

Opioid Summary Overview:

- Opioids
- Substance Use Disorder
- Opioid Tolerance, Intoxication, Overdose, And Withdrawal:
- Treatment
- Emergency Department Initiated Buprenorphine
- Patient education
- Relevant resources and websites

Opioids

The term “Opioid” refers to ALL:

- Opiates
- Derived compounds
- Natural and synthetic analogs

Type	Examples
Endogenous Opioids	Endorphins, Dynorphins, Enkephalins
Opiates	Morphine, Codeine
Semisynthetic Opioids	Buprenorphine, Heroin, Oxycodone
Fully Synthetic Opioids	Fentanyl, Methadone

Opioids produce their main pharmacological effects by interacting with opioid receptors.

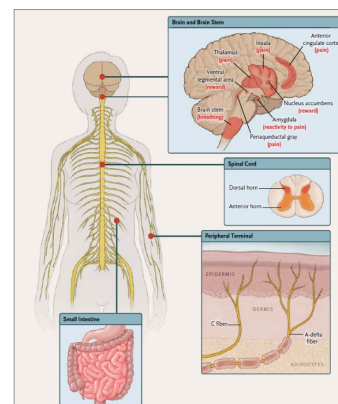
Opioid receptors are typical of G-protein coupled family of receptors and have seven transmembrane portions, intracellular and extracellular loops, an extracellular N-terminus, and an intracellular C-terminus.

Binding of opioid agonists with the receptors leads to activation of the G-protein, producing effects that are primarily inhibitory (decreased cAMP production, decreased Ca²⁺ influx, increased K⁺ efflux) and these effects ultimately culminate in membrane hyperpolarization of the cell and reduction in neuronal excitability.

- Humans have at least three types of opioid receptors located in the central nervous system, peripheral nerves, gut, and cells of the immune system
- Endogenous opioids (produced naturally in the body):
 - Part of normal physiologic responses to injury, pain, and stress
- Most of the clinically significant effects of prescribed and illicit opioids are attributed to activity at the mu receptor

Opioid Receptors	Endogenous Ligands
mu (μ)	Endorphins
kappa (κ)	Dynorphins
delta (δ)	Enkephalins

- Main target for Opioids are Mu Receptors
- Densely concentrated in:



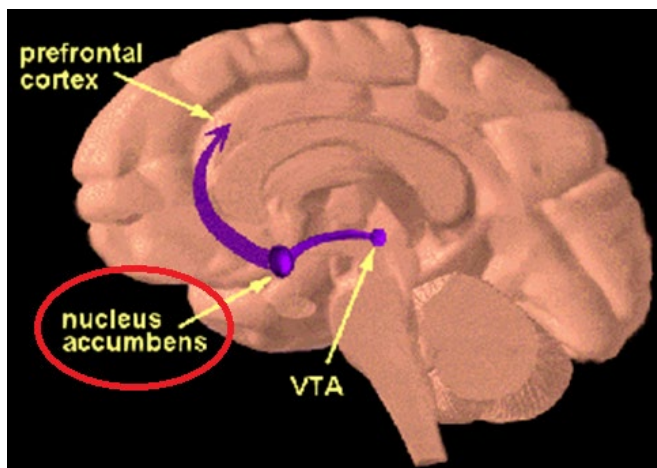
- Brain regions associated with:
 - Pain perception
 - Reward pathways
 - Respiratory function
- Spinal Cord
- GI System
- Peripheral regions

Physiology of Opioid Receptors

- Activation of mu receptors in the central nervous system causes effects including:
 - analgesia
 - sedation
 - euphoria
 - pupil constriction
 - decreased respiration (potentially lethal in overdoses)
 - decreased heart rate
 - nausea
- Activation in the gut decreases motility and can cause constipation
- Activation in peripheral tissues contributes to analgesic effects and modulates inflammatory responses

Three key components of the brain that are intimately involved in the development and persistence of substance use disorders:

- basal ganglia
- extended amygdala
- prefrontal cortex



Opioids and Brain Pathways

- Opioids act on basic motivational systems in the brain and brainstem.
 - Neurons release dopamine in the nucleus accumbens
 - The Amygdala is stimulated by sensations, thoughts, memories
- In the reward pathways involving the nucleus accumbens, opioids stimulate release of dopamine to a greater extent than natural rewards like food, leading to strong feelings of pleasure and gratification, learning of cues and behaviors that led to the experience, and motivation to repeat the behavior in the future.
- In the stress system centered in the amygdala, opioids decrease activity, producing relief from uncomfortable feelings like fear and anxiety, which again strengthens the motivation to use again in the future.

Positive reinforcement

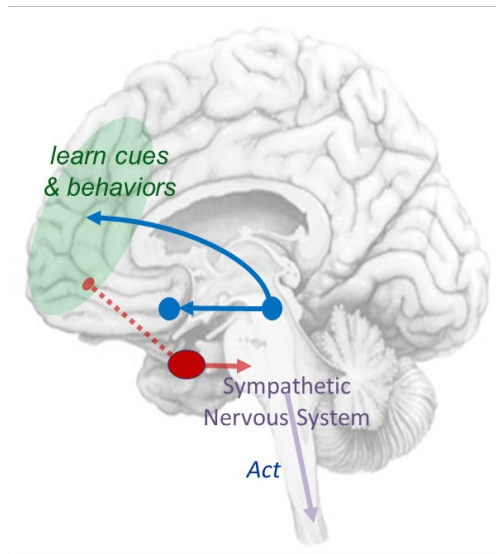
cells in the brainstem
release **dopamine** in the
nucleus accumbens



liking and wanting



seek out and do more



Negative reinforcement

cells in the **amygdala** are
stimulated



anxiety, fear, distress



avoid things that cause,
do things that relieve fear

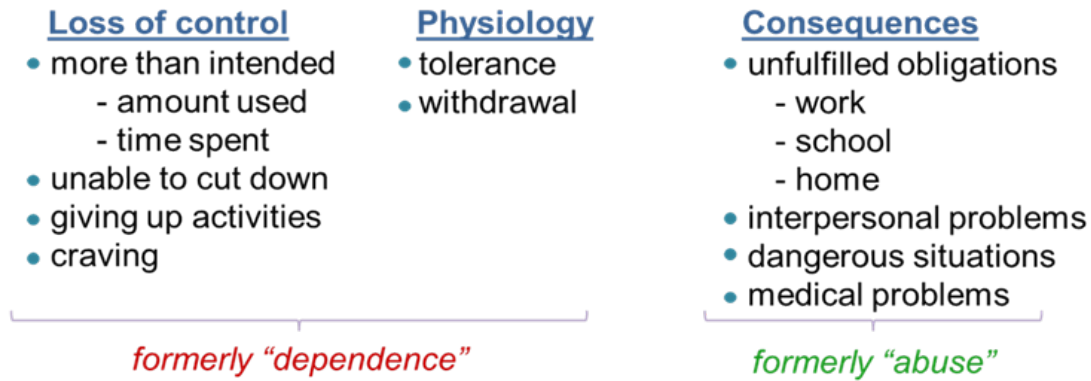
Attention, thinking, and judgment use the **prefrontal cortex**

- Chronic use leads to changes in the brain that decrease dopamine reward system associated euphoria and increases amygdala associated anxiety fear and distress.
 - Brain imaging studies in humans with substance use disorder have consistently shown long-lasting decreases in a particular type of dopamine receptor, the D2 receptor and decreases in the activity of the dopamine system have been observed during withdrawal from opioids.
- These findings suggest that people addicted to substances experience an overall reduction in the sensitivity of the brain's reward system (especially the brain circuits involving dopamine), both to addictive substances and also to natural reinforcers, such as food and sex.

