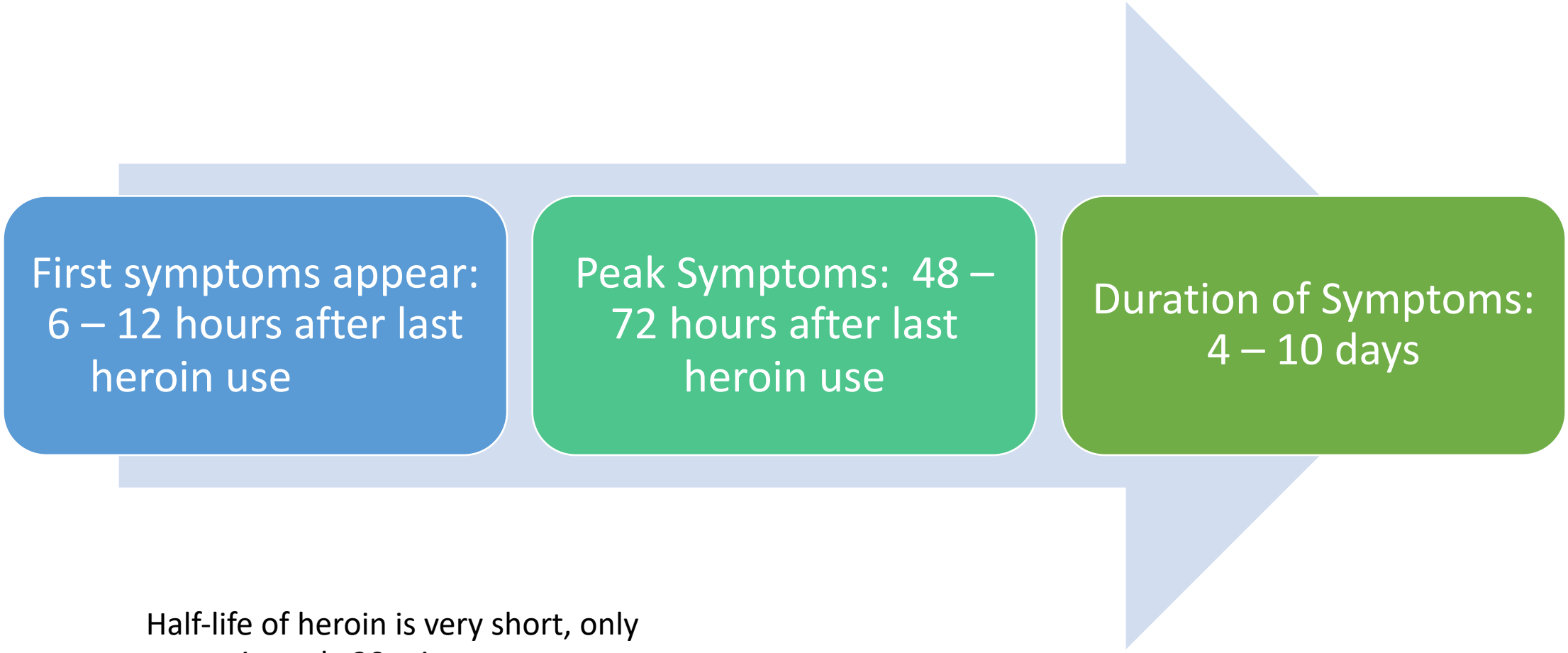
Opioid Withdrawal

- Opioid withdrawal occurs when a patient who is physiologically dependent on opioids reduces or stops use abruptly
- Precipitated opioid withdrawal can occur when a patient dependent on opioids is administered an opioid antagonist (naloxone, naltrexone) or an opioid partial agonist (buprenorphine)
- The onset of symptoms of opioid withdrawal is dependent upon the half-life of the opioid that is stopped (hours to days)
    - Rule of thumb: onset of symptoms is 2 – 3 times the half-life of the withdrawn opioid
- The duration of opioid withdrawal symptoms is variable, ranging from several days to weeks

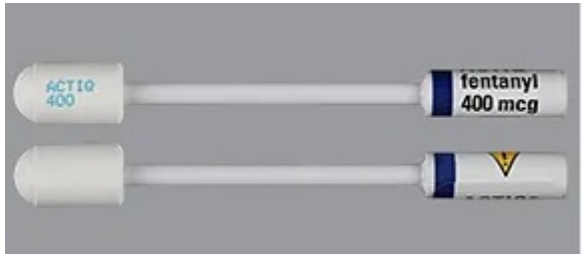
Heroin Withdrawal Symptom Timeline



Half-life of heroin is very short, only approximately 20 minutes

What about fentanyl?

- Fentanyl is a synthetic opioid 100 times more potent that morphine and 50 times more potent than heroin
- Fentanyl is commercially available as an injection, patch (Duragesic), transmucosal lozenges (lollipops (Actiq)), effervescent buccal tablets (Fentora)
- Smoking fentanyl is now more common cause of fatal overdose than injection



Comparison of lethal doses of heroin, fentanyl, carfentanil

Fentanyl Withdrawal

- Fentanyl is highly lipophilic and accumulates in fat tissues after repeated doses or chronic exposure.
- Fentanyl half-life is context-specific:
  - Single dose, very short effective half-life due to redistribution of drug out of blood into tissue
    - The short duration of action is primarily due to this redistribution rather than immediate drug metabolism or elimination
  - After prolonged continuous infusion or chronic ingestion, the half-life becomes much longer
    - The rate-limiting step in the body's clearance of fentanyl is the release of the drug from adipose tissue and other poorly perfused peripheral tissues, back into the blood stream for elimination
    - These peripheral tissues have a high affinity for fentanyl and act as a physiologic reservoir, accumulating and slowly releasing it

Fentanyl Withdrawal Timeline

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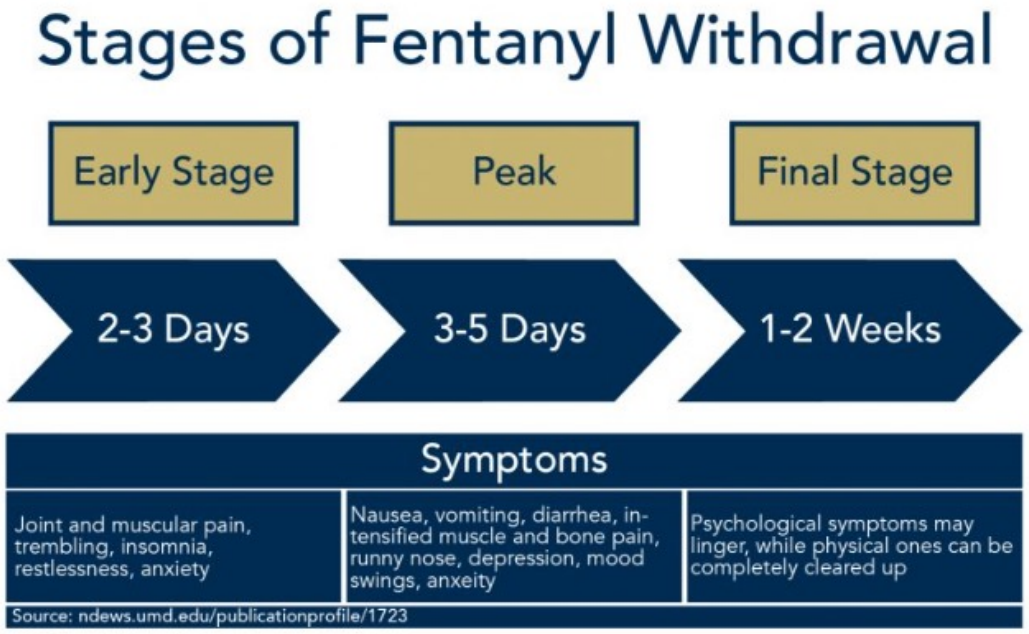
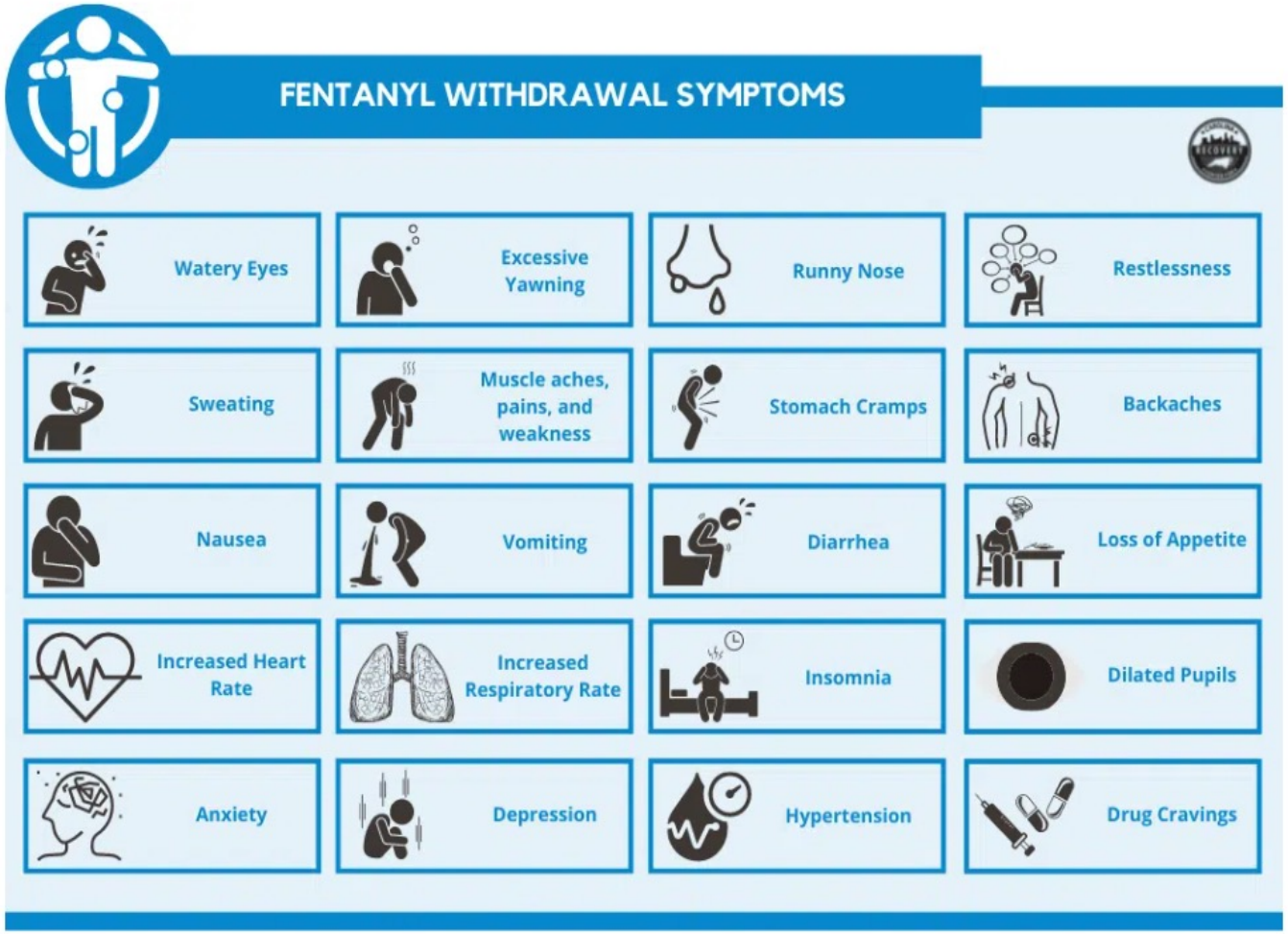
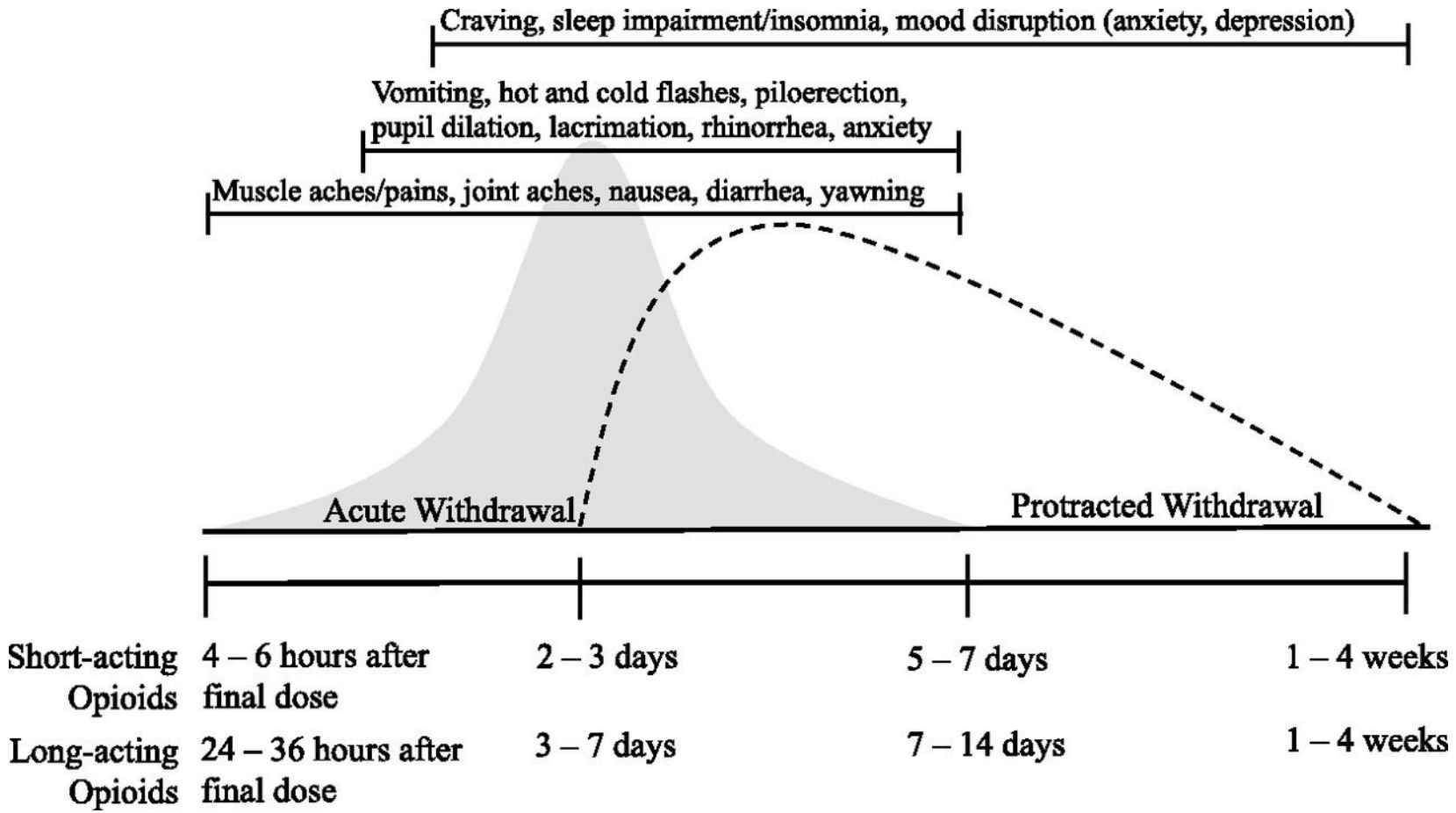


