PCSS Providers Clinical Support System

Overview

Target Audience

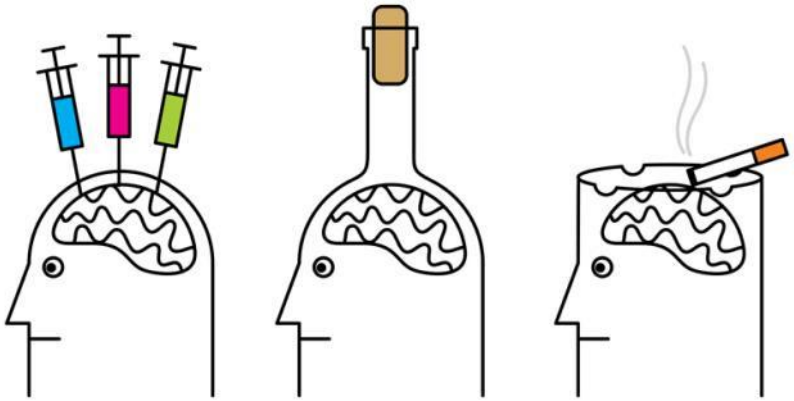
The overarching goal of PCSS is to train a diverse range of healthcare professionals in the safe and effective prescribing of opioid medications for the treatment of pain, as well as the treatment of substance use disorders, particularly opioid use disorders, with evidence-based treatments.

Objectives

1. **Describe the epidemiology of substance use disorders (SUDs) and related mortality in the United States**
2. List the DSM-5 criteria for SUD
3. Describe pivotal milestones in the treatment of opioid use disorders
4. Describe the benefits of medications for the treatment of OUD
5. Language of Addiction – Words Matter

National Institute of Drug Abuse (NIDA) Definition of Addiction

- Addiction is a *chronic, relapsing brain disease* that is characterized by compulsive drug seeking and use, despite harmful consequences. It is about behavior.
- Drug use changes the brain - they change its structure and how it works.
- These brain changes can be long lasting and can lead to many harmful, often self-destructive, behaviors.