Substance Use Disorder:

- Addictions are chronic illnesses characterized by clinically significant impairments in health, social function, and voluntary control over substance use.
- Similar to other chronic diseases addiction are chronic, subject to relapse, and influenced by genetic, developmental, behavioral, social, and environmental factors.

Figure. DSM-V Criteria for Substance Use Disorder



- A **substance use disorder** is defined by having 2 or more • in the past year resulting in distress or impairment.
- **Tolerance** and **withdrawal** alone don't necessarily imply a disorder.
- Severity is rated by the number of symptoms present:
 - 2-3 = mild
 - 4-5 = moderate
 - 6+ = severe

Figure. Spectrum of Substance Use

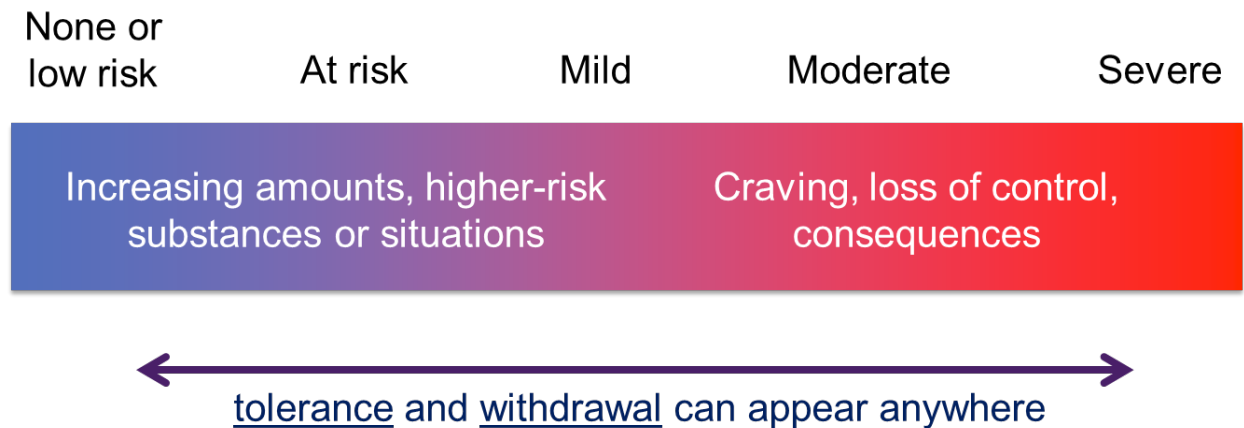


Table. Factors impacting vulnerability to substance use disorders

Genetic	Environmental
<ul style="list-style-type: none"> opioid receptors dopamine other transmitters intracellular signals novelty seeking harm avoidance impulsivity psychiatric disorders 	<ul style="list-style-type: none"> Family and social network Adverse Childhood Experiences (ACEs) psychiatric disorders stressors lack of positive experiences access to illicit sources prescription

Opioid Tolerance, Intoxication, Overdose, And Withdrawal:

Tolerance to Opioid Effects

- Opioid tolerance is characterized by a reduced responsiveness to an opioid agonist such as morphine and is usually manifest by the need to use increasing doses to achieve the desired effect.
- With repeated exposure to opioids, tolerance develops and involves changes in receptor numbers and functioning
- Tolerance develops at different rates, and to different extents, for different effects:
 - Rapid tolerance
 - sedation
 - euphoria
 - respiratory depression
 - nausea
 - little or no tolerance
 - constipation
 - pupil constriction
- Tolerance is lost while abstaining from opioids for an extended period, including during treatment with an opioid antagonist (i.e., naltrexone)

Opioid Intoxication

Opiate toxicity should be suspected when the clinical triad of central nervous system (CNS) depression, respiratory depression, and pupillary miosis are present.

- Signs
 - Bradycardia
 - Decreased respiratory rate
 - Shallow breathing
 - Pinpoint pupils
 - Hypotension
 - Hypothermia
 - Sedation
 - Slowed movement
 - Slurred speech
 - Head nodding
- Symptoms
 - Euphoria
 - Analgesia
 - Calmness
 - Somnolence

Opioid Overdose

An overdose occurs when larger quantities than physically tolerated are taken, resulting in central nervous system and respiratory depression, miosis, and apnea, which can be fatal if not treated rapidly.

Signs and Symptoms:

- Decreased level of consciousness to the point of potential unresponsiveness
- Pinpoint pupils
- Respiratory depression
- Slowed or stopped breathing (potentially leading to cardiac arrest)
- Pale Face, blue or purple lips/nails

Opioid Withdrawal

- All opioids produce similar withdrawal symptoms when stopped abruptly
 - A minor opioid withdrawal syndrome may occur after only several days' use.
- Severity of the syndrome increases with the size of the opioid dose and the duration of dependence.
- Timing of withdrawal symptoms depends on the opioid
 - With longer-acting opioids, symptoms usually begin later and last longer
- The opioid withdrawal syndrome usually includes symptoms and signs of central nervous system hyperactivity.

Opioids used	Onset of withdrawal	Symptoms peak	Duration of withdrawal
Short-acting opioids (e.g. heroin, oxycodone)	6-12 hours	36-72 hours	about 5 days
Long-acting opioids (e.g. methadone)	36-48 hours	~ 72 hours	up to 3 weeks

- Signs
 - tachycardia
 - hypertension
 - hyperthermia
 - insomnia, yawning
 - dilated pupils
 - hyperreflexia
 - tearing, runny nose
 - sweating, "gooseflesh"
 - muscle spasms
- Symptoms
 - abdominal cramps

- nausea
- vomiting
- diarrhea
- muscle/bone aches
- anxiety

Opioid Use Disorder

DSM-V Criteria for Opioid Use Disorder (OUD)

- Loss of Control
- Larger amounts, longer time
- Inability to cutback
- More time spent, getting, using, recovering
- Activities given up to use
- Craving
- Physiologic
 - Tolerance
 - Withdrawal
- Consequences
 - Hazardous use
 - Social or interpersonal problems related to use
 - Neglected major roles to use
 - Continued use after significant problems

A substance/opioid use disorder is defined as having 2 or more of these symptoms in the past year. Tolerance and withdrawal alone don't necessarily imply a disorder and severity is related by the number of symptoms:

- 2-3 = mild
- 4-5 = moderate
- ≥6 = severe

For evaluations, questions based on DSM-5 for diagnosis of Opioid Use Disorder:

1. Have you found that once you started using opioids you ended up taking more than you intended?
2. Have you found you wanted to stop or cut down on using opioids?
3. Have you spent a lot of time getting or using opioids?
4. Have you had a strong desire or urge to use opioids?
5. Have you missed work or school or often arrived late because you were intoxicated, high, or recovering from the night before?
6. Has your use of opioids caused other problems with other people such as family members, friends or people at work?

7. Have you had to give up or spend less time working, enjoying hobbies, or being with others because of your drug use?
8. Have you gotten high before doing something that requires coordination or concentration like driving, boating, climbing a ladder, or operating heavy machinery?
9. Have you continued to use even though you knew that opioids caused you problems like making you depressed anxious or irritable?
10. Have you found you needed to use much more opioids to get the same effect that you did when you first started taking it?
11. When you reduced or stopped using opioids, did you have withdrawal symptoms or felt sick when you cutdown or stopped using?

Reminder: At least 2 criteria must be met within a 12-month period.