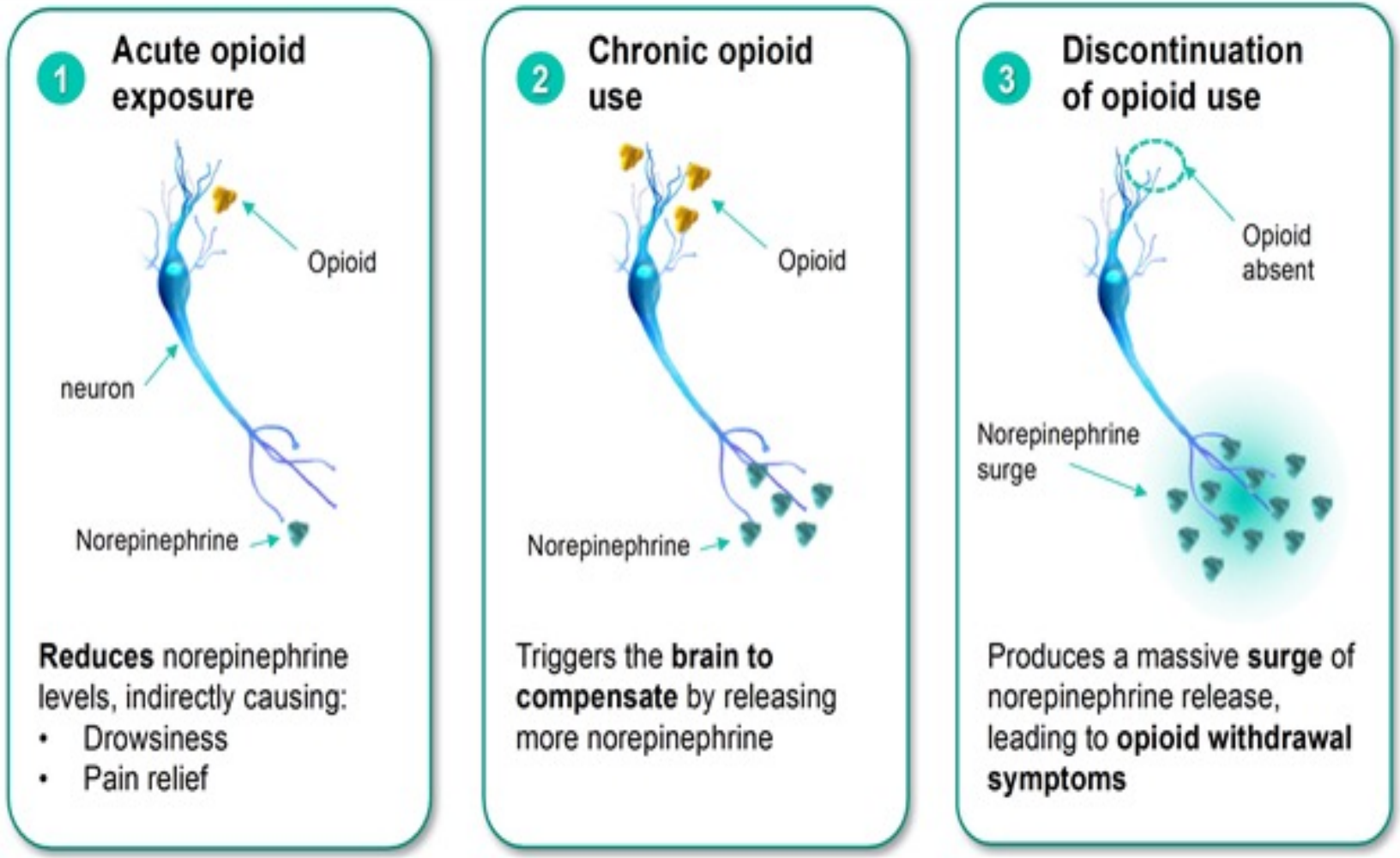


Schematic of the human opioid withdrawal syndrome.



Kelly E. Dunn et al. J Pharmacol Exp Ther 2019;371:422-452

The **locus coeruleus** region of the brain produces norepinephrine, which mediates important bodily functions



Normally when a medication is stopped, the medication effect and the unwanted side effects cease.
When an opioid tolerant patient abruptly stops taking opioids, the effects of the opioids reverse (i.e. constipation becomes diarrhea, pain relief becomes hyperalgesia, pinpoint pupils become dilated) due to norepinephrine surges at all opioid sites within the body

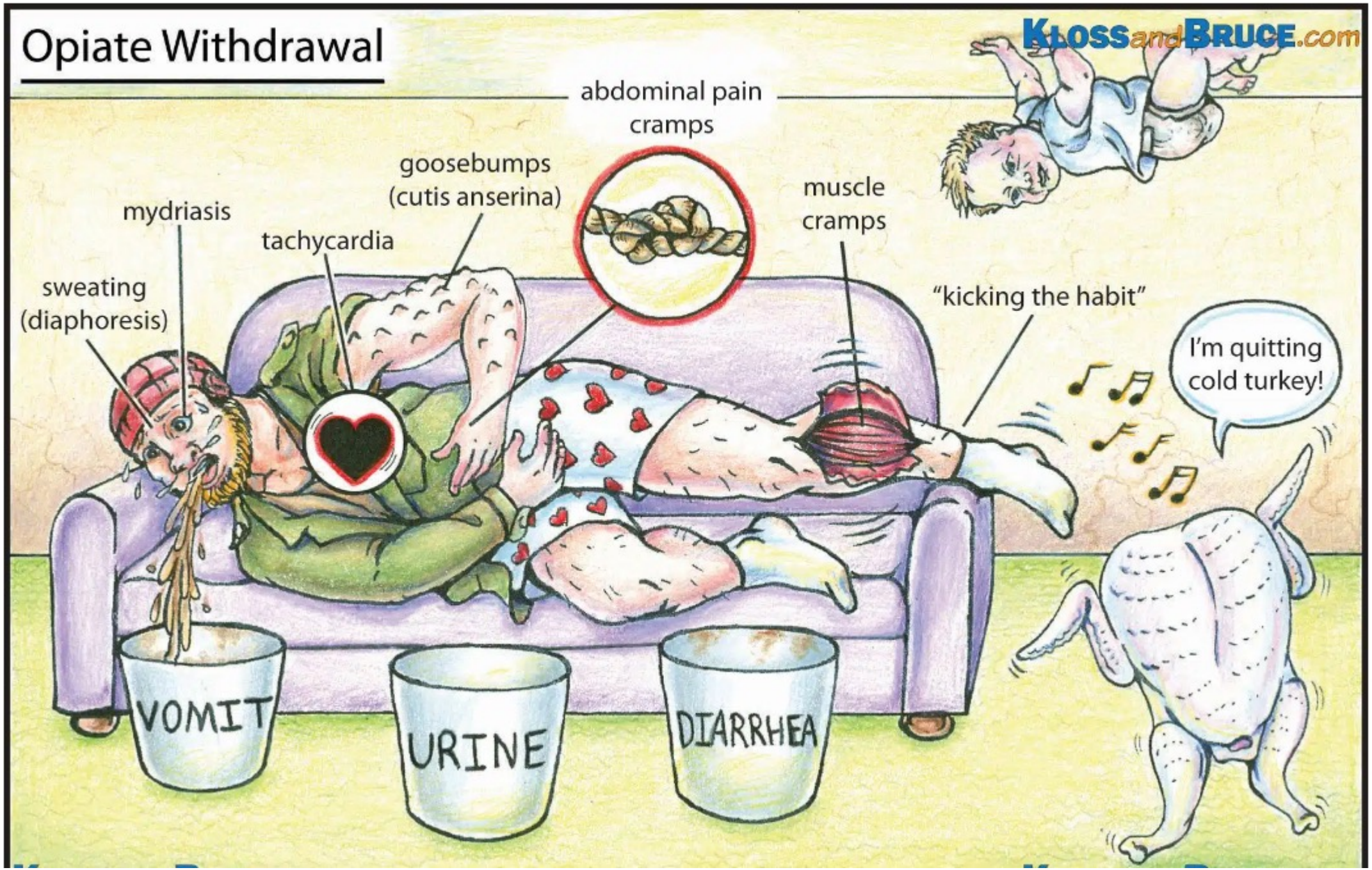
Clinical Manifestations Opioid Withdrawal

Gastrointestinal: abdominal cramps, diarrhea, nausea and/or vomiting

Flu-like symptoms: lacrimation, rhinorrhea, sneezing, diaphoresis, shivering, goosebumps

Sympathetic nervous system/central nervous system excitation: hypertension, tachycardia, anxiety, agitation, restlessness, insomnia, tremor

Other: dilated pupils (mydriasis), yawning, myalgias, arthralgias, leg cramps


Opiate Withdrawal
KlossandBruce.com
abdominal pain
cramps
goosebumps
(cutis anserina)
mydriasis
tachycardia
sweating
(diaphoresis)
muscle
cramps
"kicking the habit"
I'm quitting
cold turkey!
VOMIT
URINE
DIARRHEA

Clinical Opioid Withdrawal Scale (COWS)

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COWS Score

Clinical Opiate Withdrawal Score "COWS"

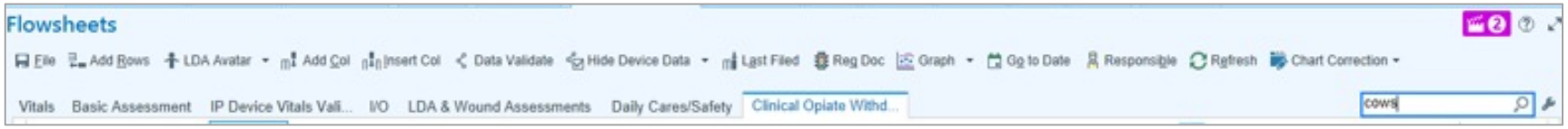
- COWS score is a validated tool to determine severity of opiate withdrawal.
- It is important to be aware that many of these symptoms are subjective. Make objective observations when possible to prevent over-estimating the score.
- It is also important to note that symptom onset will vary depending on the drug and severity of dependence.

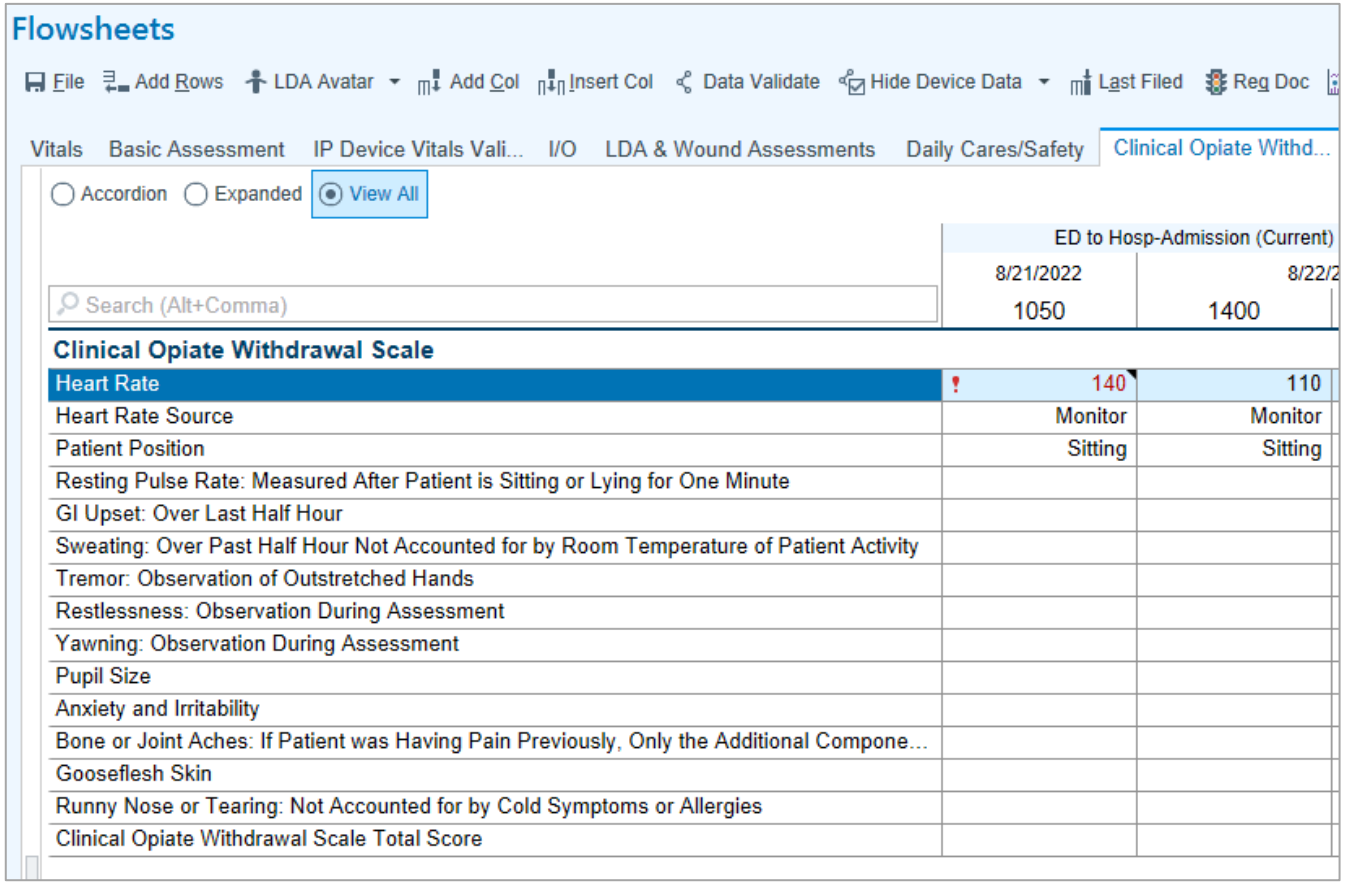
COWS Score	Opioid Withdrawal Severity
5 – 12 points	Mild
13 – 24 points	Moderate
25 – 36	Moderately Severe
Greater than 36 points	Severe

Wesson & Ling, J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

COWS Clinical Opiate Withdrawal Scale

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 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 sifting 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 anxious 4 Patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 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 Piloerrection of skin can be felt or hairs standing up on arms 5 Prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 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:_____





1. In **Flowsheets** Activity, click in the search box.
2. Type *COWS* in the Search for field.
3. Click enter key.
4. Clinical Opiate Withdrawal Scale (COWS) Flowsheet rows open.

How to access from EPIC

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Treatment of Opioid Withdrawal

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Did you know……?

- Over 2 million patients in the US have opiate use disorder (OUD) but only 20% receive medication assisted therapy (MAT) despite strong evidence and clinical guideline support as a potentially life-saving treatment
- There are over 140,000 ED visits for opioid overdose ED visits per year
- In one study of 11,557 patients treated for opioid overdose in the ED:
  - 635 patients died within 1 year (5.5%)
    - 130 of these patients died within 1 month (20.5% of deaths)
    - 29 of these patients died within 2 days (4.6% of deaths)

Hawk KF, et al. Barriers and Facilitators to Clinician Readiness to Provide Emergency-Department-Initiated Buprenorphine. JAMA Netw Open. 2020 May; 3(5): e204561.

Weiner SG, et al. One year Mortality of Patients after Emergency Department Treatment for Nonfatal Opioid Overdose. Ann Emerg Med. 2020 Jan; 75(1):13-17.

Buprenorphine Prescribing Patterns after Opioid Overdose

Despite thousands of ED visits for opioid overdoses and injection drug-related medical problems, few patients with OUD are initiated on buprenorphine or methadone during or immediately after an ED visit

Review of 148,966 national ED visits for opioid overdose

- Buprenorphine prescribed in 8.5% of patients (*only 3.9% of these were for initiation without prior prescription*)

- Naloxone prescribed for 7.4% of patients (*6.3% dispensed*)

*Retrospective query of pharmacy claims including insurance, Medicare, and cash-pay

Chua KP, et al. Naloxone and Buprenorphine Prescribing Following US Emergency Department Visits for Suspected Opioid Overdose: August 2019 to April 2021. Ann Emerg Med. 2022 Mar;79(3):225-236.