ASAM, 2011
NIDA, 2014

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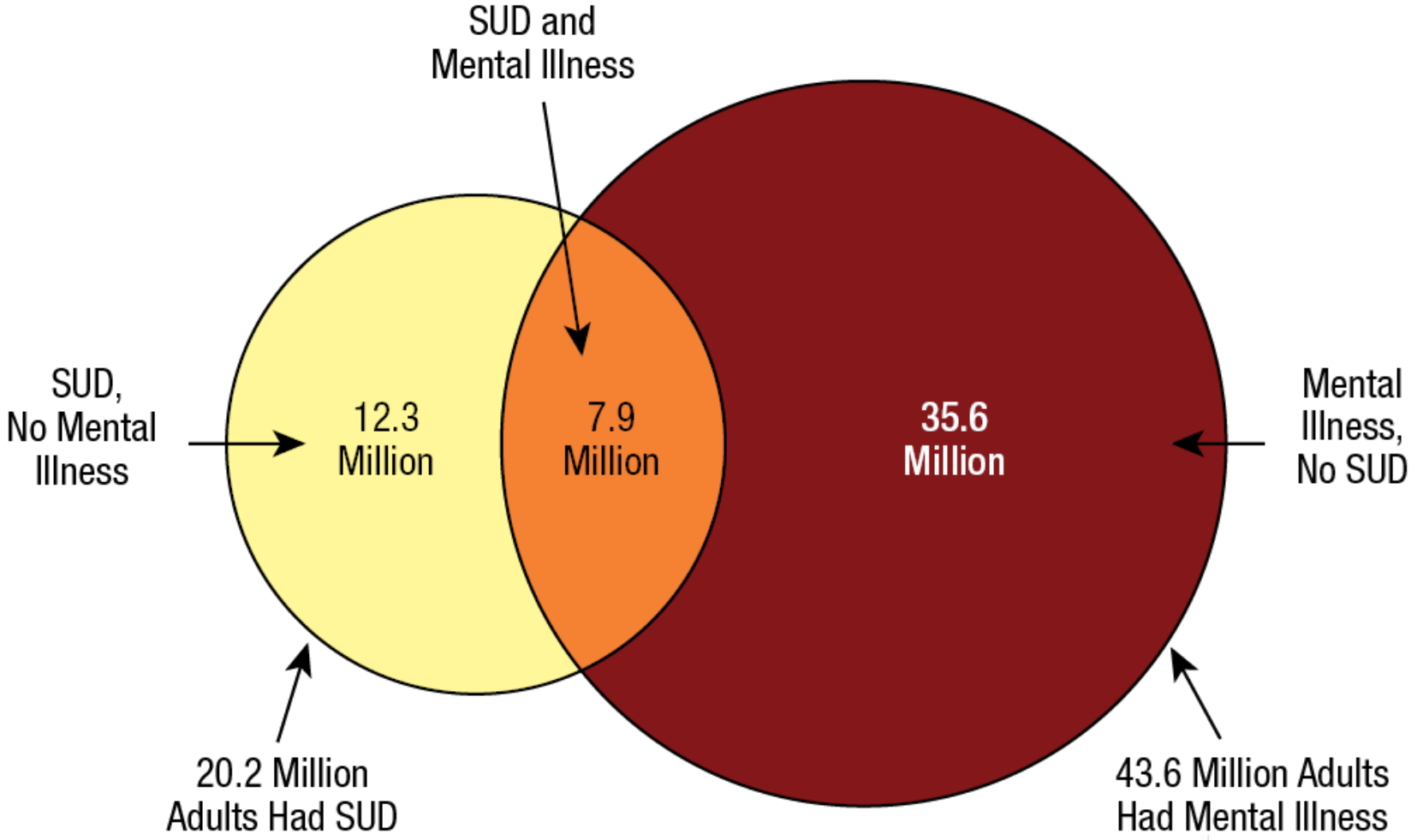
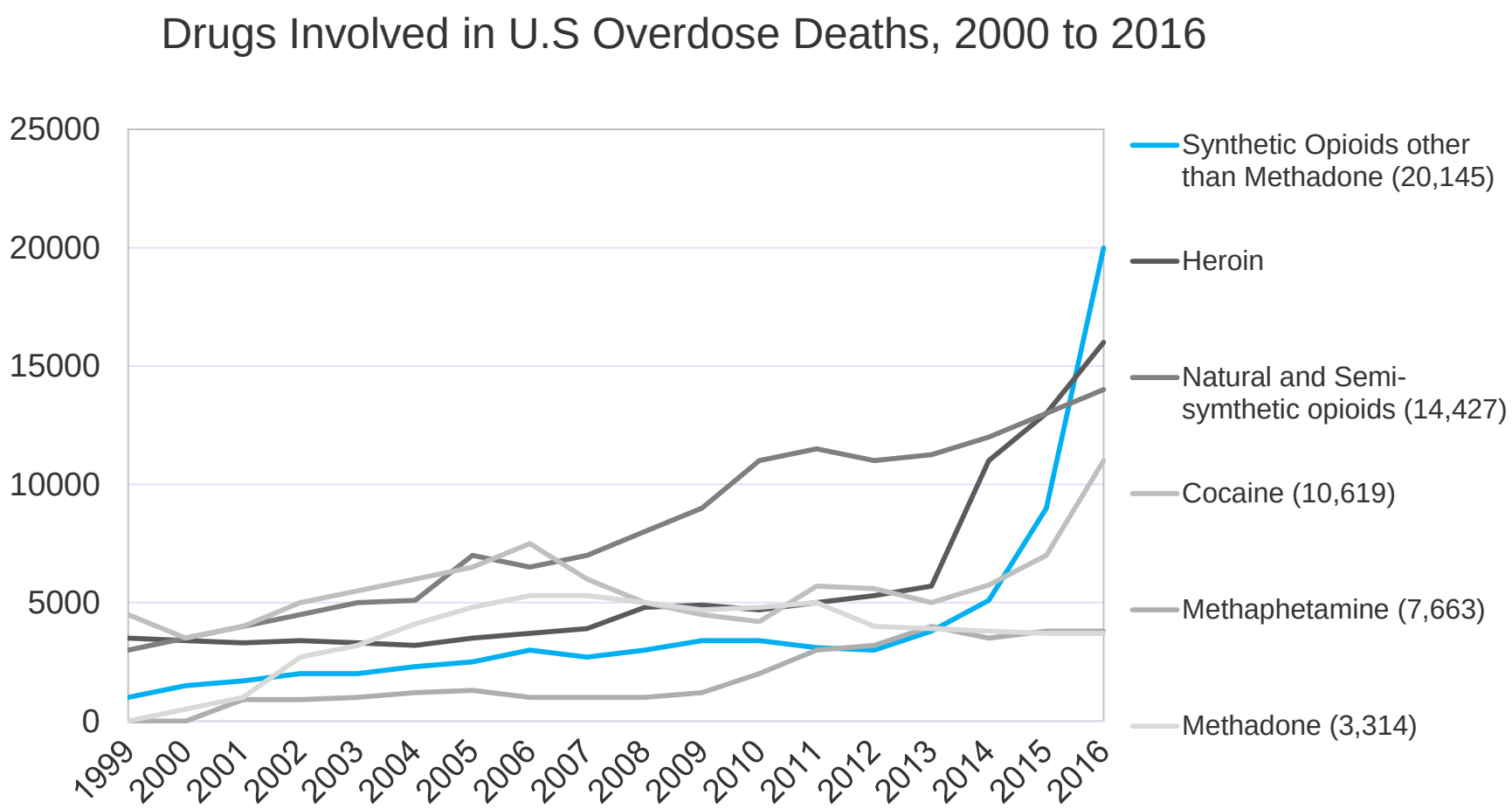
Epidemiology of SUDs in the US