Assessing for Opioid Withdrawal:

Several useful tools are available for assessing withdrawal severity. The Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS) are two such scales:

- COWS: Assessment is made by a clinician, nurse, or addiction specialist before starting treatment and then every hour until the patient is comfortable.
 - <5 - no active withdrawal
 - 5-12 - mild withdrawal
 - 13-24 - moderate withdrawal
 - 25-36 - moderately severe withdrawal
 - >36 - severe withdrawal
- SOWS: Assessment is made by the patient, 1 to 2 times a day, and it is used as a basis for decisions on treatment:
 - 0 to 10 points: mild withdrawal
 - 10 to 20 points: moderate withdrawal
 - 20 to 30 points: severe withdrawal

COWS Score for Opiate Withdrawal

Category	Sign/Symptom	Score
Resting Pulse Rate (BPM) Measure pulse rate after patient is sitting or lying down for 1 minute	≤80	0
	81-100	+1
	101-120	+2
	>120	+4
Sweating Sweating not accounted for by room temperature or patient activity over the last 0.5 hours	No report of chills or flushing	0
	Subjective report of chills or flushing	+1
	Flushed or observable moistness on face	+2
	Beads of sweat on brow or face	+3
	Sweat streaming off face	+4
Restlessness observation during assessment	Able to sit still	0
	Reports difficulty sitting still, but is able to do so	+1
	Frequent shifting or extraneous movements of legs/arms	+3
	Unable to sit still for more than a few seconds	+5
Pupil size	Pupils pinned or normal size for room light	0
	Pupils possibly larger than normal for room light	+1
	Pupils moderately dilated	+2
	Pupils so dilated that only the rim of the iris is visible	+5
Bone or joint aches If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored	Not present	0
	Mild diffuse discomfort	+1
	Patient reports severe diffuse aching of joints/ muscles	+2
	Patient is rubbing joints or muscles and is unable to sit still because of discomfort	+4
Runny nose or tearing Not accounted for by cold symptoms or allergies	Not present	0
	Nasal stuffiness or unusually moist eyes	+1
	Nose running or tearing	+2
	Nose constantly running or tears streaming down cheeks	+4
GI Upset Over last 0.5 hours	No GI symptoms	0
	Stomach Cramps	+1
	Nausea or loose stool	+2
	Vomiting or diarrhea	+3
	Multiple episodes of vomiting or diarrhea	+5
Tremor observation of outstretched hands	No tremor	0
	Tremor can be felt, but not observed	+1
	Slight tremor observable	+2
	Gross tremor or muscle twitching	+4
Yawning observation during assessment	No yawning	0
	Yawning once or twice during assessment	+1
	Yawning three or more times during assessment	+2

	Yawning several times per minute	+4
Anxiety or irritability	None	0
	Patient reports increasing irritability or anxiousness	+1
	Patient obviously irritable/anxious	+2
	Patient so irritable or anxious that participation in the assessment is difficult	+4
Gooseflesh skin	Skin is smooth	0
	Piloerection of skin can be felt or hairs standing up on arms	+3
	Prominent piloerection	+5

Opioid Overdose

Risk factors for opioid overdose include:

- Taking higher dosages of opioids (≥ 50 morphine milligram equivalents (MME)/day)
- Having certain medical conditions such as chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea which may increase their risk of overdose (regardless of opioid dose), or reduced kidney or liver function
- Having been prescribed benzodiazepines in addition to opioids (regardless of opioid dose)
- Receiving medication for opioid use disorder (OUD), such as methadone, buprenorphine, or naltrexone
- history of overdose
- History of use of drugs such as heroin and/or stimulants, including methamphetamine and cocaine or pills purchased “on the street,” which could potentially be contaminated with illicit synthetic opioids like fentanyl
- Age 65 years and older
- Having a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (regardless of opioid dose)
- History of opioid use and were recently released from incarceration or other controlled settings where tolerance to opioids

During an overdose, a person’s breathing can be dangerously slowed or stopped, causing brain damage or death. It’s important to recognize the signs and act fast, even before emergency workers arrive. Signs of an overdose may include:

- Small, constricted “pinpoint pupils”
- Falling asleep or loss of consciousness
- Limp body
- Slow, shallow breathing
- Choking or gurgling sounds

Respiratory Support

Supporting respiration is a critical intervention for opioid overdose and may be lifesaving on its own therefore it is important to begin CPR. Ideally, individuals who are experiencing opioid overdose should be ventilated with oxygen before naloxone is administered to reduce the risk of acute lung injury.

Naloxone administration

- Naloxone competitively binds opioid receptors and is the antagonist of choice for the reversal of acute opioid toxicity.
- Naloxone should be administered to anyone who presents with signs of opioid overdose or when opioid overdose is suspected.
- Naloxone can be given by injection intranasally, intramuscularly, subcutaneously, or intravenously.

Pregnant Patients

Naloxone can be used in life-threatening opioid overdose circumstances in pregnant women.

Monitoring

- Patients should be monitored for reemergence of signs and symptoms of opioid toxicity for at least 4 hours following the last dose of naloxone; however, patients who have overdosed on long-acting opioids require more prolonged monitoring.
- Most patients respond to naloxone by returning to spontaneous breathing, with mild withdrawal symptoms.
- The response generally occurs within 2 to 3 minutes of naloxone administration. Continue rescue breathing while waiting for the naloxone to take effect.
- The duration of effect of naloxone depends on dose and route of administration and is shorter than the effects of some opioids. Patients should be observed after administration for reemergence of overdose symptoms.
- The goal of naloxone therapy should be restoration of adequate spontaneous breathing, but not necessarily complete arousal.
- More than one dose of naloxone may be required to revive the patient.
- Those who have taken longer-acting opioids or opioid partial agonists may require additional doses, additional intravenous bolus doses, or an infusion of naloxone.
- Therefore, it is essential to get the person to an emergency department or other source of acute care as quickly as possible, even if the person revives after the initial dose of naloxone and seems to feel better.

Opioid Withdrawal Signs

- Withdrawal triggered by naloxone can feel unpleasant. Some people may become agitated or confused, which may improve by providing reassurance and explaining what is happening.

- The signs and symptoms of opioid withdrawal in an individual who is physically dependent on opioids may include body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection (gooseflesh), sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, tearing, insomnia, opioid craving, dilated pupils, and increased blood pressure.
- These symptoms are uncomfortable, but not life threatening unless vomiting and diarrhea result in extreme dehydration.
- After an overdose, a person dependent on opioids should be medically monitored for safety and offered treatment for OUD.

Absence of Response to Naloxone

- If a patient does not respond to naloxone, an alternative explanation for the clinical symptoms should be considered.
- The most likely explanation is that the person is not overdosing on an opioid but rather some other substance or may even be experiencing a non-overdose medical emergency.
- Support of ventilation, oxygenation, and blood pressure should be sufficient to prevent the complications of opioid overdose and should be given the highest priority if the patient's response to naloxone is not prompt.

Fentanyl-Involved Overdose

- Suspected opioid overdoses, including suspected fentanyl-involved overdoses, should be treated according to standard protocols. However, because of the higher potency of fentanyl and fentanyl analogs compared to that of heroin, larger doses of naloxone may be required to reverse the opioid-induced respiratory depression from a fentanyl-involved overdose.
- Many anecdotal accounts report more rapid respiratory depression with fentanyl than with heroin, although other reports do not reflect such rapid depression.
- Because of these effects, quicker oxygenation efforts and naloxone delivery may be warranted compared to heroin-only overdose.
- However, naloxone is an appropriate response for all opioid overdoses, including fentanyl-involved overdoses.

Naloxone

- Naloxone displaces opioids from receptor sites in the brain and reverses respiratory depression that usually is the cause of overdose deaths. On the other hand, naloxone is not effective in treating overdoses of benzodiazepines, barbiturates, clonidine, GHB, or ketamine. It is also not effective against overdoses of stimulants, such as cocaine and amphetamines (including methamphetamine and MDMA). However, if opioids are taken in combination with other sedatives or stimulants, naloxone may be helpful.