Overcoming Barriers To Initiation of Buprenorphine or Methadone for OUD

- Knowledge gaps and provider concerns about managing the logistics of buprenorphine induction and writing prescriptions
- Lack of understanding of regulatory requirements for prescribing
  - DATA 2000 training requirements (“X-waiver”) (NOW REMOVED BY DEA)
  - Misunderstanding of exceptions including 72-hour rule and inpatient ordering
- Perceived lack of follow-up care in outpatient setting
  - Socio-economically complex patient population
  - Provider unawareness of resources
- Competing priorities and lack of resources and/or institutional support
- Lack of training on approaching patients to discuss addiction recovery and medication assisted therapy
- Concern about precipitated withdrawal

Hawk KF, et al. Barriers and Facilitators to Clinician Readiness to Provide Emergency-Department-Initiated Buprenorphine. JAMA Netw Open. 2020 May; 3(5): e204561.

Patient-Clinician Shared Decision Making

Decisional Needs

What do people need to help them make the decision?

Are they **ready** to talk about it?
Do they have enough **information**? Do they endorse **misinformation**?
Do they have unrealistic **expectations**?
Do they know what they **value**?
What are their **personal and clinical needs**?
Do they have adequate support and resources **(self-efficacy, skills, motivation)**?

Decisional Needs

What do people need to help them make the decision?

A full understanding of all the options
- Pros and cons of each option
- Consequences of each option
- Logistical details of each option

Knowledge that ED has these options available
An invitation from the clinician to engage in a conversation

Example Questions*

Are you familiar with buprenorphine (suboxone) and/or methadone? What do you know?
- Probe understanding and myths

Tell me about your experiences
- Probe challenges, benefits, logistics

What do you think about these medications?
What do you think about starting these medications in the Emergency Department?

Schoenfeld EM, et al. "Just give them a choice": Patients' perspectives on starting medications for opioid use disorder in the ED. Acad Emerg Med. 2022 Aug;29(8):928-943.

Patient-Clinician Shared Decision Making

Decisional Support

What can health care professionals do to help people make the right decision for themselves?

How can professionals establish **rapport** and facilitate **interactive communication**?
What would **tailored support** look like?
What **information** do professionals need to share?
What **myths** should be addressed?
How can professionals help clarify **values**?
Do they know what they **value**?
What are their **personal and clinical needs**?

Decisional Support

What can health care professionals do to help people make the right decision for themselves?

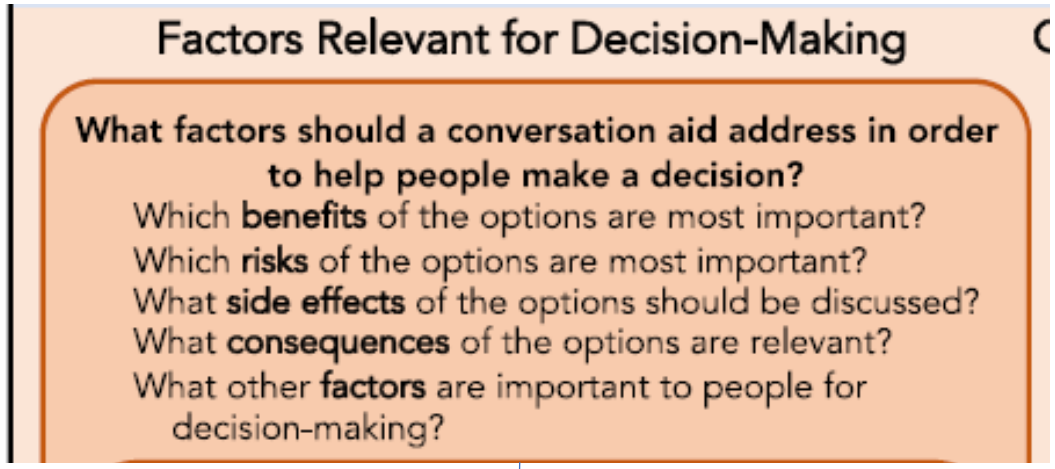
"Just give them a choice:" present options clearly, present all options
Understand that different circumstances will lead to different choices
Communicate without judgement
Address residual stigma in healthcare settings
Offer options regardless of patient "readiness"
Offer other support (e.g. psychiatric care, harm reduction, "warm handoff," comfort medications)

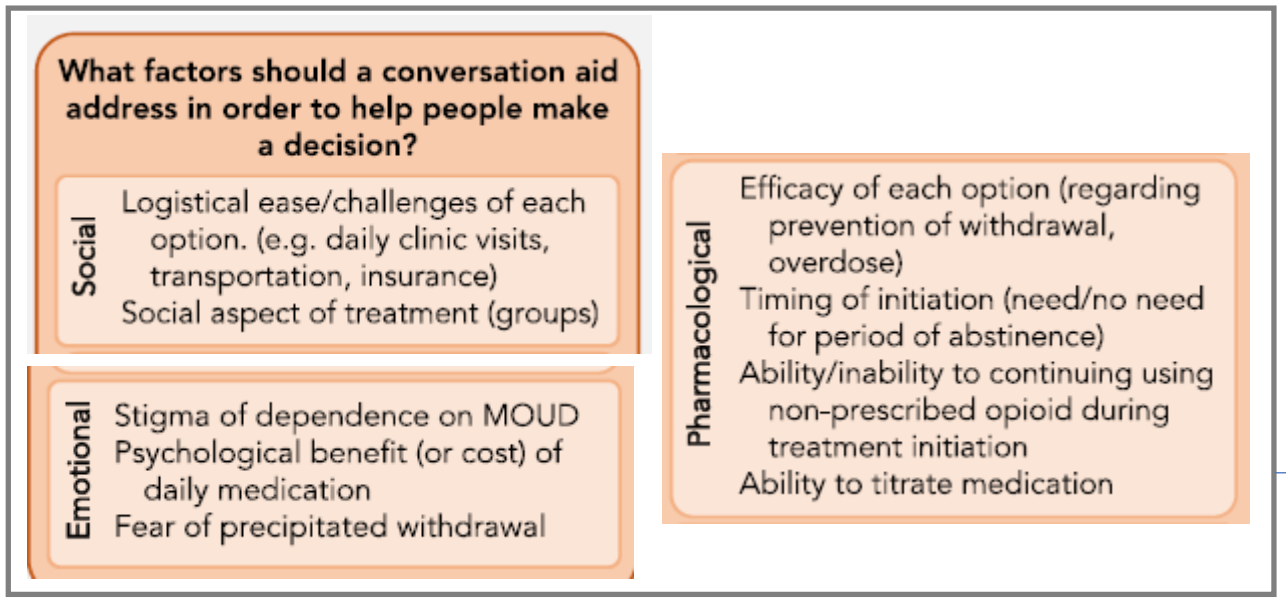
Example Questions*

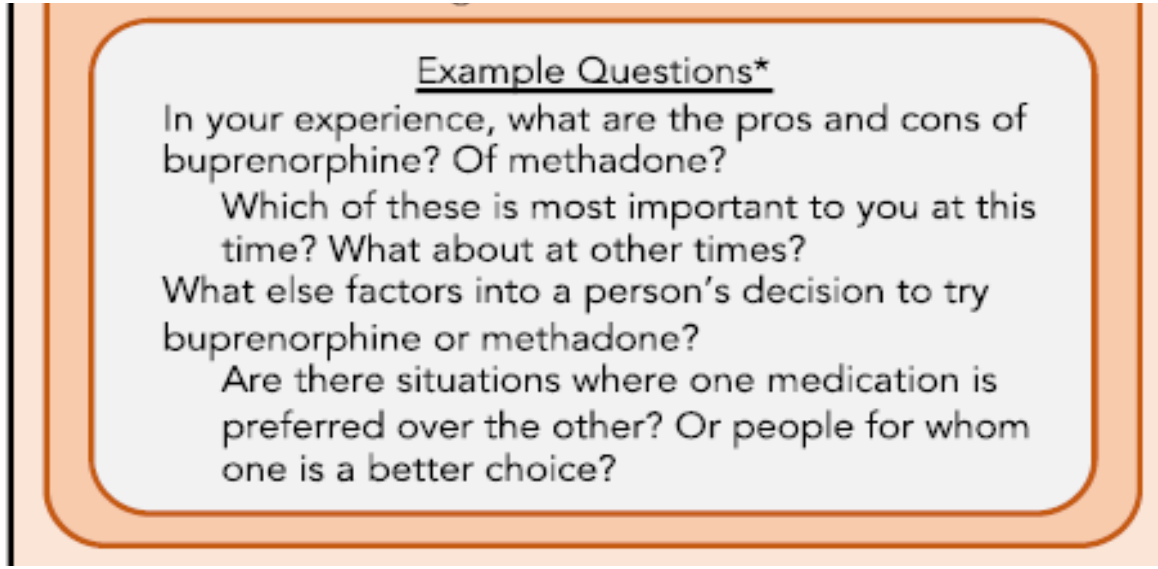
From your experience, what do doctors need to know in order to have this conversation?
If you were offered this medication in the ED, what else would you need to know?
What advice would you give to doctors who are new to this conversation?
What else could the ED do to help you decide to start one of these medications?

Schoenfeld EM, et al. "Just give them a choice": Patients' perspectives on starting medications for opioid use disorder in the ED. Acad Emerg Med. 2022 Aug;29(8):928-943.

Patient-Clinician Shared Decision Making







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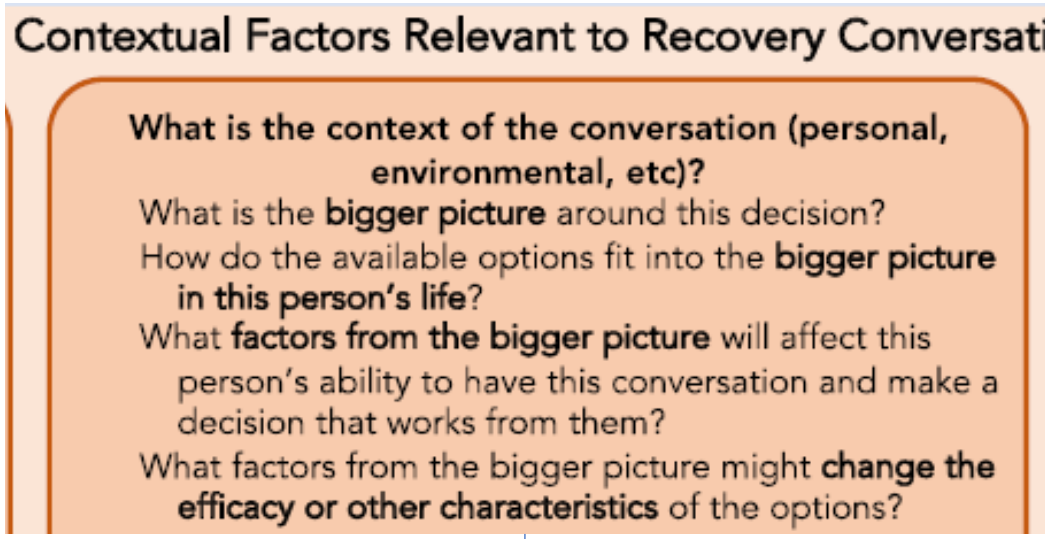
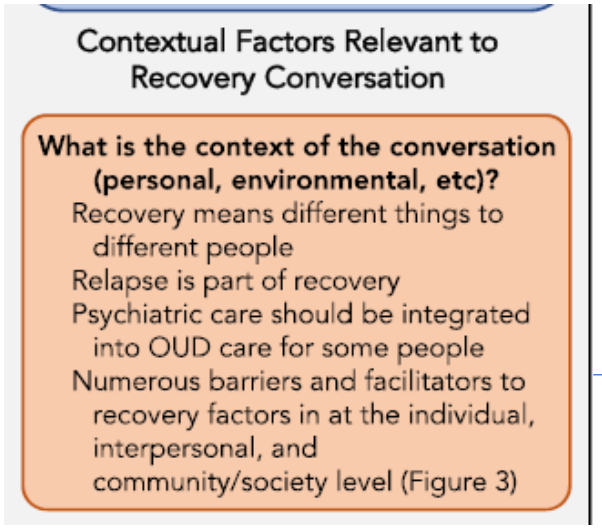
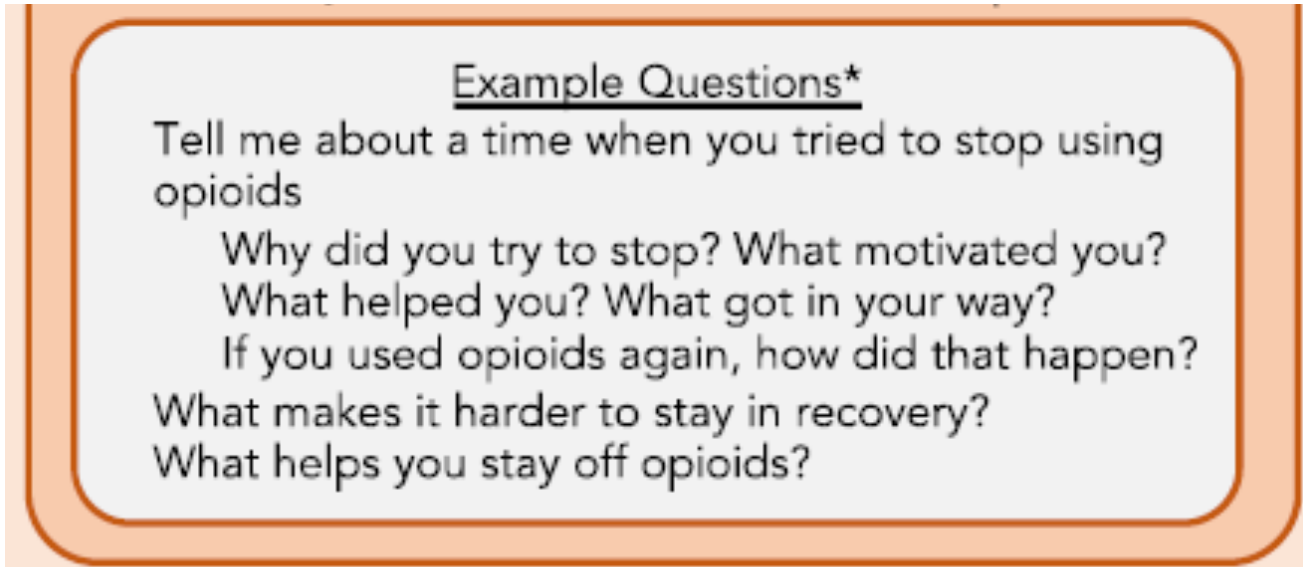
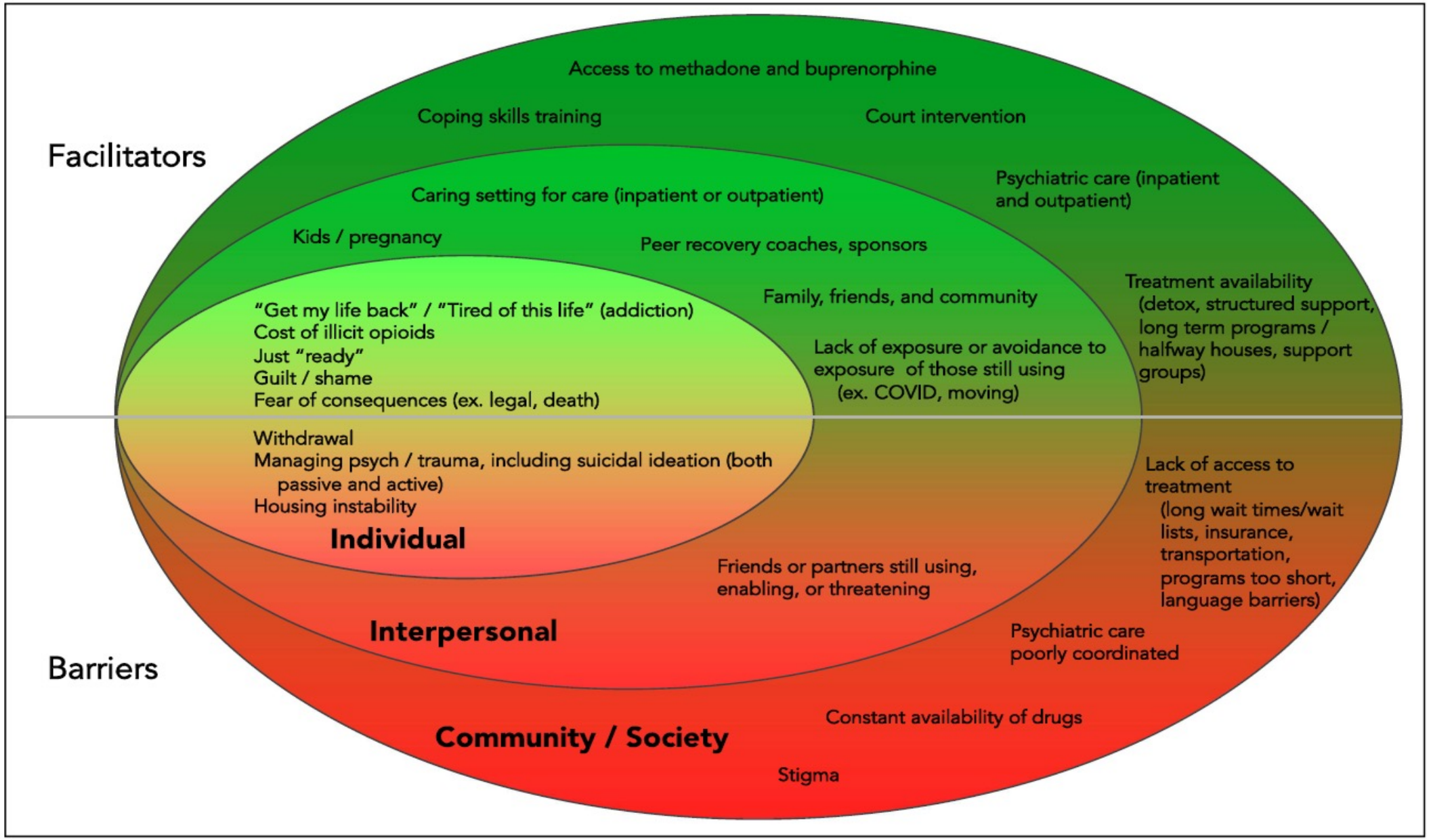






Schoenfeld EM, et al. "Just give them a choice": Patients' perspectives on starting medications for opioid use disorder in the ED. Acad Emerg Med. 2022 Aug;29(8):928-943.

Contextual Factors Relevant to Recovery Conversation



Schoenfeld EM, et al. "Just give them a choice": Patients' perspectives on starting medications for opioid use disorder in the ED. Acad Emerg Med. 2022 Aug;29(8):928-943.

Patient Perspectives: Clinician Communication

- Patients hope that clinicians will avoid judgment
- Patients want clinicians to be knowledgeable about OUD, the pros and cons of medication assisted treatment, and choice of agents → but also want providers to be humble and honest about what they do not know
- “Peer recovery” coaches may be even more beneficial than a physician (many patients value the advice and support of someone with lived experience)
- The “readiness” paradox: many clinicians will not initiate conversations with patients that do not appear ready to stop using illicit opioids. However, it may be the caring health care professional and the information provided in the course of this conversation that is what influences readiness. At the minimum it is an invitation through an open door.

Initiation of Medication Assisted Therapy (MAT) For OUD

- 25 year old male patient presents to the Emergency Department after a heroin overdose. He was found by a family member difficult to arouse so they called 9-1-1 and EMS arrived and patient responded to naloxone but was brought to the emergency department for observation.
- The patient expresses interest in initiating medication therapy for OUD, which agent will you recommend?

Buprenorphine (Suboxone, Subutex)

- Buprenorphine is a recommended treatment for opioid use disorder (OUD)
  - Available as buprenorphine/naloxone (Suboxone) or buprenorphine (Subutex) tablets administered sublingually
  - Note the naloxone present in Suboxone is not systemically absorbed and is not the active ingredient
    - It is present in the formulation to deter misuse in the outpatient setting, because it will prevent euphoria if the film is dissolved and injected inappropriately
- Buprenorphine is not initiated until signs of moderate opioid withdrawal are present:
  - Generally, when COWS score is GREATER than 8 - 12 points

Mechanism of Action

Buprenorphine is a partial agonist at mu-opioid receptors.

This means it can cause immediate withdrawal in the presence of opiates, such as heroin or fentanyl, but will relieve withdrawal symptoms caused by their absence.

Administration

Buprenorphine tablets are administered sublingually since swallowing reduces bioavailability. Keep tablet under tongue until completely dissolved. Can be administered once or twice daily.

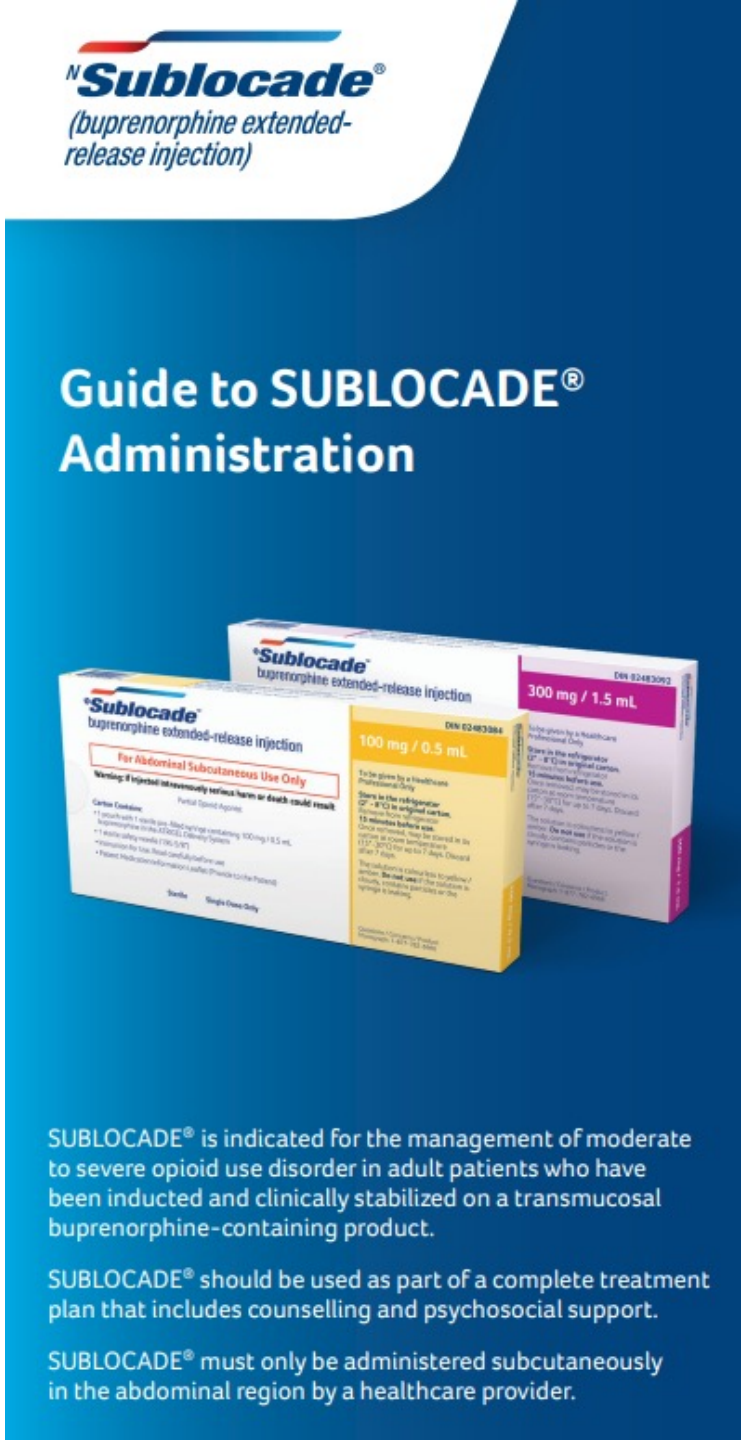
Safety

Buprenorphine has MUCH less risk of respiratory depression than opiates. For safety, order set contains naloxone PRN for respiratory rate less than 9 breaths per minute.

Buprenorphine Dosage Forms

Buprenorphine Long-Acting Injection

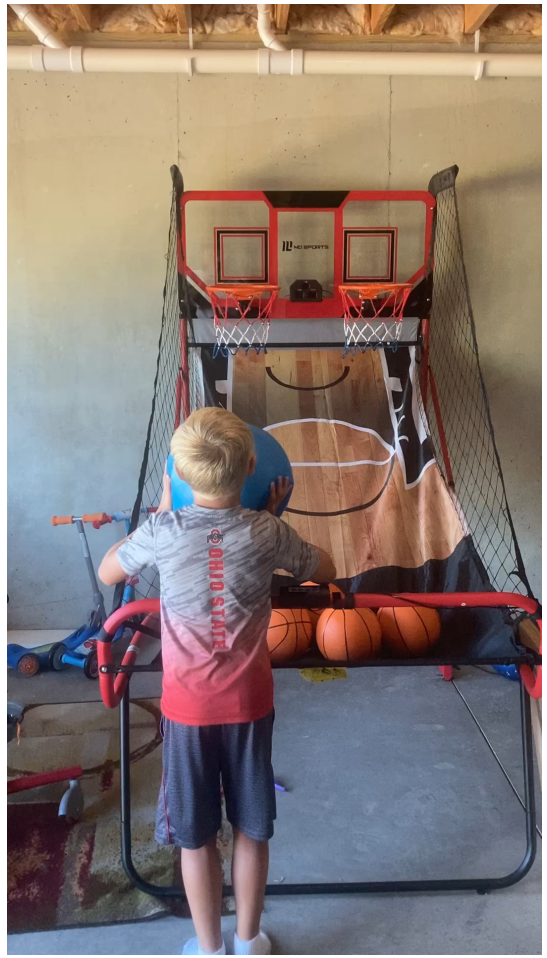
- Sublocade (buprenorphine long-acting monthly injection) is given subcutaneously
  - Before first injection: patients must first undergo induction and stabilization with transmucosal buprenorphine containing product equivalent to 8 – 24 mg/day of buprenorphine for a minimum of 7 days
  - Initial dose: 300 mg SC monthly (doses at least 26 days apart) for the *first two months*
  - Maintenance: 100 mg SC monthly, increasing up to 300 mg monthly if patient does not demonstrate satisfactory clinical response



Buprenorphine: Partial Opioid Agonist

Buprenorphine acts as a partial agonist at mu-opioid receptor.

Analgesia and any euphoria potential plateaus at higher doses



Buprenorphine binds with higher affinity than full agonist agents and will displace opioid agonists (such as heroin) from the receptor, in this circumstance, buprenorphine behaves almost like an antagonist

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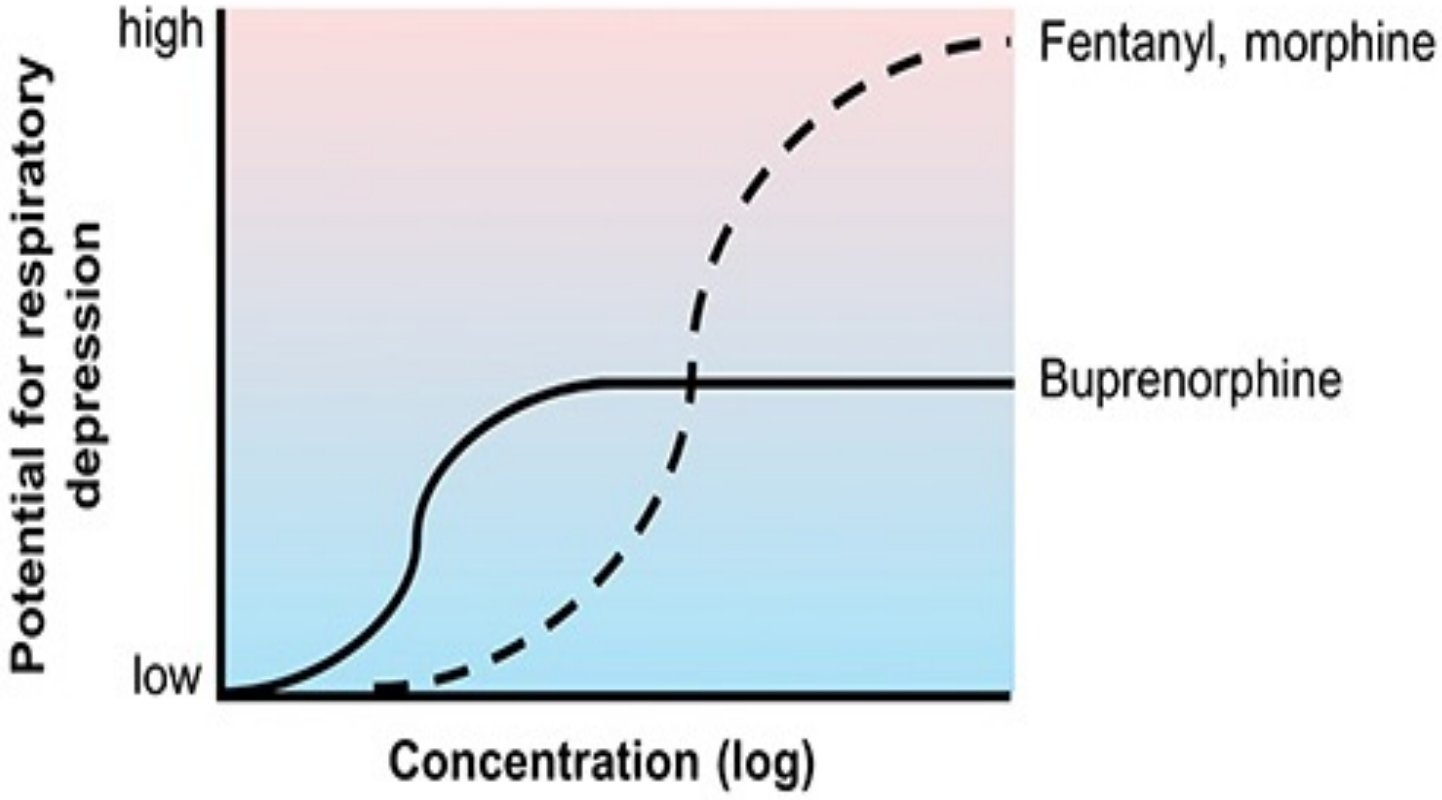
Buprenorphine: Partial Agonist Safety

- Buprenorphine-associated respiratory depression is rarely seen in the clinical setting due to the ceiling effect of partial opioid agonists



Buprenorphine Precipitated Withdrawal

- Precipitated withdrawal is an acute worsening of withdrawal symptoms after taking the first dose of buprenorphine (usually within 30 minutes of the dose)
- Buprenorphine is a partial agonist with high receptor affinity and displaces full opioid agonists from the receptor which may precipitate acute withdrawal symptoms (muscle pain/aches, vomiting, tachycardia, excessive diarrhea, diffuse sweating, etc)
  - Onset: 0.5 – 2 hours following first dose of buprenorphine
  - Duration: 6 – 24 hours (but may be pronged depending on the opioid of abuse)
- Precipitated withdrawal occurred in 9% of buprenorphine inductions in one published trial (most commonly occurring in patients using methadone)
- To avoid precipitated withdrawal, patient must be in mild to moderate withdrawal at the time of first dose of buprenorphine

Whitley S, et al. Factors Associated with complicated buprenorphine inductions. J Subst Abuse Treat 2010;39:51-7.