- Naloxone injection has been approved by the FDA and used for more than 40 years by emergency medical services personnel to reverse opioid overdose and resuscitate individuals who otherwise might have died in the absence of treatment.
- Naloxone comes in several forms, including injectable, intranasal, and auto-injector. Injectable naloxone is typically supplied as a kit with a minimum of two doses and two syringes.
- The FDA has also approved an intranasal naloxone product (a nasal spray) and a naloxone auto-injector that delivers a therapeutic dose of naloxone in an overdose situation. The intranasal spray is a prefilled, needle-free device that requires no assembly. The auto-injector can deliver a dose of naloxone through clothing, if necessary, when placed on the outer thigh.

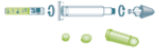





Duration Of Effect

- The duration of effect of naloxone depends on dose, route of administration, and overdose symptoms² and is shorter than the effects of some opioids.
- The goal of naloxone therapy should be to restore adequate spontaneous breathing, but not necessarily complete arousal. As mentioned before more than one dose of naloxone may be needed to revive someone who is overdosing. People who have taken longer acting or more potent opioids may require additional intravenous bolus doses or an infusion of naloxone.
- Withdrawal triggered by naloxone can feel unpleasant and some people may become agitated or confused, which may improve by providing reassurance and explaining what is happening.

Safety

- The safety profile of naloxone is remarkably high, especially when used in low doses and titrated to effect. When given to individuals who are not opioid intoxicated or opioid dependent, naloxone produces no clinical effects, even at high doses. Naloxone can be used in life-threatening opioid overdose circumstances in pregnant women. Moreover, although rapid opioid withdrawal in opioid-tolerant individuals may be unpleasant, it is not life threatening.
- The FDA has approved an injectable naloxone, an intranasal naloxone, and a naloxone auto-injector as emergency treatments for opioid overdose.
- Naloxone kits include a syringe and naloxone ampules or vials should receive brief training on how to assemble and administer the naloxone to the victim.
- The nasal spray is a prefilled, needle-free device that requires no assembly and that can deliver a single dose into one nostril.
- The auto-injector is injected into the outer thigh to deliver naloxone to the muscle (intramuscular) or under the skin (subcutaneous). Once turned on, the currently available device provides verbal instruction to the user describing how to deliver the medication, similar to automated defibrillators. Both the nasal spray and naloxone auto-injector are packaged in a carton containing two doses to allow for repeat dosing if needed.

Naloxone product comparison chart (available at [PrescribeToPrevent](http://PrescribeToPrevent.org))

Naloxone Product Comparison								
	Injectable (and intranasal-IN) generic		Intranasal branded		Injectable generic ¹		Auto-injector branded	
Brand name			Narcan Nasal Spray				Evzio Auto-Injector	
Product comparison								
								
			(Product not yet released ²)				(yellow & purple)  (Formulation to be discontinued ³)	
							 (blue & purple)	
FDA approved Labeling includes instructions for layperson use	X (for IV, IM, SC)		X X		X		X X	
Assembly required	X				X			
Fragile	X							
Can titrate dose	X				X			
Strength	1 mg/mL		4 mg/0.1 mL 2mg/0.1mL		0.4 mg/mL 4 mg/10 mL		0.4 mg/0.4mL 2 mg/0.4mL	
Storage requirements (All protect from light)	Store at 59-86 °F Fragile: Glass.		Store at 59-77 °F Excursions from 39-104 °F		Store at 68-77 °F Breakable: Glass.		Store at 59-77 °F Excursions from 39-104 °F	
Cost/kit⁴	\$\$		\$\$		\$		\$\$\$	
Prescription variation								
Refills	Two		Two		Two		Two	
Rx and quantity	#2 2 mL Luer-Jet™ Luer-Lock needleless syringe plus #2 mucosal atomizer devices (MAD-300)		#1 two-pack of two 4 mg/0.1 mL intranasal devices		#1 four-pack of four 2 mg/0.1 mL intranasal devices		#2 single-use 1 mL vials PLUS #2 3 mL syringe w/ 23-25 gauge 1-1.5 inch IM needles	
	#1 10mL multidose vial PLUS #2 3 mL syringe w/ 23-25 gauge 1-1.5 inch IM needles		#1 two-pack of two 0.4 mg/0.4 mL prefilled auto-injector devices		#1 two-pack of two 2 mg/0.4 mL prefilled auto-injector devices			
Naloxone Product Comparison								
	Injectable (and intranasal-IN) generic		Intranasal branded		Injectable generic ¹		Auto-injector branded	
Sig. (for suspected opioid overdose)	Spray 1 ml (1/2 of syringe) into each nostril. Repeat after 2-3 minutes if no or minimal response.		Spray 0.1 mL into one nostril. Repeat with second device into other nostril after 2-3 minutes if no or minimal response.		Inject 1 mL in shoulder or thigh. Repeat after 2-3 minutes if no or minimal response.		Inject into outer thigh as directed by English voice-prompt system. Place black side firmly on outer thigh and depress and hold for 5 seconds. Repeat with second device in 2-3 minutes if no or minimal response.	
Ordering information								
How supplied	Box of 10 Luer-Jet™ prefilled glass syringes		Two-pack of single use intranasal devices		Box of 10 or package of 25 single-dose flip-top vials (1 ml)		Case of 25 multi-dose flip-top vials (10 ml)	
Manufacturer	IMS/ Amphastar		Teleflex (off-label IN adapter)		Adapt Pharma		Pfizer, Mylan and West-Ward Pharmaceuticals	
Web address	Amphastar.com		Teleflex.com		Narcannasalspray.com		Pfizerinjectables.com Mylan.com West-ward.com	
Customer service	800-423-4136		866-246-6990		844-462-7226		877-946-7747 (P) 724-514-1800 (M) 800-631-2174 (W)	
NDC	76329-3369-01		DME- no NDC		69547-353-02 69547-212-04		00409-1215-01 (P) 67457-0292-02 (M) 0641-6132-25 (W)	
							Pfizerinjectables.com	
							Evzio.com	
							855-773-8946	
							00409-1219-01	
							60842-030-01 60842-051-01	

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Treatment

Agonists and antagonists

An agonist is a drug that activates certain receptors in the brain. Full agonist opioids activate the opioid receptors in the brain fully resulting in the full opioid effect. Partial agonist opioids activate the opioid receptors in the brain, but to a much lesser degree than a full agonist.

An antagonist is a drug that blocks opioids by attaching to the opioid receptors without activating them. Antagonists cause no opioid effect and block full agonist opioids.

Current medication examples include:

- Full opioid agonist – Methadone
- Partial opioid agonist – Buprenorphine
- Partial opioid agonist/antagonist – Buprenorphine/Naloxone
- Opioid Antagonist – Naltrexone

Buprenorphine

Buprenorphine is a high affinity, partial agonist for the mu opioid receptor, and as such suppresses opioid withdrawal and craving, reduces illicit opioid use, and blocks exogenous opioid effects including respiratory depression. The properties of buprenorphine contributing to its efficacy in OUD treatment include:

- mu opioid receptor-related factors (e.g., high affinity, low efficacy, & slow dissociation kinetics)
- non-mu opioid receptor-related factors (e.g., long terminal half-life, lipophilicity).

Because of its partial agonist effects and slow receptor association, buprenorphine, when taken sublingually as intended, is much less euphoriant.

Buprenorphine has a high affinity for the mu receptor and this high affinity means that buprenorphine is difficult (but not impossible) to displace from the mu opioid receptor, which explains its ability to block subjective and physiological effects of other opioids.

Buprenorphine is a high-potency medication. This is important when understanding why buprenorphine dose escalation does not pose increasing overdose risk like the full opioid agonists due to its low efficacy. While comparatively low doses of buprenorphine may elicit some degree of respiratory depression compared to morphine, the potency of buprenorphine does not significantly increase with doses within the clinical range.

Buprenorphine also has slow dissociation kinetics, contributing to its long duration of action and allowing for daily or less-than-daily dosing.