Delaying Initiation of Buprenorphine

- Why shouldn't my patient be initiated on buprenorphine until the COWS score is greater than 8 – 12 points?
  - Buprenorphine (Suboxone, Subutex) and the opiate to which the patient is addicted (heroin, fentanyl, etc.) compete for the same chemical receptor in the brain. Buprenorphine is not as potent as the opiate (*partial agonist*) but has higher receptor affinity, so if given too soon, it will knock the opiate off the receptor causing the patient to experience severe withdrawal symptoms. This is called *precipitated withdrawal.*
  - This could lead the patient to feel very sick, thus causing the perception that buprenorphine is ineffective. This may cause the patient to leave against medical advice to use heroin or other opioids to relieve the symptoms.
  - It is important to explain to patients experiencing opiate withdrawal the reasons for waiting to begin the medication until they are moderately symptomatic.

Treatment of Opioid Withdrawal: Laws and Policy Related

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Drug Enforcement Agency (DEA) Code of Federal Regulations (CFR) Title 21

§ 1306.07 Administering or dispensing of narcotic drugs.

(a) A practitioner may administer or dispense directly (but not prescribe) a narcotic drug listed in any schedule to a narcotic dependant person for the purpose of maintenance or detoxification treatment if the practitioner meets both of the following conditions:

(1) The practitioner is separately registered with DEA as a narcotic treatment program.

(2) The practitioner is in compliance with DEA regulations regarding treatment qualifications, security, records, and unsupervised use of the drugs pursuant to the Act.

(b) Nothing in this section shall prohibit a physician who is not specifically registered to conduct a narcotic treatment program from administering (but not prescribing) narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms when necessary while arrangements are being made for referral for treatment. Not more than one day's medication may be administered to the person or for the person's use at one time. Such emergency treatment may be carried out for not more than three days and may not be renewed or extended.

(c) This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

eCFR :: 21 CFR 1306.07 -- Administering or dispensing of narcotic drugs.

Interpreting Hospital Policy for Prescribing Buprenorphine or Methadone

- Patients enrolled in a treatment program and prescribed outpatient buprenorphine or methadone therapy for addiction may need to be admitted to the hospital for a medical or surgical issue
  - Providers can continue their home Methadone, Subutex, or Suboxone (efforts should be made to confirm current dose and/or active prescription)
- Patients who take methadone or buprenorphine for pain control can have these medications continued upon admission (no restrictions on these medications prescribed for pain and not addiction)
- Patients with OUD who are *admitted to the hospital for reasons other than addiction/withdrawal* (i.e. infection requiring IV antibiotics) who may experience withdrawal that complicates the underlying medical condition may be initiated on buprenorphine or methadone without any special licensing or limit on duration of inpatient therapy
- If the patient is *admitted for reasons of addiction/withdrawal*, provider may initiate buprenorphine or methadone but may only order doses for 3 days per DEA rule and document referral to treatment center upon discharge
  - If the patient is hospitalized longer than 3 days, there is no exception to continue buprenorphine or methadone beyond the initial 3 days.

X-waiver eliminated Removing Barriers to Prescribing Buprenorphine

- An " X-waiver" refers to the previous requirement under Drug Addiction Treatment Act (DATA 2000) legislation that authorized outpatient prescribing of buprenorphine (schedule III) for the treatment of opioid use disorder and limited the number of patients a provider can manage on buprenorphine

Situation	Review Process	Time Limit
Inpatient CONTINUATION of outpatient prescription of buprenorphine or methadone	"PDMP" (OARRS in Ohio) reviewed by pharmacist to confirm active prescription for buprenorphine or methadone	None
INITIATION of inpatient buprenorphine or methadone for patient admitted to hospital ***for*** *reasons of addiction/OUD*	Review reason for admission is addiction/detoxification/opiate withdrawal while making arrangements for outpatient addiction recovery follow-up appointment	3 days
INITIATION of inpatient buprenorphine or methadone for patient admitted ***for*** condition *other than addiction* where opioid withdrawal is incidental adjunct	Confirm patient admitted for medical or surgical reason other than addiction	None
Dispensing buprenorphine	No longer requires X-waiver but DEA 3-day rule is technically still in place for "administering" but not prescribing. Initial rule specifies that only 1-day at a time may be dispensed by the hospital, requiring a patient to return to the ER on consecutive days. DEA created a waiver where hospitals may e-mail and ask permission to dispense up to 3-day at a time. Mount Carmel Health System is the first site in Columbus to trial Suboxone 3-day take home kits	3 days
Outpatient prescriptions for buprenorphine	No X-waiver requirement. Any provider with standard DEA registration number may prescribe.	None
Prescriptions for methadone	Methadone is schedule II. The X-waiver never applied to methadone, so its elimination does not affect methadone prescribing. Methadone must be dispensed by a specially certified provider in certified opioid treatment program (OTP)	Dispensed only by methadone clinic when prescribed for OUD

PDMP = prescription drug monitoring program OUD = opiate use disorder https://www.samhsa.gov/medications-substance-use-disorders/waiver-elimination-mat-act

Consolidated Appropriations Act of 2023

What is the impact of the Consolidated Appropriations Act of 2023 on prescribing buprenorphine for opioid use disorder? –

Section 1262 of the 'Consolidated Appropriations Act of 2023 (PDF | 3.8 MB)' removes the federal requirement for practitioners to apply for a special waiver prior to prescribing buprenorphine for the treatment of opioid use disorder. It also removes other federal requirements associated with the waiver such as discipline restrictions, patient limits, and certification related to provision of counseling. Separately, section 1263 of the 'Consolidated Appropriations Act of 2023 (PDF | 3.8 MB)' requires new or renewing Drug Enforcement Administration (DEA) registrants, starting June 27, 2023, upon submission of their application, to have at least one of the following:

- A total of eight hours of training from certain organizations on opioid or other substance use disorders for practitioners renewing or newly applying for a registration from the DEA to prescribe any Schedule II-V controlled medications;
- Board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or the American Osteopathic Association; or
- Graduation within five years and status in good standing from medical, advanced practice nursing, or physician assistant school in the United States that included successful completion of an opioid or other substance use disorder curriculum of at least eight hours.

What does this mean for providers? –

This means that the special waiver (e.g., a DATA-Waiver) is no longer required to treat patients with opioid use disorder (OUD). Additionally, the DATA-Waiver registration number is no longer required on opioid use disorder prescriptions. Opioid use disorder prescriptions, like all prescriptions, now only require a standard DEA registration number.

- Those prescribers currently registered with the DEA as a DATA-Waived prescriber should have received, or will be receiving, an updated DEA registration certificate to reflect the elimination of the DATA-Waiver registration number. No action is necessary on the registrant's part.
- It should be noted that state laws applicable to this issue may still be in effect. Registrants should take note of their state's requirements because they may differ from federal law.

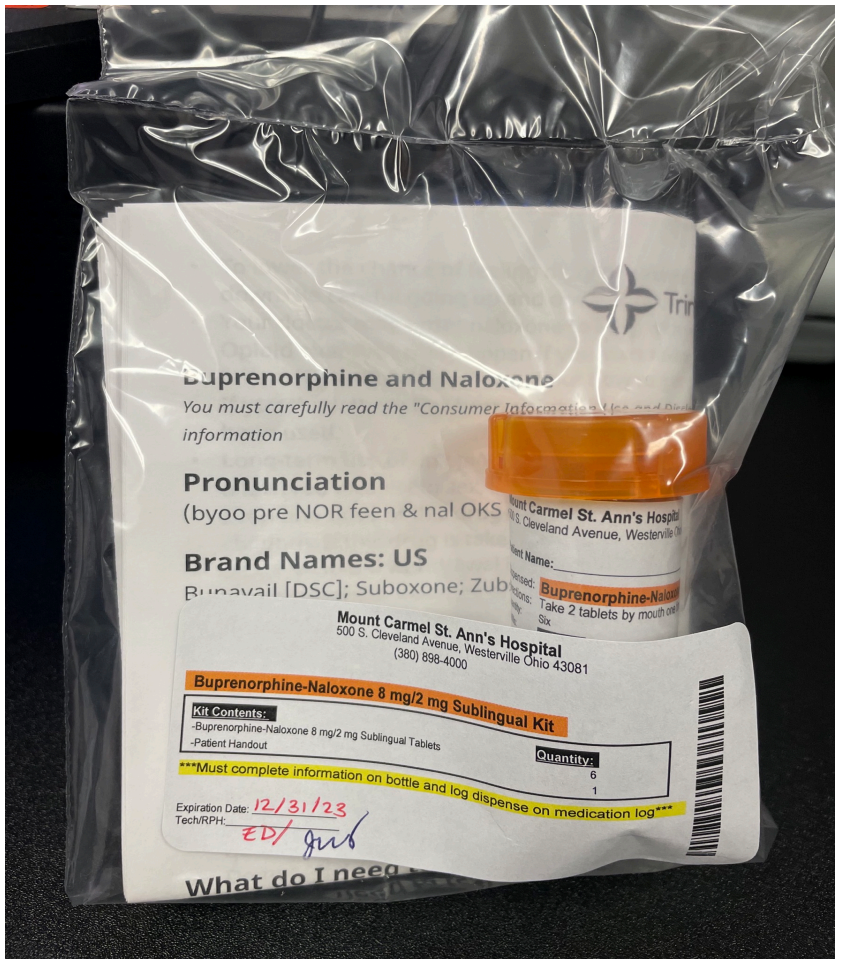
When can a prescriber start prescribing buprenorphine for opioid use disorder without a DATA-Waiver? –

Immediately. Practitioners seeking to prescribe buprenorphine for the treatment of opioid use disorder no longer need to apply for, or possess, a DATA-Waiver prior to prescribing the medication. They should be aware of their state's requirements because they may differ from federal law. Additionally, from June 27, 2023, practitioners will need to ensure that they are in compliance with the educational requirements as described above, since practitioners will need to have completed this training by the time they either newly apply for or are renewing their DEA registration.

Section 1262 of the 'Consolidated Appropriations Act of 2023' removes the federal requirement for practitioners to apply for a special waiver prior to prescribing buprenorphine for the treatment of opioid use disorder. It also removes other federal requirements associated with the waiver such as discipline restrictions, patient limits, and certification related to provision of counseling.

MAT in ED: 72-Hour Rule

- MAT = Medication Assisted Therapy (for opiate use disorder)
- ED provider may dispense buprenorphine dose directly to the patient (one dose at a time) and have the patient return to the ED for up to two additional daily doses after the initial day of buprenorphine or buprenorphine/naloxone administration
- Hospitals may e-mail the DEA and request permission to dispense the entire 72-hour supply at once (Mount Carmel Franklinton site was the first site in Columbus to operationalize this process)



- Kit contents:
  - 1 amber vial containing 6 buprenorphine-naloxone 8 mg/2 mg tabs
  - Lexicomp patient education

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Example of Inpatient Order set/: Opioid Withdrawal

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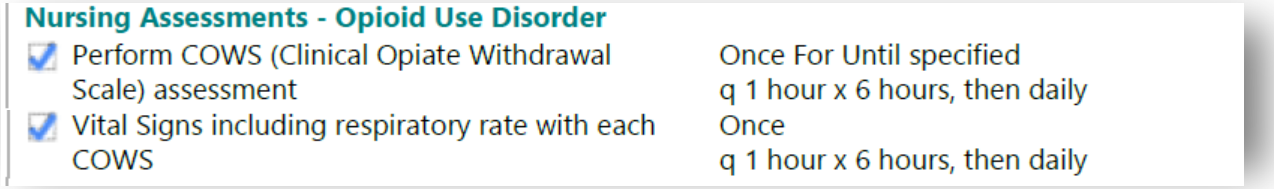
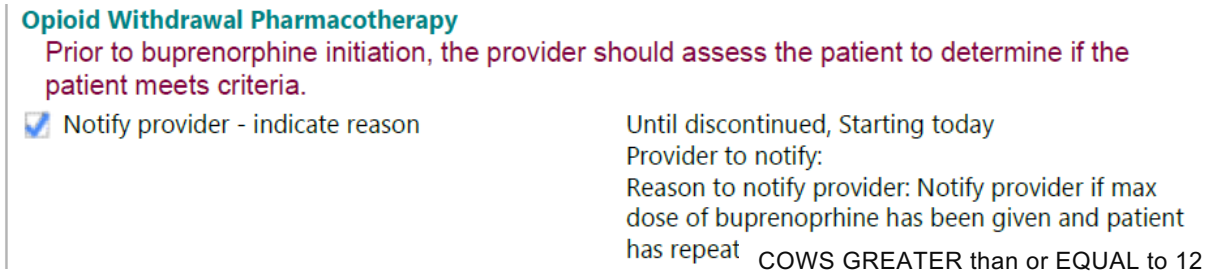
Default Nursing Orders

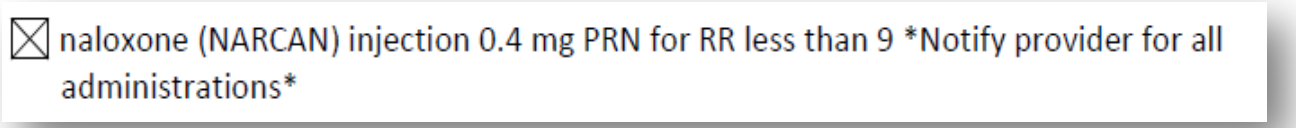
- **Nursing Assessments**
  - Default: COWS with Vital Signs and RR every hour x 6 hours

- **Notify provider**: If patient has been given maximum ordered dose of buprenorphine and has a repeat COWS greater than or equal to 12

- Naloxone administration for RR less than 9, and notify provider if given







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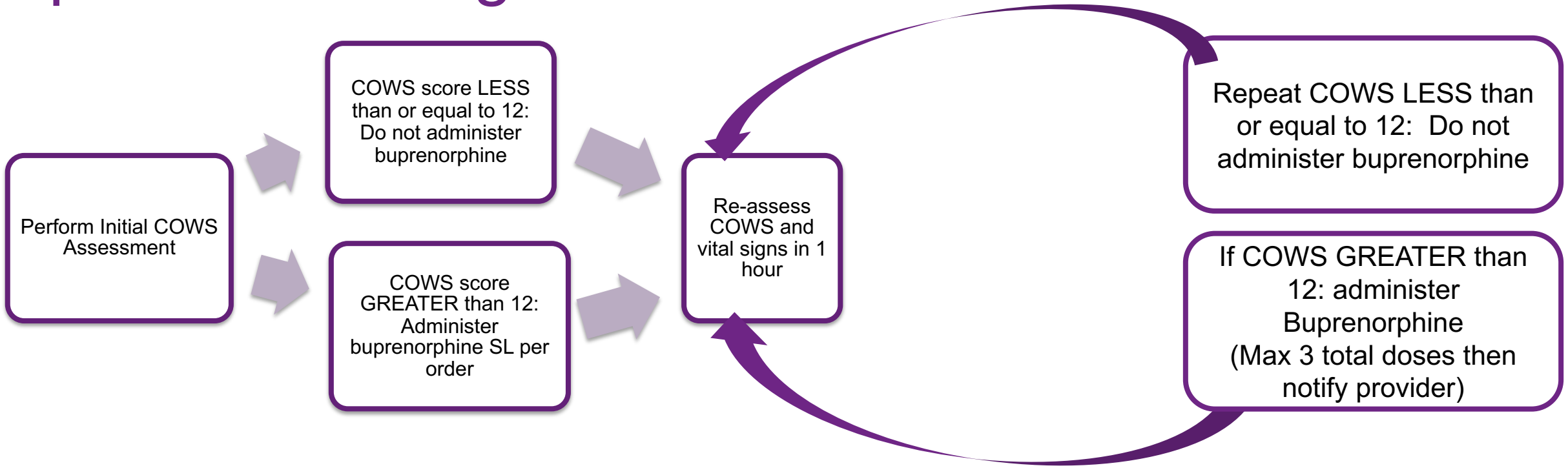
Inpatient Nursing Workflow Per Provider Orders