These pharmacologic properties give buprenorphine unique features that distinguish its effects from full agonist opioids. Since buprenorphine is a partial agonist, there is a ceiling effect on respiratory depression, which means that as the dose of buprenorphine increases and increased numbers of mu

receptors are bound to buprenorphine, you will see a typical dose response curve up to a certain point, and after that point, higher doses of buprenorphine will not cause more respiratory depression. This is an extraordinary safety advantage over full agonist opioids, because opioid overdose deaths can occur by respiratory depression.

However, caution should be taken, and patient education is important with regards to potential for severe respiratory depression in certain populations as buprenorphine behaves more like a full agonist in infants and toddlers. Additionally, caution should also be taken in the elderly, particularly those with COPD, or other chronic respiratory illness, or if taking other potentially respiratory depressing medications.

Buprenorphine's high affinity is also the primary reason that buprenorphine can precipitate withdrawal, known as "buprenorphine-precipitated withdrawal (BPW)", when given to individuals physically dependent on opioids. BPW can be avoided, particularly among persons dependent on short-acting opioids, by waiting to administer buprenorphine until signs of opioid withdrawal emerge (a time of low receptor occupancy) or patient has completed acute physiologic withdrawal before treating with buprenorphine.

Buprenorphine has moderate (~30% to <50%) bioavailability sublingual and has low bioavailability when ingested. Therefore, dosing likely to be subtherapeutic and patients should be advised not to swallow sublingual tablets or strips.

Methadone

Methadone is a synthetic full agonist for the mu opioid receptor and has a weak affinity for the receptor since it can be displaced by partial agonists (such as buprenorphine) and antagonists (such as naloxone, naltrexone). Methadone has a slow metabolism and very high fat solubility, making it longer lasting than morphine-based drugs. Methadone has a typical elimination half-life of 15 to 60 hours with a mean of around 24. However, metabolism rates vary greatly between individuals.

Additionally, the bioavailability and elimination half-life of methadone are subject to substantial interindividual variability. Its main route of administration is oral. Adverse effects include sedation, hypoventilation, constipation and miosis, in addition to tolerance, dependence and withdrawal difficulties. The withdrawal period can be much more prolonged than with other opioids, spanning anywhere from two weeks to several months.

The metabolic half-life of methadone differs from its duration of action as well, with the metabolic half-life being anywhere from 8 to 59 hours.

The action of methadone at opioid receptors can lead to opioid-related side effects including sedation, respiratory depression, and constipation. These effects are additive with other medications that cause these effects as well as with concomitant medications that increase methadone levels. Methadone can also cause serotonin syndrome when given with other serotonergic medications such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and certain tricyclic antidepressants. It can also cause QT-prolongation, which can lead to

Torsades de Point (TdP) and sudden cardiac death. Patients are high doses and with an underlying native prolonged QT are at increased risk.

Medication Type and Examples	Action with Methadone	Recommended Treatment Response
SSRIs (fluvoxamine, fluoxetine, sertraline)	Some SSRIs inhibit the metabolism of methadone and thus increase methadone blood levels. Fluvoxamine has the most dangerous interactions with methadone and should be avoided	Monitor closely for signs of methadone overmedication during initial stages of treatment
Carbamazepine	Increases methadone metabolism, potentially causing severe opioid withdrawal symptoms	Preferred recommendation is to use alternatives such as valproate. If it is absolutely clinically necessary to use carbamazepine then consider increasing and/or splitting the methadone dose
Tricyclics (desipramine, nortriptyline, imipramine, doxepin)	Impairs Tricyclic metabolism and can cause increased tricyclic levels	Monitor closely and adjust doses as needed
Monoamine Oxidase (MAO) Inhibitors	Potential for dangerous interactions	Use extreme caution
Lithium	None	Close monitoring due to narrow therapeutic window

Naltrexone

Naltrexone is a full antagonist with very competitive binding at the mu-opioid receptor. Naltrexone is also a weaker antagonist of the kappa and delta-opioid receptors. Naltrexone competes for opiate receptors and displaces opioid drugs from these receptors, thus reversing their effects. It is capable of antagonizing all opiate receptors. Naltrexone absorption is almost complete after oral administration, but it has an extensive first-pass effect. After oral administration, the half-life is 4 hours, and following an intramuscular injection (IM), the half-life is 5 to 10 days.

Naltrexone should not be started until several (typically 7–10) days of abstinence from opioids have been achieved. This is due to the risk of acute opioid withdrawal if naltrexone is taken, as naltrexone will displace most opioids from their receptors. Some physicians use a naloxone challenge to determine whether an individual has any opioids remaining. The challenge involves giving a test dose of naloxone and monitoring for opioid withdrawal. If withdrawal occurs, naltrexone should not be started.

Naltrexone has been reported to cause liver damage when given at doses higher than recommended and carries an FDA warning for this rare side effect. Due to these reports, some physicians may check liver function tests prior to starting naltrexone, and periodically thereafter.

Emergency Department Initiated Buprenorphine

Patient History

Obtain a history of substance use, treatment history, most recent opioid use to assess whether patient is a candidate for buprenorphine, and if so, if it can safely be started in the ED. This will also help determine safety of prescribing buprenorphine from the ED, and the dose to prescribe.

- Type of Opioid(s) Used:
 - Heroin vs. Rx formulations.
 - Methadone
- Duration and Severity of Use – approximate:
 - How much (approximately)
 - How often (on average)
 - How long (months vs. years)
 - Routine of administration e.g., injection use, smoking, etc. (this can impact the bioavailability of the substance being used)
- Co-occurring use of other substances, specifically alcohol, sedatives such as benzodiazepines (prescribed or illicit), other sedating substances
- Last opioid use, type, and mode of delivery
- Prior experience with treatment, what kind, and length of time prior to return to use

Buprenorphine Induction Based on COWS and Last Opioid Use

Consider ED-initiation of buprenorphine if patient:

- Exhibits acute opioid withdrawal symptoms and
- Reports last use was greater than
 - 12-16 hours for short-acting opioids
 - 24 hours for sustained-release opioid medications
 - 48-72 hours for methadone

It is also important to assess the patient to determine the Clinical Opiate Withdrawal Scale (COWS) score and document mild, moderate or severe withdrawal.

- Especially, if there is any doubt that the patient is in at least moderate withdrawal.
- Use caution for induction if COWS <13 and unclear recent history of opioid use, recent methadone use (<72 hours), or recent long-acting opioid use

Suggested Laboratory Testing

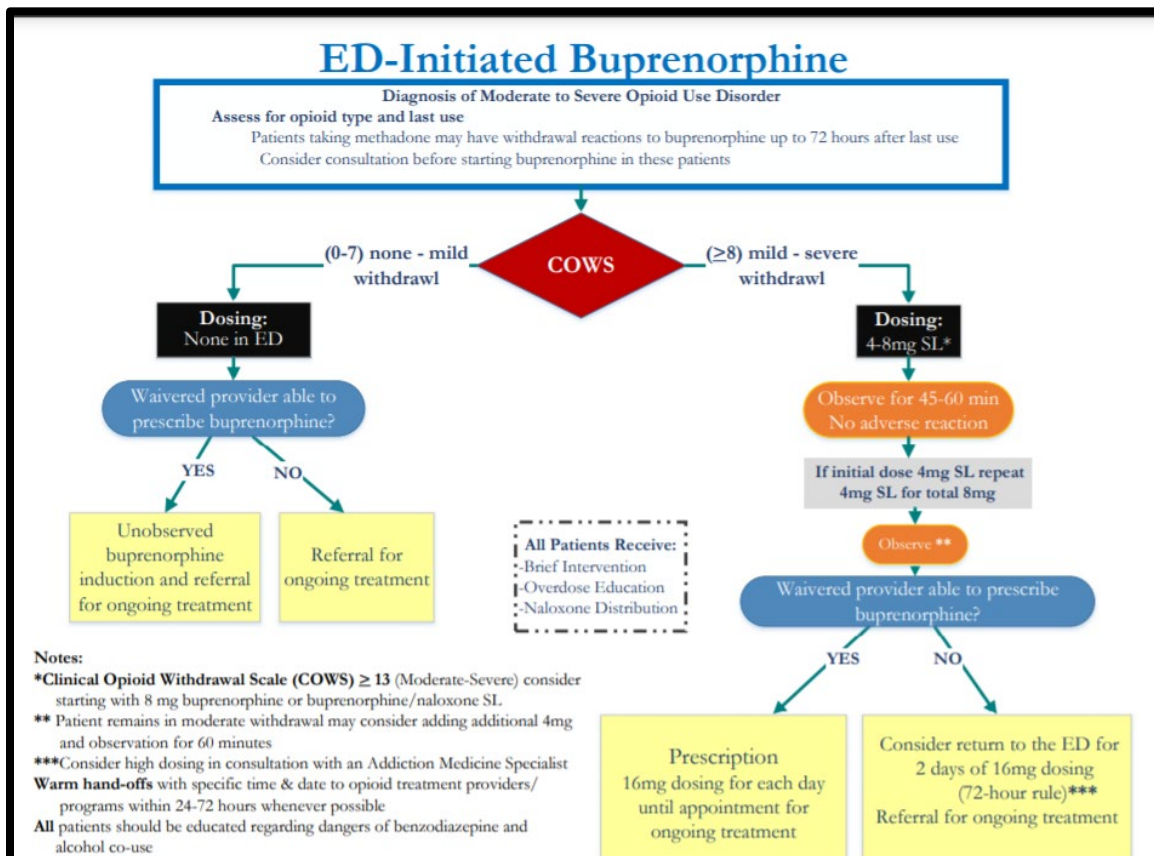
Do not delay administration of buprenorphine for the patient who is clearly in at least moderate withdrawal. Routine laboratory testing is not necessary, and definitely should not be delayed in the patient who would benefit from prompt administration of buprenorphine. However, once acute

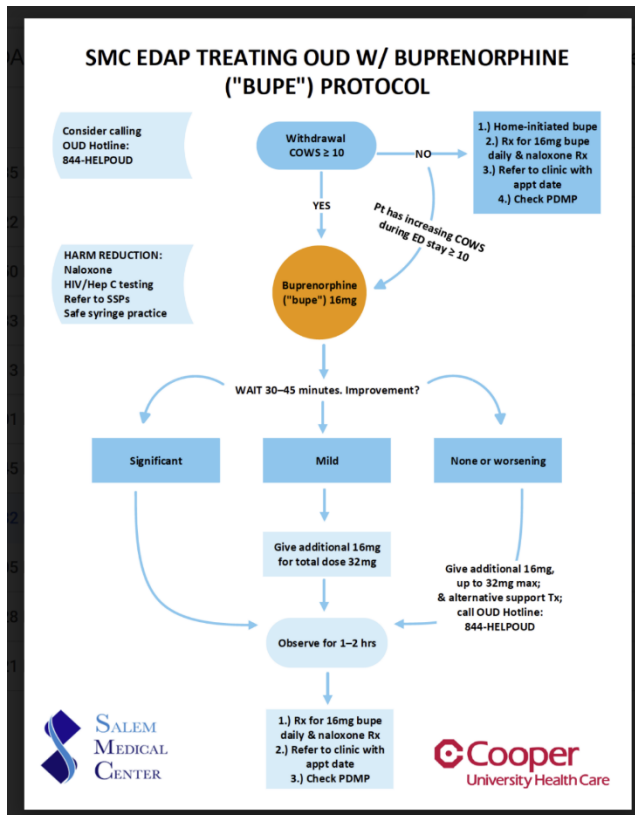
withdrawal has been addressed, if laboratory tests can be obtained quickly in the ED, this may facilitate follow-up clinic treatment.

- Pregnancy testing for women in reproductive years
 - This is not an exclusion criterion but can help guide referral process and assist earlier acceptance
- Urine Toxicology
 - Consider if concerned about accuracy of opioid use history or long-acting opioid use (Methadone)
 - Note that fentanyl will not show up in most hospital urine drug screens
- Blood Toxicology
 - Consider testing for LFTs if clinical suspicion of liver failure (Buprenorphine: relative contraindication if LFTs >5 x normal – necessitates close monitoring, dosing reduction)
 - Consider HIV and Hepatitis B and C, but most likely drawn at referral site

Buprenorphine ED initiation

Example Algorithms





Patient instructions for Buprenorphine:

- Sublingual tablets and films must be held under the tongue several minutes to dissolve
- Buccal delivery films take fewer minutes to dissolve and are stuck to the buccal mucosa
- Instruct to:
 - Start with a moist mouth, avoid acidic drinks (coffee or fruit juice)
 - Avoid using nicotine products as this interferes with absorption
 - Avoid speaking with the sublingual medication
 - Keep dissolving medicine under tongue
 - Don't swallow until entire tablet or film is dissolved

If patient is not currently in opioid withdrawal or recent naloxone reversal, there is an option of unobserved home induction. The key instruction is to wait at least 12 hours since last opioid usage to avoid precipitating withdrawal and it is critical to stress the importance of this delay

Initiating Buprenorphine at Home

Observed and home induction have similar safety and efficacy outcomes and the traditional process for this includes:

- educating patient about buprenorphine pharmacology and absorption
- Review of withdrawal symptoms and guide patient regarding:

- How to assess withdrawal symptoms
- How to administer buprenorphine when feeling “very sick”
- Monitoring and assessment after first dose
- Evaluate the need for a follow-up dose
- Education with regards to how may and maximum combined dose

Example of a traditional home guideline for patients with OUD who are naive to buprenorphine

A Guide for Patients Beginning Buprenorphine Treatment at Home

Before you begin you want to feel very sick from your withdrawal symptoms

<p>It should be at least . . .</p> <ul style="list-style-type: none"> • 12 hours since you used heroin/fentanyl • 12 hours since snorted pain pills (Oxycontin) • 16 hours since you swallowed pain pills • 48-72 hours since you used methadone 	<p>You should feel at least three of these symptoms . . .</p> <ul style="list-style-type: none"> • Restlessness • Heavy yawning • Enlarged pupils • Runny nose • Body aches • Tremors/twitching • Chills or sweating • Anxious or irritable • Goose pimples • Stomach cramps, nausea, vomiting or diarrhea
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Once you are ready, follow these instructions to start the medication