- Continue hourly COWS during induction then daily
- Administer buprenorphine (if COWS is GREATER than 12 points), Re-assess COWS and vital signs in 1 hour, continue to administer buprenorphine until COWS LESS than or equal to 12, UP TO A MAXIMUM OF 3 PRN DOSES
  - If COWS remains GREATER than or equal to 12 after the maximum ordered doses are administered, notify provider for further instructions (will likely require additional doses of buprenorphine until COWS < 8, usually not more than 32 mg of buprenorphine for induction)

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Sam Jones – A Case Study

Clinical Opiate Withdrawal Scale				
Heart Rate	88	86	85	86
Heart Rate Source				Monitor
Patient Position				Lying
Resting Pulse Rate: Measured After Patient is Sitting or Lying for One Minute				1
GI Upset: Over Last Half Hour				0
Sweating: Over Past Half Hour Not Accounted for by Room Temperature of Patient Activity				0
Tremor: Observation of Outstretched Hands				0
Restlessness: Observation During Assessment				0
Yawning: Observation During Assessment				0
Pupil Size				1
Anxiety and Irritability				2
Bone or Joint Aches: If Patient was Having Pain Previously, Only the Additional Compone...				1
Gooseflesh Skin				0
Runny Nose or Tearing: Not Accounted for by Cold Symptoms or Allergies				1
Clinical Opiate Withdrawal Scale Total Score				6

- You are caring for Sam Jones, a 38-year-old male who has been admitted for cellulitis related to IV heroin use. Sam arrived to the hospital at 12:00 and states the last time he used heroin was approximately 8 hours ago. The Provider has initiated the Opioid Withdrawal Management Order Set and you have added the COWS assessment to the Flowsheets in Epic.
- Sam scores a 6 points on the COWS assessment. What do you do next?
  - A) Administer Suboxone per order
  - B) Do not administer Suboxone and reassess in 1 hour
  - C) Hold Suboxone and reassess in 6 hours
  - D) Administer Suboxone and reassess in 1 hour

Rationale for Case Answer:

- Reminder, Sam Jones, in this case, is not yet experiencing symptoms of moderate opioid/heroin withdrawal since his COWS score is 6 points
- Buprenorphine-based therapy should not be initiated until COWS score is greater than 12 points to avoid precipitating acute withdrawal that can be associated with severe symptoms
- Re-assess COWS score every hour for 6 hours per nursing order

COWS Score	Opioid Withdrawal Severity
5 – 12 points	Mild
13 – 24 points	Moderate
25 – 36	Moderately Severe
Greater than 36 points	Severe

Knowledge Check

Why is it important to not administer buprenorphine (Suboxone) until the patient is moderately symptomatic?

a) It will put the patient at an increased risk of becoming addicted to Suboxone

b) Administering Suboxone too soon puts the patient at risk of respiratory depression

c) Administering Suboxone too soon can cause precipitated withdrawal (acutely worsened opioid withdrawal symptoms)

d) It’s not important and can be given at any time

Case Continued

- Sam Jones is re-assessed in 1 hour and his COWS score is now 18 (HR 110 bpm, diarrhea, sweating, restlessness, dilated pupils, anxiousness, anxiousness, irritability, and diffuse joint pain)

Clinical Opiate Withdrawal Scale

Heart Rate	110
Heart Rate Source	Monitor
Patient Position	Sitting
Resting Pulse Rate: Measured After Patient is Sitting or Lying for One Minute	2
GI Upset: Over Last Half Hour	3
Sweating: Over Past Half Hour Not Accounted for by Room Temperature of Patient Activity	3
Tremor: Observation of Outstretched Hands	0
Restlessness: Observation During Assessment	3
Yawning: Observation During Assessment	0
Pupil Size	2
Anxiety and Irritability	4
Bone or Joint Aches: If Patient was Having Pain Previously, Only the Additional Compone...	1
Gooseflesh Skin	0
Runny Nose or Tearing: Not Accounted for by Cold Symptoms or Allergies	0
Clinical Opiate Withdrawal Scale Total Score	18

COWS Score	Opioid Withdrawal Severity
5 – 12 points	Mild
13 – 24 points	Moderate
25 – 36	Moderately Severe
Greater than 36 points	Severe

Example Case: Treatment

- What should you next based on COWS of 18 points?

    a. Reassess COWS in 15 minutes
    b. Administer buprenorphine 0.5 mg SL once
    c. Administer buprenorphine 4 mg SL once
    d. Administer naloxone 0.4 mg

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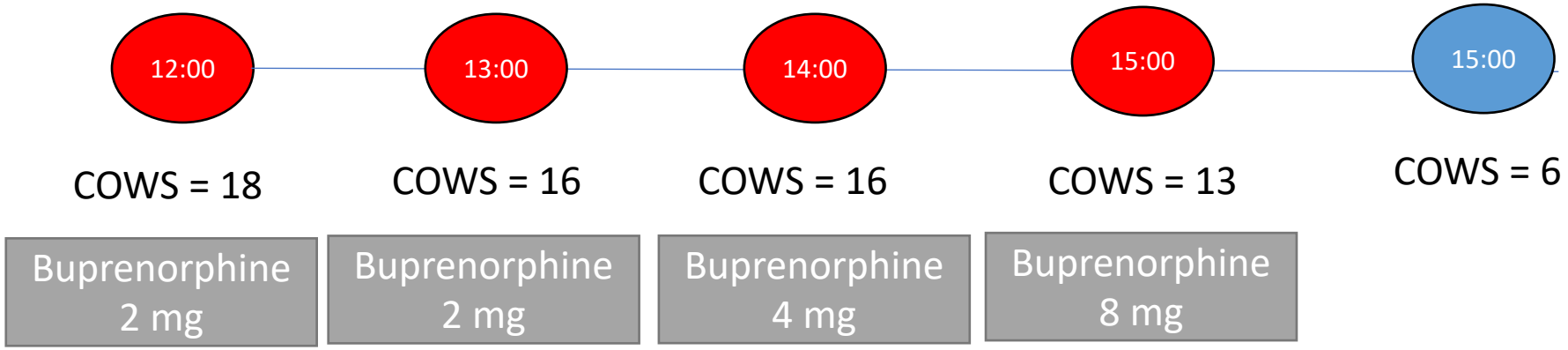
Buprenorphine Induction and Maintenance Dose

- Buprenorphine initial dose should be 2 – 4 mg when COWS score at least 8 (but preferably ≥ 12), then doses may be repeated upon reassessment in 1 – 2 hours, increasing dose in increments of 2 – 4 mg (usually not to exceed 32 mg total daily dose)
- Maintenance dose after the first day of treatment: maintain total daily dose from day 1 and adjust dose in increments of 4 mg to a level that maintains treatment and suppresses opioid withdrawal
  - Typical maintenance dose Suboxone 8/2 mg SL BID

Example Induction:

- 32-year-old female patient presents to Emergency Department in acute opioid withdrawal (last use of fentanyl 3 days prior) and current COWS score 16
- Buprenorphine initiation with re-assessment hourly and re-dosed, incrementally increasing buprenorphine dose until COWS < 8



What should maintenance dose be for this patient?

Total induction dose = 16 mg, start maintenance dose tomorrow:
Suboxone 8/2 mg SL BID

Knowledge Check

Providers can order buprenorphine (Suboxone) if (select all that apply):

a) The patient is admitted for a medical or surgical reason and begins to go through withdrawal

b) The patient is already taking Suboxone as part of narcotic treatment program

c) The patient is discharging

d) The patient is admitted for reasons of addiction and arrangements are being made to enroll the patient into a treatment program within 3 days

Methadone vs Buprenorphine for OUD

Methadone is alternative to buprenorphine for OUD

Methadone is a synthetic full opioid agonist

Pros:

- Patient does not need to develop moderate opioid withdrawal symptoms before initiating
- No risk for precipitated withdrawal upon induction
- More potent analgesic, may be preferred in patients with chronic pain

Cons:

- Schedule II (vs. buprenorphine which is schedule III) so more regulatory restrictions for dispensing
- Obtaining methadone may be more difficult as it may only be prescribed by registered providers from registered methadone clinics typically one dose at a time
- Risk of QTc prolongation
- Risk of respiratory depression (no ceiling effect), more euphoria potential

How to Initiate Methadone (New Start)

Initial Dose: Methadone 10 – 30 mg

Titration: increase methadone by 10 mg every 5 days based on patient response

Maintenance Dose: Methadone 60 – 120 mg/day

- Methadone is a slow-acting full opioid agonist (time to peak 1 to 7.5 hours) with long half-life (8 – 59 hours)
  - Methadone accumulates in the body after repeated doses since it is cleared very slowly
- When used for OUD, it reaches the brain slowly, dampening the rewarding effect
- **Initial dose: 10 – 20 mg** with reassessment (2.5 – 10 mg if transitioning from naltrexone, patients re-entering community after incarceration)
- Due to risk of overdose in the first 2 weeks and variable tolerance, federal law mandates initial dose cannot exceed 30 mg
  - The total amount of methadone administered on day one of initiation must not exceed 40 mg
- Increase dose slowly based on patient response, do not titrate rapidly
  - Suggest no faster than 10 mg increment at 5 day intervals (or 5 mg increments no at 2 – 3 day intervals)
- Maintenance dose is typically 60 – 120 mg per day, which typically creates sufficient tolerance to minimize a euphoric response to other opioids of abuse

ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. J Addict Med. 2020 Mar/Apr;14(2S Suppl 1):1-91.
Federal Guidelines for Opioid Treatment Programs (samhsa.gov)

Methadone Adverse Effects

- Unique pharmacokinetics, variable absorption, long half-life, large volume of distribution due to lipophilicity, high tissue binding affinity, and slow elimination lead to accumulation and increased risk of oversedation, respiratory depression and death due to overdose
- Methadone prolongs QTc
  - Methadone blocks voltage gated potassium channels during phase III of cardiac action potential therefore delaying cardiac repolarization and prolongs QTc (risk for Torsades de Pointes)
  - Screen patients for QTc prolonging medications
  - Avoid hypokalemia and/or hypomagnesemia
  - Obtain baseline ECG (discuss risks and benefits if QTc > 450 msec; do not initiate if baseline QTc > 500 msec)

Table 3: Incidence of QT prolongation with methadone exposure[64-69]

Length of QT interval (ms)	Incidence (%)
>430	41-49
>450	19-29
>470	7-15
>500	1.8-16.2

QT prolongation with methadone exposure is not rare

[Comprehensive Review on Methadone-Induced QT Prolongation and Torsades (sagepub.com)]

Methadone QTc Prolongation

- 93-patients in urban opioid treatment program on maintenance methadone underwent 12-lead ECG screening prior to initiation and again at steady-state to determine incidence of QTc prolongation (QTc ≥ 480 women, ≥ 480 men, and/or ≥ 60 msec increase from baseline
- 15% of patients developed QT prolongation (no cases of TdP)
- Note: cocaine is an inhibitor of I_{Kr}, and has been identified as a risk factor for methadone-associated QT interval prolongation

Characteristic	QTc prolongation (*n* = 14)	No QTc prolongation (*n* = 79)	*p*
Age (years, mean ± SD)	41 ± 13	35 ± 9	0.03
Female, *n* (%)	9 (64)	59 (75)	0.42
White race, *n* (%)	12 (86)	57 (72)	0.56
Weight (kg, mean ± SD, *n* = 28)	78.2 ± 16.3 (*n* = 13)	79.6 ± 16.8 (*n* = 15)	0.28
Methadone dose at time of ECG (mg, mean ± SD)	85 ± 28	76 ± 22	0.70
Time from baseline ECG to on-treatment ECG (days, mean ± SD)	44 ± 17	47 ± 15	0.50
Hypertension, *n* (%)	2 (14)	9 (11)	0.67
Coronary artery disease, *n* (%)	1 (7)	3 (4)	0.49
Any QT-prolonging medication[a], *n* (%)	6 (43)	18 (23)	0.11
≥2 QT-prolonging medications[a], *n* (%)	2 (14)	4 (5)	0.18
Pregnant, *n* (% of women)	1/9 (11)	4/59 (7)	0.57
Positive urine test for cocaine[b], *n* (%)	5 (36)	11 (14)	0.06
Positive urine test for THC, *n* (%)	3 (21)	18 (23)	>0.99

Abbreviations: ECG, electrocardiogram; SD, standard deviation; TCH, tetrahydrocannabinol

[a]QT interval-prolonging drugs taken by patients (from the list of drugs "known" to cause torsades de pointes on the QT drugs list at www.crediblemeds.org[3]) were as follows: azithromycin, citalopram, escitalopram, fluconazole, ondansetron, and cocaine (based on positive urine test).

[b]Urine tests for cocaine were conducted within 3.8 ± 4.6 days of the on-methadone ECGs.

Titus-Lay EN, et al. Methadone-associated QT interval prolongation in patients undergoing maintenance therapy in an urban opioid treatment program. Pharmacotherapy. 2021 Mar;41(3):238-246.

Methadone Common Drug Interactions: QTc

KNOWN RISK (Highest)	POSSIBLE RISK	CONDITIONAL RISK
Amiodarone/ Dronedarone	Aripiprazole	Amantadine
Azithromycin/Clarithromycin/ Erythromycin	Buprenorphine	Amitriptyline
Chlorpromazine	Clozapine	Fluoxetine
Ciprofloxacin/Levofloxacin/ Moxifloxacin	Lithium	Hydroxyzine
Citalopram	Mirtazapine	Ketoconazole
Dofetilide	Nortriptyline	Loperamide
Droperidol/ Haloperidol	Paliperidone	Metoclopramide
Flecainide	Palonosetron	Metronidazole
Fluconazole	Tizanidine	Olanzapine
Hydroxychloroquine /Quinidine	Tramadol	Paroxetine
Ibutilide	Vardenafil	Propafenone
Methadone	Venlafaxine	Risperidone
Ondansetron		Trazodone
Sotalol		Ziprasidone

Transitioning from Methadone to Suboxone

- 58 –year-old male patient presents after syncopal episode and work up is in progress during an inpatient stay. ECG demonstrates QTc 600 msec. Patient has home prescription for methadone 150 mg PO daily for OUD. Primary care team is considering transitioning him to suboxone since the QTc is too high to continue methadone, how should they proceed?

In this case cross-tapering is not possible since methadone cannot be continued due to very high QTc and risk of Torsades de Pointes. Wait for methadone withdrawal symptoms (COWS ≥ 12), which may take days, before initiating buprenorphine due to risk of precipitated withdrawal

Transitioning from Methadone to Suboxone: Example without Tapering Methadone

- Microdosing of partial agonist (buprenorphine) concurrently with a full opioid agonist (methadone) until it occupies a substantial portion of opioid receptors to prevent precipitated withdrawal
- Taper up the buprenorphine while maintaining full dose methadone
- Once methadone at daily maintenance dose, stop methadone

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

Day	Buprenorphine dosage	Methadone dose
1	0.5 mg[a] SL once/day	Full dose
2	0.5 mg[a] SL twice/day	Full dose
3	1 mg SL twice/day	Full dose
4	2 mg SL twice/day	Full dose
5	4 mg SL twice/day	Full dose
6	8 mg SL once/day	Full dose
7	8 mg SL in A.M. and 4 mg SL in P.M.	Full dose
8	12 mg SL/day	Stop

SL = sublingually.
[a]For our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Terasaki D, et al Transitioning Hospitalized Patients with Opioid Use Disorder from Methadone to Buprenorphine without a period of Opioid Abstinence Using a Microdosing Protocol. Pharmacotherapy. 2019 Oct;39(10):1023-1029.

Initiation MAT for OUD in Patients who Abuse Fentanyl

- 28-year old male patient presents to the ED with finger laceration after a construction accident. During the course of the visit the patient expresses interest in initiation suboxone. He states that he has been smoking fentanyl daily for 2 years and the last use was 24 hours prior to this visit and he is not currently displaying any symptoms of opioid withdrawal. How will you proceed?

Wait until COWS ≥ 12 before initiating buprenorphine. Or consider microdosing of buprenorphine beginning at lower COWS score of 8 if patient unwilling to wait for moderate withdrawal or threatening to leave against medical advice.