<p>DAY 1: 8-12mg of buprenorphine</p> <p>Most people feel better the first day after 8-12mg. (Dosing depends on how early on the first day you started)</p>	<p>DAY 2: 16mg of buprenorphine</p>																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th colspan="2" style="background-color: #e0f2f1; padding: 5px;">Step 1.</th> <th colspan="2" style="background-color: #e0f2f1; padding: 5px;">Step 2.</th> <th colspan="2" style="background-color: #e0f2f1; padding: 5px;">Step 3.</th> </tr> <tr> <td style="width: 50%; padding: 5px;"> <p>Take the first dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 40px; margin: 10px auto;">4mg</div> </td> <td style="width: 50%; padding: 5px;"> <p>Wait 45 minutes</p> <div style="text-align: center; border: 1px solid gray; border-radius: 50%; padding: 5px; width: 40px; height: 40px; margin: 10px auto;">45 minutes</div> </td> <td style="width: 50%; padding: 5px;"> <p>Still feel sick? Take next dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 40px; margin: 10px auto;">4mg</div> </td> <td style="width: 50%; padding: 5px;"> <p>Wait 6 hours</p> <div style="text-align: center; border: 1px solid gray; border-radius: 50%; padding: 5px; width: 40px; height: 40px; margin: 10px auto;">6 hours</div> </td> <td style="width: 50%; padding: 5px;"> <p>Still uncomfortable? Take last dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 40px; margin: 10px auto;">4mg</div> </td> <td style="width: 50%; padding: 5px;"> <p>Stop</p> <div style="text-align: center; border: 1px solid gray; border-radius: 50%; padding: 5px; width: 40px; height: 40px; margin: 10px auto;">Stop</div> </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> <ul style="list-style-type: none"> • Put the tablet or strip under your tongue • Keep it there until fully dissolved (about 15 min.) • Do NOT eat or drink at this time • Do NOT swallow the medicine </td> <td colspan="2" style="padding: 5px;"> <p>Most people feel better after two doses = 8mg</p> </td> <td colspan="2" style="padding: 5px;"> <ul style="list-style-type: none"> • Stop after this dose • Do not exceed 12mg on Day 1 </td> </tr> </table>	Step 1.		Step 2.		Step 3.		<p>Take the first dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 40px; margin: 10px auto;">4mg</div>	<p>Wait 45 minutes</p> <div style="text-align: center; border: 1px solid gray; border-radius: 50%; padding: 5px; width: 40px; height: 40px; margin: 10px auto;">45 minutes</div>	<p>Still feel sick? Take next dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 40px; margin: 10px auto;">4mg</div>	<p>Wait 6 hours</p> <div style="text-align: center; border: 1px solid gray; border-radius: 50%; padding: 5px; width: 40px; height: 40px; margin: 10px auto;">6 hours</div>	<p>Still uncomfortable? Take last dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 40px; margin: 10px auto;">4mg</div>	<p>Stop</p> <div style="text-align: center; border: 1px solid gray; border-radius: 50%; padding: 5px; width: 40px; height: 40px; margin: 10px auto;">Stop</div>	<ul style="list-style-type: none"> • Put the tablet or strip under your tongue • Keep it there until fully dissolved (about 15 min.) • Do NOT eat or drink at this time • Do NOT swallow the medicine 		<p>Most people feel better after two doses = 8mg</p>		<ul style="list-style-type: none"> • Stop after this dose • Do not exceed 12mg on Day 1 		<p>Take one 16mg dose</p> <p>Most people feel better with a 16mg dose</p> <div style="text-align: center; border: 1px solid gray; padding: 5px; width: 60px; margin: 10px auto;">16mg</div> <p>Repeat this dose until your next follow-up appointment</p>
Step 1.		Step 2.		Step 3.															
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If you develop worsening symptoms while starting buprenorphine before your scheduled outpatient appointment return to the emergency department

Patient education

Introduction / Relevance

- Despite several decades of teaching which asserted that opioids prescribed for pain could not lead to misuse, we now know that a fraction of opioid-naive patients who receive a prescription for opioids from the ED are set down the path of long-term use and addiction, from that prescription.
- Estimates of long-term use arising from a prescription from the ED vary widely depending on the population studied and criteria for long term use, but is likely between 2% and 5%, which means that between 1/50 and 1/20 opioid-naive patients sent home from the ED with a prescription for opioids develop long term opioid use from that prescription. (Barnett 2017, Beaudoin 2016, Delgado 2018, Hoppe 2015, Meisel 2019)
- The most crucial concept to keep in mind when considering discharging a patient with a prescription for opioids is the asymmetry of benefits and harms arising from such a prescription: The benefit of an opioid prescription is the amelioration of acute pain not adequately managed by non-opioid therapies. The harms of an opioid prescription include a variety of consequential immediate harms (e.g., confusion, falls, unintentional overdose) and the devastating outcome of long-term use, which often forever alters—and not infrequently ends—that patient’s life, and profoundly affects the lives of the patient’s loved ones. (Strayer 2020)
- The most important way to reduce the number of patients who develop long term use from a prescription for acute pain is to reduce the number of opioid-naive patients who are discharged from acute care with an opioid prescription; this is done by doing an explicit calculation of benefit and harm whenever a prescription is considered. If a prescription is offered, there are a variety of ways to reduce the likelihood that prescription will cause harm.

Patients who should be considered for a discharge opioid prescription

- When a discharge prescription is considered, the prescription drug monitoring program (PDMP) should be checked (this is mandatory in some jurisdictions). A negative query does not suggest that a prescription is appropriate, but a positive query should inform decision-making and further discussion with the patient.
- Opioid-naive patients (patients who have never used or rarely use opioids) who have severe acute pain expected to last beyond the duration of their emergency visit should be considered for an opioid prescription.
- Patients who use prescribed opioids daily or regularly (e.g. chronic pain patients), who request an opioid prescription, are poorly managed in an acute care setting. These patients should be treated in close collaboration with their outpatient prescribers. Because opioid benefit and harm is widely variant in this group, it is difficult to make broadly-applicable recommendations; many of these patients are harmed by their daily opioid use and the focus of care is reducing that harm, which is very difficult within the constraints of an emergency visit. The decision of whether or not to prescribe opioids in this group is actually less consequential compared to opioid-naive patients, however, treating pain with opioid alternatives is generally favored. If

opioids are prescribed, the prescription should be for the minimum number of pills required to bridge the patient to an appointment with their outpatient provider.

- Patients who manifest features of opioid use disorder (e.g. use of street opioids, compulsive use, loss of social/occupational function, use of prescribed opioids in amounts or ways not prescribed, continued use of opioid despite clear harms) should be treated for OUD, ideally with buprenorphine.
- For patients in pain or distress at the end of life, the balance of opioid benefit and harm shifts significantly; these patients should generally be treated aggressively with opioids and non-opioids to relieve their symptoms. When these patients present for emergency care, they should be managed in collaboration with their outpatient providers.

Estimating Benefit and Harm

- **Estimating Benefit.** The possible benefit of an opioid prescription is a reduction of suffering from pain beyond what can be achieved with optimal use of safer non-opioid alternatives.
- **Estimating Acute Harm.** The possible harms of an opioid prescription include common bothersome adverse effects such as nausea, constipation, and pruritus; more dangerous acute harms include loss of occupational/social function, dysphoria, confusion, falls, and motor vehicle collisions. Acute harms are more likely in older patients, or patients with significant comorbidities. Be extremely cautious prescribing opioids to opioid-naïve patients with advanced liver, kidney, or cardiorespiratory disease and patients with obstructive sleep apnea. These patients are at particular risk to develop dangerous opioid toxicity.
- **Estimating Long Term Use Harm.** Long term use harms begins with the development of acute physical dependence and hyperalgesia, which can occur in some people within days of taking opioids regularly. With continued use the patient develops classic physical dependence, as manifested by opioid withdrawal syndrome upon decreasing or discontinuing therapy, and then, in unfortunate cases, progression to the incalculable harms of dose escalation and addiction. The risk factors for developing long term use and addiction in opioid-naïve patients are existing substance use (including alcohol and tobacco), psychiatric disease, social isolation, physical disability and chronic pain, and young age (adolescents and young adults).
- **Shared Decision Making.** For the large majority of patients discharged from emergency departments, the potential harms of an opioid prescription will clearly exceed benefits, and an opioid prescription should not be offered. For those patients where benefits may exceed harms, it is appropriate to have a discussion with the patient around opioid harms and benefits as they pertain to that patient. If the provider judges likelihood of benefit to exceed harms, and, subsequently, the patient agrees and wishes to have an opioid prescription, it is reasonable to prescribe opioids according to safe opioid prescribing principles.

Safer opioid prescriptions

- Once the decision has been made to prescribe opioids, the most important way to decrease the likelihood of the patient developing long term use from that prescription is to prescribe a small number of pills. The risk of long term use escalates with each additional day after the third day.