Fentanyl Considerations

- Fentanyl is a highly lipophilic opioid that rapidly distributes into body tissues giving it rapid onset (passing through blood brain barrier) and relatively short duration in the CNS
- Fentanyl is conceptually considered to be a short-acting opioid because of its short-duration of clinical effect but it persists in peripheral tissues
- After pronged and/or persistent use, significant accumulation can occur in adipose tissue resulting in extended excretion period (two-compartment pharmacokinetic model)
- Case reports of patients with chronic fentanyl abuse/exposure testing positive for fentanyl 2 – 4 days after last use and many case reports of precipitated withdrawal despite appropriate abstinence period

Shearer D, et al. Challenges with buprenorphine inductions in the context of the fentanyl overdose crisis: A case series. Drug Alcohol Rev. 2022 Feb;41(2):444-448.

Method for Successfully Initiation Suboxone in Patients Using Illicit Fentanyl

- Patients with chronic fentanyl use seem to be able to abstain from opioid use for longer periods (~48 hours) without going into severe withdrawal due to its unique pharmacokinetic properties
  - Lipophilicity leading to high volume of distribution with chronic use → prolonged clearance from body
- Wait until COWS score is > 12, utilize lower initial dose of buprenorphine ≤ 2 mg, and shorten re-dose interval ≤ 60 minutes

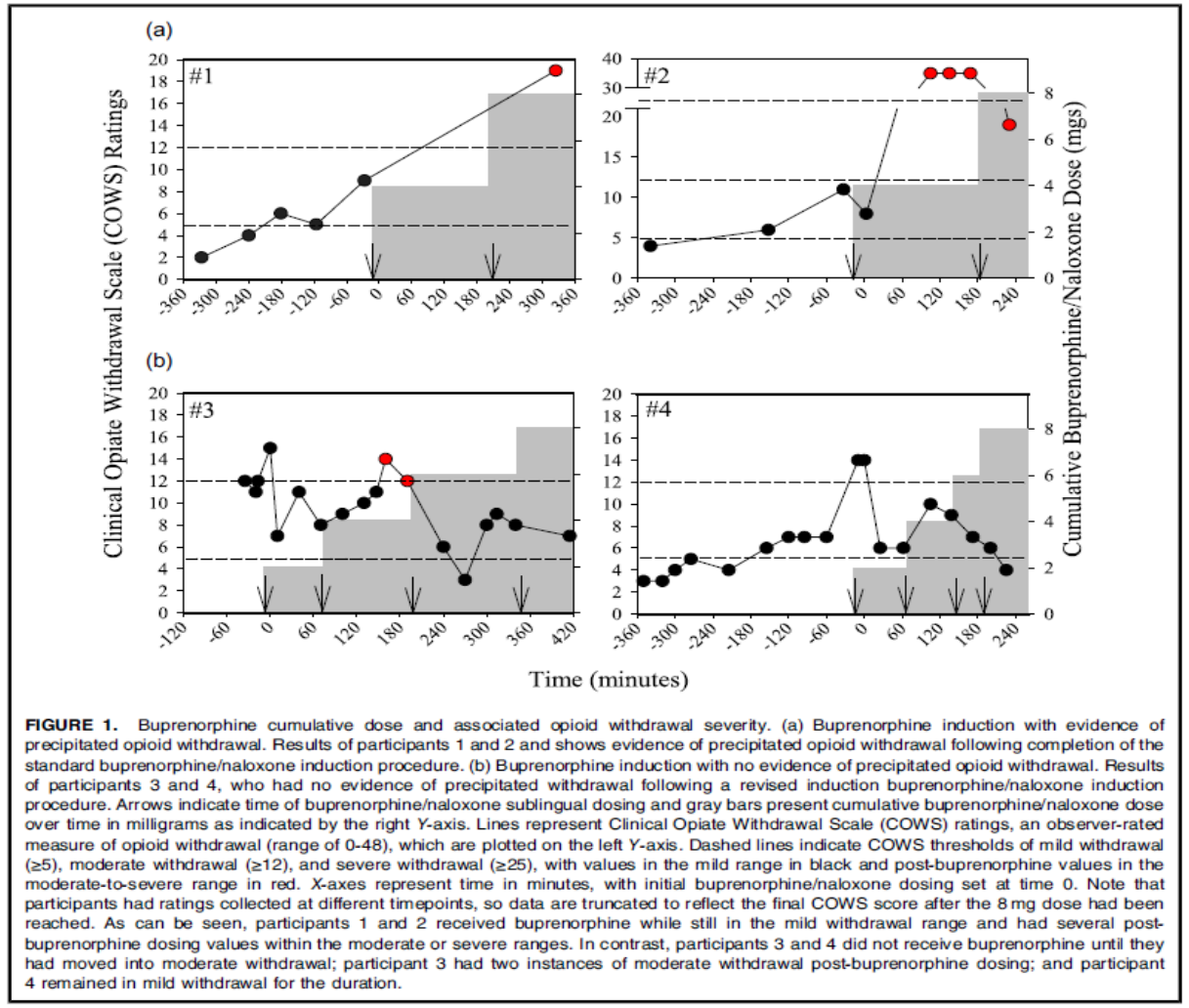
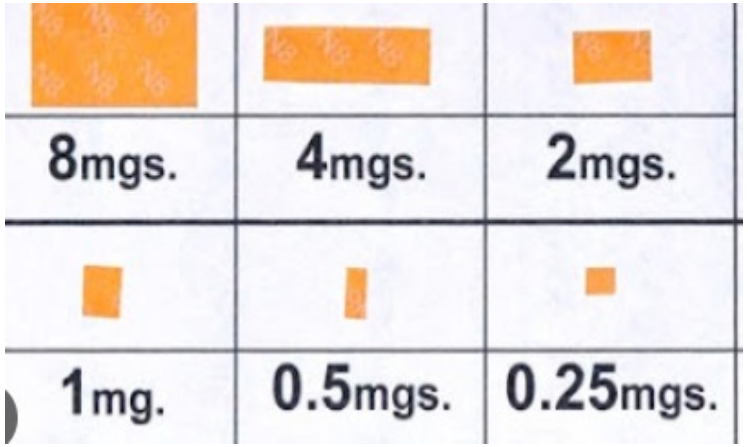


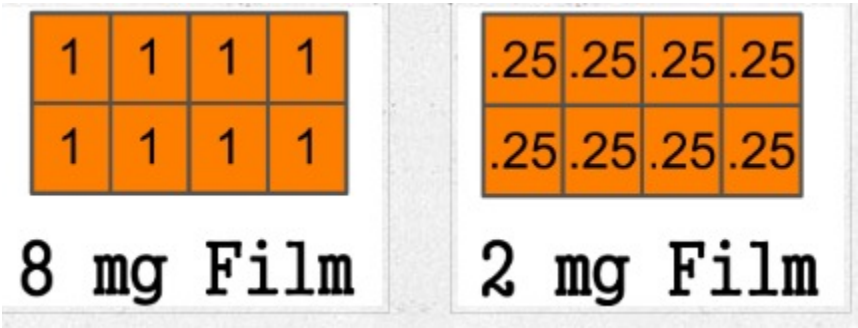
FIGURE 1. Buprenorphine cumulative dose and associated opioid withdrawal severity. (a) Buprenorphine induction with evidence of precipitated opioid withdrawal. Results of participants 1 and 2 and shows evidence of precipitated opioid withdrawal following completion of the standard buprenorphine/naloxone induction procedure. (b) Buprenorphine induction with no evidence of precipitated opioid withdrawal. Results of participants 3 and 4, who had no evidence of precipitated withdrawal following a revised induction buprenorphine/naloxone induction procedure. Arrows indicate time of buprenorphine/naloxone sublingual dosing and gray bars present cumulative buprenorphine/naloxone dose over time in milligrams as indicated by the right *Y*-axis. Lines represent Clinical Opiate Withdrawal Scale (COWS) ratings, an observer-rated measure of opioid withdrawal (range of 0-48), which are plotted on the left *Y*-axis. Dashed lines indicate COWS thresholds of mild withdrawal (≥5), moderate withdrawal (≥12), and severe withdrawal (≥25), with values in the mild range in black and post-buprenorphine values in the moderate-to-severe range in red. *X*-axes represent time in minutes, with initial buprenorphine/naloxone dosing set at time 0. Note that participants had ratings collected at different timepoints, so data are truncated to reflect the final COWS score after the 8 mg dose had been reached. As can be seen, participants 1 and 2 received buprenorphine while still in the mild withdrawal range and had several post-buprenorphine dosing values within the moderate or severe ranges. In contrast, participants 3 and 4 did not receive buprenorphine until they had moved into moderate withdrawal; participant 3 had two instances of moderate withdrawal post-buprenorphine dosing; and participant 4 remained in mild withdrawal for the duration.

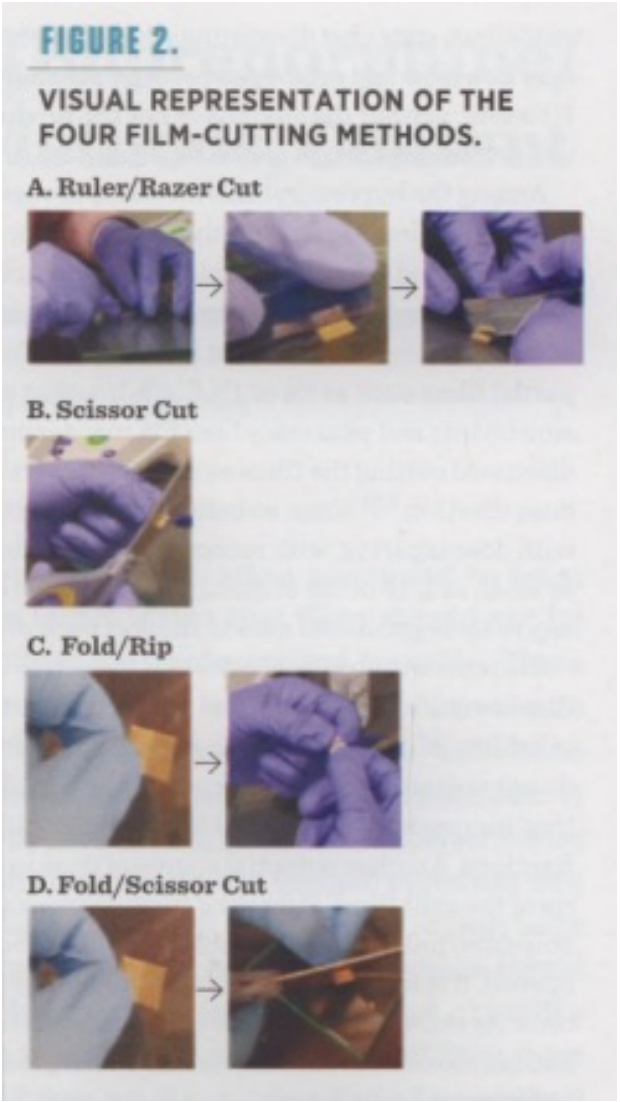
Shearer D, et al. Challenges with buprenorphine inductions in the context of the fentanyl overdose crisis: A case series. Drug Alcohol Rev. 2022 Feb;41(2):444-448.

Buprenorphine Microdosing

- Commercially available Suboxone lowest buprenorphine dose is 2 mg
- Microdosing involves cutting strips for smaller doses







[An Exploratory Study of Suboxone (Buprenorphine/ Naloxone) Film Splitting: Cutting Methods, Content Uniformity, and Stability (sjf.edu)]

Microdosing Buprenorphine to Avoid Need to Circumvent Need for Withdrawal

- If buprenorphine is preferred for MAT to treat OUD but patient cannot tolerate the emergence of moderate opioid withdrawal symptoms – some alternative dosing strategies have been published
- Buprenorphine is partial agonist with higher binding affinity for mu-opioid receptor but lower dissociation constant → allows low incremental doses to be co-administered with full agonists and slowly cross taper until buprenorphine monotherapy without precipitating withdrawal

TABLE 2. Titration schedule for Case 2

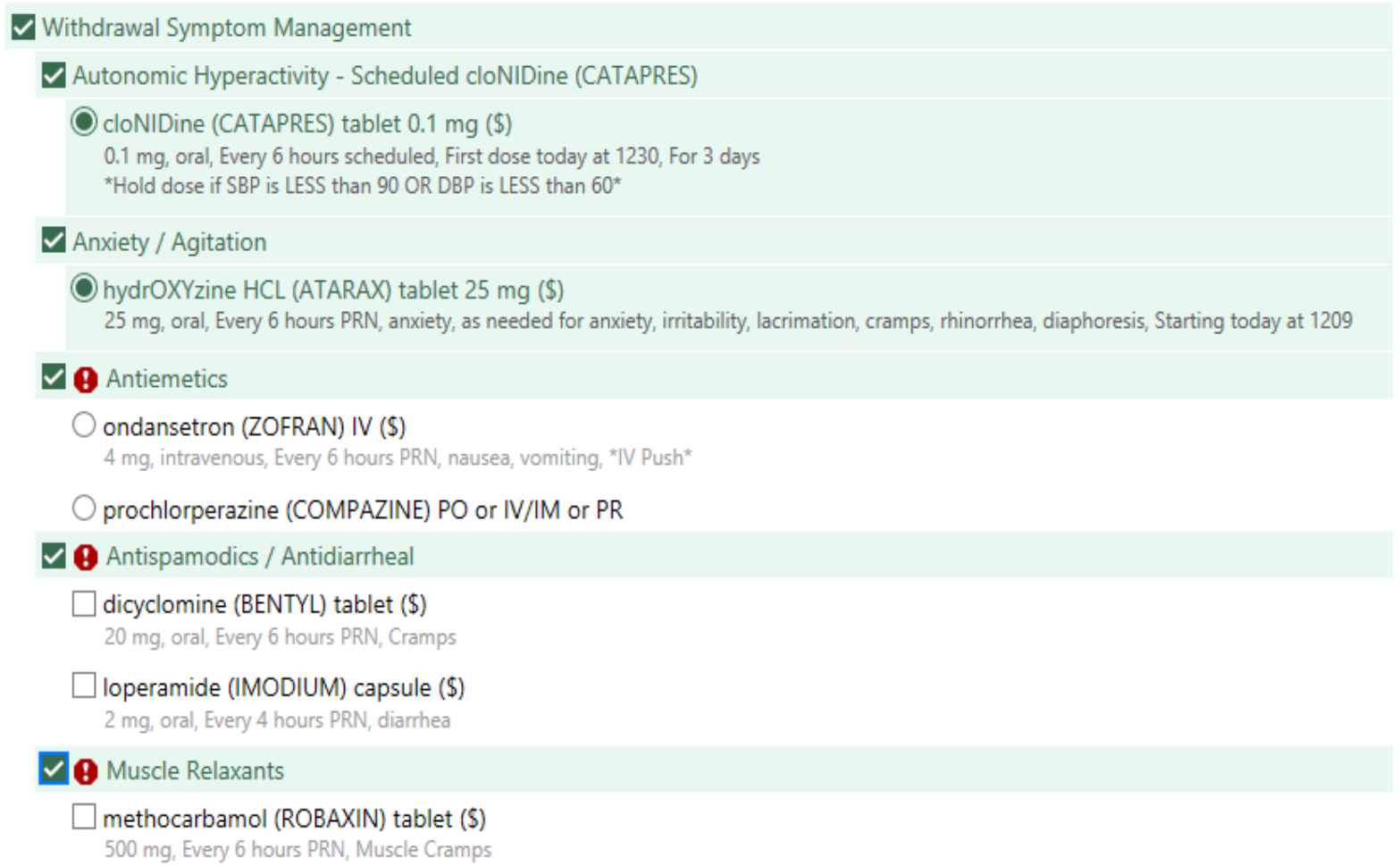
	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

Klaire S, et al. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: A case series. Am J Addict. 2019 Jul;28(4):262-265.

Adjunctive Therapies for Opioid Withdrawal

- Example of order panel for symptom management



Adjunctive Treatments for Opioid Withdrawal

Gastrointestinal Symptoms of Opioid Withdrawal:
- Abdominal cramps
- Diarrhea
- Nausea/vomiting

Bentyl (dicyclomine) 20 mg PO every 6 hours PRN for GI cramping

Imodium (loperamide) 4 mg followed by 2 mg with each loose stool; maximum 16 mg/day

Zofran (ondansetron) 4 – 8 mg PO every 6 hours PRN nausea

CNS Symptoms of Opioid Withdrawal:
- Hypertension/tachycardia
- Agitation/anxiety/restlessness
- Lacrimation, rhinorrhea (cholinergic excess)

Clonidine 0.1 mg q6 hours scheduled or q1hr PRN anxiety or tachycardia/HTN up to 4 doses/day

Vistaril (hydroxyzine) 25 mg PO q6 hr prn anxiety, lacrimation, rhinorrhea, diaphoresis

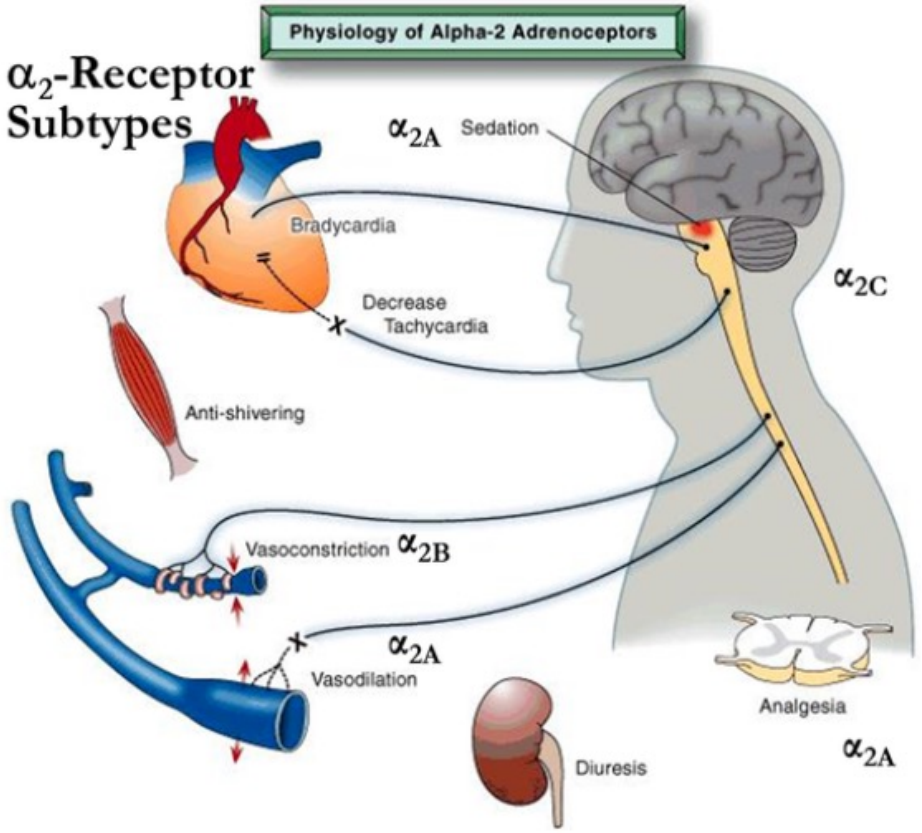
Musculoskeletal symptoms of Opioid Withdrawal:
- Muscle cramps (diffuse undifferentiated body/joint pain)

Ibuprofen or Acetaminophen PRN pain

Robaxin (methocarbamol) 500 mg PO q6hr prn muscle cramps
Or Flexeril (cyclobenzaprine) 5 mg q8hr prn muscle cramps

Clonidine Adjunctive for Opioid Withdrawal

- Clonidine is an alpha-2 adrenergic agonist
  - The alpha 2 receptor is an allosteric inhibitor that inhibits adenylyl cyclase to reduce the levels of cAMP and causes hyperpolarization of adrenergic neurons → this suppresses norepinephrine release
  - Agonism of the alpha-2 receptor in the corpus coeruleus results in decreased anxiety (sedating effect)
  - Decreasing sympathetic outflow causes hypotension and bradycardia



Giovannitti JA, et al. Anesth Prog. 2015;62(1):31-38.

Clonidine for Opioid Withdrawal

- Clonidine should no longer be used as the sole agent for opioid withdrawal since it has been shown to be inferior to buprenorphine for retention
- Buprenorphine and clonidine may be used together and may be synergistic since they work by different mechanisms
- Clonidine dose: 0.1 mg PO; may schedule q8 hr (hold if SBP < 90 or HR < 60 bpm), or may administer PRN, doses may be repeated q1hr for agitation, tachycardia, or hypertension up to 4 doses per day
- Onset: 0.5 – 1 hour
- Half-life: 12 – 16 hours

Acute Pain Management – Example Order Panel

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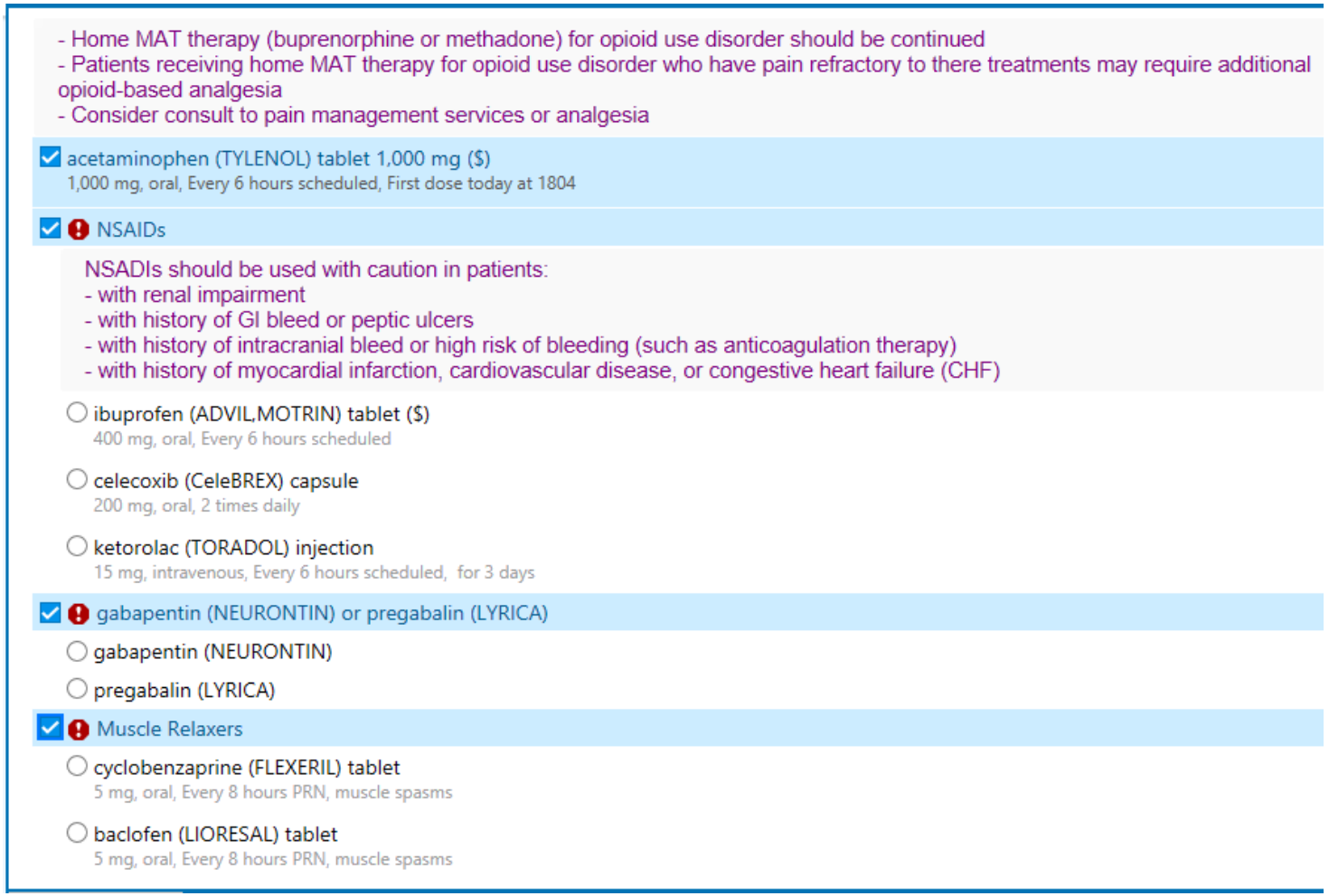
Acute Pain in Patients with Opioid Use Disorder

- Although multimodal pain regimens may be used, severe acute pain and postoperative pain may require the use of opioids despite the patient diagnosis of OUD
  - Opioids should not be withheld for management of acute severe pain due to fear of worsening the OUD
- Pain management in patients who receive methadone maintenance therapy is complicated due to often unpredictable cross tolerance
- It is common for severe acute pain to be inadequately controlled in the hospital and postoperative setting, likely because postoperative opioid doses are too low or not titrated rapidly enough

Acute Pain Management – Inpatient Opioid Use Disorder Order Panel

- Non-opioid acute pain management options include acetaminophen, NSAIDS (ketorolac, ibuprofen), GABA analogs (gabapentin), GI muscle relaxer (dicyclomine), muscle relaxer (cyclobenzaprine)



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Non-Opioid Pain Management Options

Muscle relaxant	- Methocabamol (Robaxin) 500 mg PO q6hr PRN muscle cramps - Cyclobenzaprine (Flexeril) tablet 5 mg q8hr PRN muscle spasms - Baclofen (Lioresal) 5 mg PO q8hr PRN muscle spasms
Chronic/Acute Pain	- Acetaminophen 1000 mg PO q6hr PRN pain NSAIDS: *avoid with renal impairment, GI bleed, peptic ulcer, history of intracranial bleed or high risk of bleeding, history of MI, CVD, or CHF* - Ibuprofen 400 mg PO q6hr PRN pain - Celecoxib 200 mg PO BID PRN pain - Ketorolac 15 mg q6hr PRN pain
Neuropathic pain	- Gabapentin 200 mg PO q8 hr <u>scheduled</u> o If age > 65 or CrCL < 30 mL/min; adjust to 100 mg q8hr - Pregabalin 100 mg PO q 12 hr <u>scheduled</u> o If age> 65 or CrCL < 30 mL/min; adjust to 50 mg PO q12hr

Perioperative Management of Patients Taking Buprenorphine

- Buprenorphine creates a unique challenge to anesthesia and surgeons that need to manage acute pain in the perioperative setting
- Options include:
  - Use non-opioid options including anesthetic nerve blocks
  - Continue the buprenorphine (potentially taper dose down) and overcome partial agonism with higher doses of opioids
  - Taper off the buprenorphine and use opioids then resume buprenorphine once post-op pain resolved (not recommended)

Perioperative Opioid Requirements in Patients Maintained on MAT for OUD

- 17 patients undergoing TKA or THA receiving methadone or suboxone perioperatively
- Surgery and anesthesia utilized regional blocks in 35% of cases and PCA in 35%
- Continued methadone or buprenorphine and up-titrated systemic opioids
- Mean MME was 7 times higher in perioperative period in patients on methadone or buprenorphine compared to opioid-naïve patients

Hansen LE, et al. Total Joint Arthroplasty in Patients Taking Methadone or Buprenorphine/Naloxone Preoperatively for Prior Heroin Addiction: A Prospective Matched Cohort Study. J Arthroplasty 2016:31(8):1698.

Continuing Methadone or Buprenorphine in Perioperative Setting

- Confirm patient's baseline outpatient methadone dose
- Continue methadone and do not attempt to calculate equianalgesic dosing or conversions since methadone has distinctive PK/PD profile, conversions are notoriously inaccurate
- Add non-opioid analgesics including acetaminophen, NSAIDS, muscle relaxants, neuropathic pain agents
- If opioids introduced →
  - Add short acting opioid and re-evaluate efficacy, add hold parameters for somnolence or RR < 10 breaths/min
  - Consider reducing buprenorphine dose by 50% and divide the reduced dose into q8-12hr scheduled regimen

Other Option for Opioid Withdrawal Treatment: Naltrexone

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Naltrexone

Naltrexone is an opioid antagonist

Available as generic oral tablet (50 mg) (usual dose 25 mg once daily x 1 – 3 days, then if no withdrawal, 50 mg once daily thereafter). Use only in highly motivated patients due to very poor compliance and high rates of relapse.

Available as long-acting monthly intramuscular injection (380 mg per injection) $$$

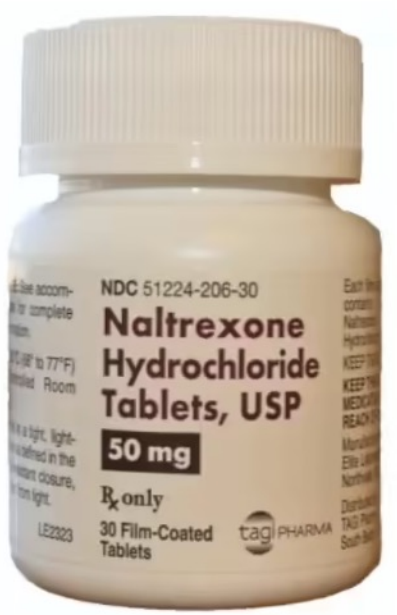
Complicated initiation → patient must be abstinent from opioids for 7 – 10 days (including buprenorphine) before first dose AND pass a naloxone challenge

Naltrexone (Extended release = Vivitrol)

- Vivitrol (Naltrexone extended release injection) is a long-acting opioid antagonist with no opioid agonist activity thus no intrinsic action except opioid blocking properties
- Naltrexone is not a controlled substance
- Initiation: To avoid precipitating severe withdrawal → DO NOT initiate until patient has been opioid abstinent for 7 – 10 days and/or has passed a naloxone challenge test
  - Abstinence for up to 14 days for methadone or buprenorphine
- Dose Vivitrol: 380 mg IM once every 4 weeks
  - If patient experiences breakthrough symptoms, may use 3 week interval
- Patients who discontinue naltrexone should be made aware of the increased risks associated with opioid overdose with death if they return to illicit opioid use

Vivitrol Considerations

- Use of naltrexone effectively removes opioid tolerance which exposes the patient to increased risk of opioid overdose if they cease treatment and return to using opioids
- $$$ Naltrexone 380 mg syringe = $1,969.33 each
- If patient requires emergency pain management (i.e. trauma) opioid therapy will be ineffective and non-opioid alternatives will need to be used until the effect of the monthly depot injection wears off
- Naltrexone would likely need to be discontinued prior to any painful procedure or surgery (72 hours for oral naltrexone, 30 days for IM injection)
- Consider naltrexone if patient unable to take buprenorphine or methadone
    - Employer does not allow any opioid including partial agonists
    - Patient’s goal is stop taking all opioid agents
    - Patient refuses buprenorphine or methadone



Resources

- Local Resources: https://needs.relink.org/services/medication-assisted-treatment?cid=20

- RREACT (Rapid Response Emergency Addiction Crisis Team) Emergency Department Direct Notification

  - Hospital staff notifies **RREACT team** by phone: 614-360-0199

  CFD RREACT | Emergency Addiction Crisis Team | Columbus OH

- Maryhaven Addiction Stabilization Center (MASC)

  - 1430 South High St, Columbus, 43207

  - Phone: 614-445-8131

- CompDrug
  - 547 E. 11th Ave, Columbus 43211
  - Phone: 614-224-4506
  - Physician contact: Dr. A. Dean Agra, MD, Medical Director (cell: 614-563-1785)

Columbus near Franklinton ED:

- Basecamp Recovery Center
  - 815 West Broad St Suite 200 Columbus, 43222
  - Hotline: 614-717-0822

Questions