Because acute severe pain inadequately relieved by non-opioids should be short-lived, it is appropriate to prescribe no more than 9 to 12 pills. (Shah 2017)

- Extended release or long-acting opioid preparations are more likely to cause both immediate and long term harms and should not be prescribed for acute pain. These preparations include Morphine Sulfate ER or CR (many brand names), Oxycontin, Oxycodone (Opana), and Fentanyl patches. Methadone should never be prescribed for acute pain.
- Despite their prevalence in American medicine, opioids combined with a non-opioid (usually acetaminophen) are not more effective than opioid monotherapy, lead to accidental acetaminophen hepatotoxicity, and hinder using the optimal dose of acetaminophen as an adjunct to the opioid. Combination opioid products (e.g. Percocet, Vicodin, Lortab, Norco) are therefore best avoided.
- Certain oral opioid preparations are known to be more euphoric and therefore abuse-prone, most importantly oxycodone and hydrocodone. These preparations are ideally avoided in favor of less abuse-prone opioids such as immediate release morphine sulfate.
- Avoid opioid prodrugs. Codeine is variably metabolized to morphine, and for most patients offers little analgesic benefit over non-opioids, if any. Some patients, however, may develop dangerous opioid toxicity from what would generally be considered a safe dose; codeine is especially risky and should never be prescribed for children. Tramadol is variably metabolized to an opioid and an SNRI, and is associated with a variety of idiosyncratic harms such as hypoglycemia, seizures, and serotonin syndrome. Avoid codeine and tramadol.
- For patients judged to benefit from an opioid prescription, we recommend Morphine Sulfate Immediate Release 15 mg tablets, 7.5 mg (one half of one 15 mg tablet) every 4-6 hours as needed for pain, dispense #9. If 5 mg tablets are available (outside the US), Morphine Sulfate Immediate Release 5 mg tablets, 1-2 tabs every 4-6 hours as needed for pain, dispense #12.

Discharge planning

- Patients being discharged with an opioid prescription must be counseled on harms both verbally and in written instructions; sample discharge instructions are below.
- Patients must be specifically counseled on safe storage: opioids should be stored in their original packaging inside a locked cabinet, a lockbox, or other secure location, with particular attention to the potential for a child to accidentally ingest pills or an older child/young adult to experiment.
- Patients should be advised to dispose of any unused pills. Unused pills can be returned to many pharmacies and some police stations. As a second choice, unused pills may also be buried in an unpalatable substance (coffee, cat litter) and disposed in the trash, or flushed down the toilet.
- For any patient being discharged with an opioid prescription, it is reasonable to also prescribe naloxone and instruct the patient (and the patient's family members) on its use. Naloxone is not only life-saving in overdose, but prescribing or dispensing naloxone also highlights the dangers of an opioid prescription.
- Sample discharge instructions:

- *You are being discharged with a prescription for an opioid pain medication. Opioids are powerful analgesics that can be very effective for pain but also have the potential to harm you. You should only take opioid pain medications if you are still suffering with pain after you've optimized non-medication strategies (rest, position of comfort, ice, heat, etc) and non-opioid medications such as acetaminophen (Tylenol) and ibuprofen (Motrin). Take opioid pain medications as prescribed; do not take more than prescribed or take the pills in a different way than prescribed.*
- *Opioids often cause constipation, nausea, and itching. Opioids can also cause more dangerous problems such as feeling ill, excessive sleepiness, confusion, and falls. Older people and people with liver or kidney disease are more prone to these harms. You should not drive or perform dangerous work while using opioid pain medications.*
- *If you take too much opioid pain medication, your breathing can slow or even stop, which can be fatal. This is how people die from an opioid overdose.*
- *Opioids can cause acute physical dependence after only a few days, which means that if you take opioid pain medications for a few days and then stop, you might experience withdrawal symptoms such as muscle aches, pain, insomnia, feeling nauseated and ill, depressed, agitated, or anxious, and you might even crave more pills. If you take more opioid pills, these symptoms will be greatly relieved, however this is the beginning of a very dangerous cycle of dependence, which can lead to addiction. If it is possible that you are experiencing acute physical dependence, do not take more opioid pills and discuss the problem with your doctor.*
- *Opioids should be stored in their original packaging inside a locked cabinet, a lockbox, or other secure location. Be mindful of small children who could accidentally get into opioid pills, and especially careful of young adults who may wish to experiment with opioid pills.*
- *Lastly, once this painful episode is over, dispose of any unused pills—you can take them back to the pharmacy or flush them down the toilet. Leftover opioid pills can be extremely dangerous to children, and are a major source of recreational use, especially among adolescents and young adults.*

ACEP:

Policies and Statements:

- [Clinical Policy: Opioids](#)
- Policy Statements:
 - [Naloxone Access and Utilization for Suspected Opioid Overdoses](#)
 - [Naloxone Prescriptions by Emergency Physicians](#)
 - [Optimizing the Treatment of Acute Pain in the Emergency Department](#)
 - [Sub-dissociative Dose Ketamine for Analgesia](#)
- [Consensus Recommendations on the Treatment of Opioid Use Disorder in the ED](#)

EQUAL Opioids:

- [Webinar Series \(4 waves\)](#)
- [Podcasts](#)
- [Toolkits on Treatment of Opioid Use Disorder & Harm Reduction Strategies and Pain Management and Safe Opioid Use](#)

POC Tools:

- [Managing Acute Pain](#)
- [Buprenorphine use in the Emergency Department](#)

Education/Courses:

- [Emergency Medicine Medication for Addiction Treatment: Core Training](#)
- [US-Guided Nerve Blocks \(Virtual Grand Rounds February 2022\)](#)
- [Buprenorphine Initiation and Pain Management Workshop](#)
- [New Approaches to Opioid Use Disorder - Pathway](#)
- [Buprenorphine Initiation in Emergency Departments: Interactive Case Vignettes](#)
- [Pain Management and Acute Exacerbation of Chronic Pain \(Part 1\)](#)
- [Pain Management and Acute Exacerbation of Chronic Pain \(Part 2\)](#)

Other resources:

- Video: [Ending the Stigma of Opioid Use Disorder](#)
- [Opioid Regulations: State by State Guide \(PDF\)](#)
- [6 Part Webinar Series on Opioid Use Disorder, Federal and State Regulations, Regulatory Considerations, and State Initiatives](#)
- [Substance Use Disorder EM Residency Curriculum](#)

Other resources/websites:

- [Providers Clinical Support System](#)
- [CA Bridge Tools](#)
- [MATTERS Network Services](#)
- [Addiction Policy Forum](#)

SAMSHA:

- [Medication-Assisted Treatment \(MAT\)](#)
- [Buprenorphine Waiver Notification](#)
- [Use of Medication-Assisted Treatment in Emergency Departments](#)
- [TIP 63: Medications for Opioid Use Disorder - Full Document](#)

CDC:

- [Website for HCPs](#)

ASAM:

- [National Practice Guideline 2020 Focused Update](#)
- [Opioid Addiction Treatment: A Guide for Patients, Families, and Friends](#)
- [OUD Mini-Course: Treatment in the Emergency Department](#)
- [Buprenorphine Mini-Course: Building on Federal Prescribing Guidance](#)

ACMT:

- [Buprenorphine Administration in the Emergency Department](#)
- [Recommending Removing the Waiver Requirement For Prescribing Buprenorphine For Opioid Use Disorder](#)
- [SUSTAIN-ED Substance Use Screening and Treatment Approach in the ED](#)

AAEM:

- [Management of Opioid Use Disorder in the Emergency Department: A White Paper Prepared for the American Academy of Emergency Medicine](#)
- [White Paper on Acute Pain Management in the Emergency Department](#)
- [AAEM Model ED Pain Treatment Guidelines](#)

Patient facing websites:

- [Shatterproof](#)
- [National Alliance on Mental Illness](#)
- [Addiction Policy Forum](#)