SAMHSA, 2017

Worsening Epidemic



CDC, 2016

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DSM-5 Criteria for SUDs

Loss of control
- more than intended
  - amount used
  - time spent
- unable to cut down
- giving up activities
- craving

Physiology
- tolerance
- withdrawal

formerly "dependence"

Consequences
- unfulfilled obligations
  - work
  - school
  - home
- interpersonal problems
- dangerous situations
- medical problems

formerly "abuse"

- 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

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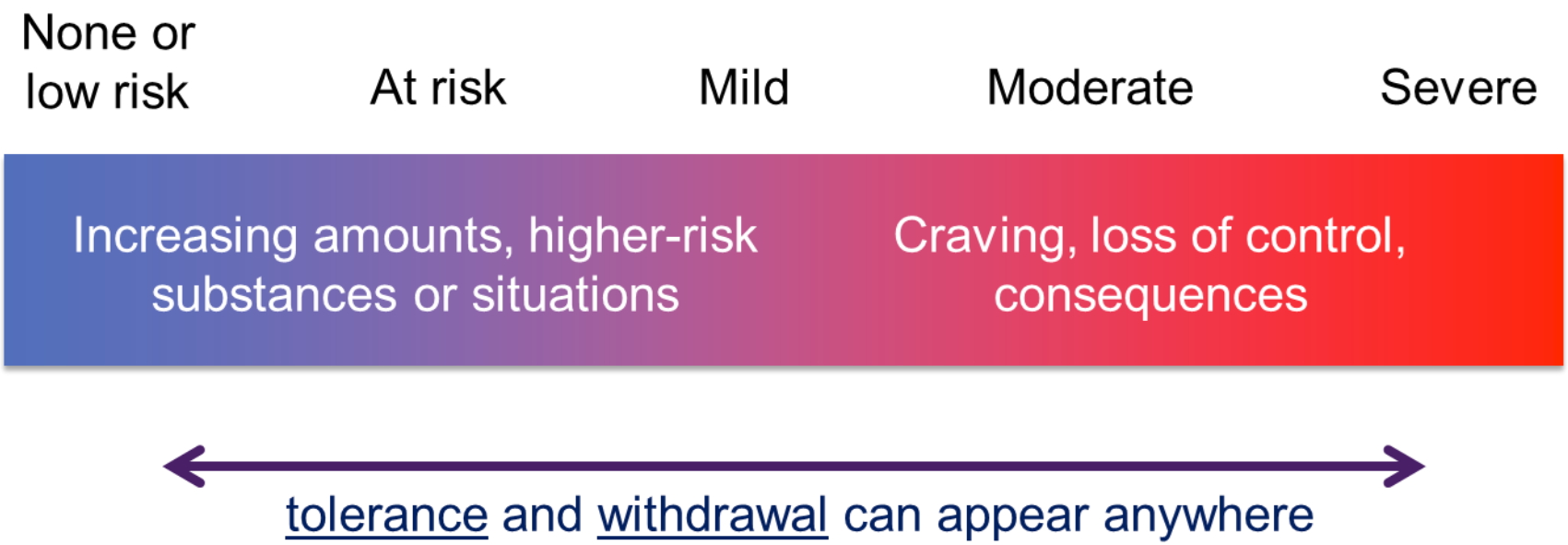
APA, 2013

Spectrum of Substance Use



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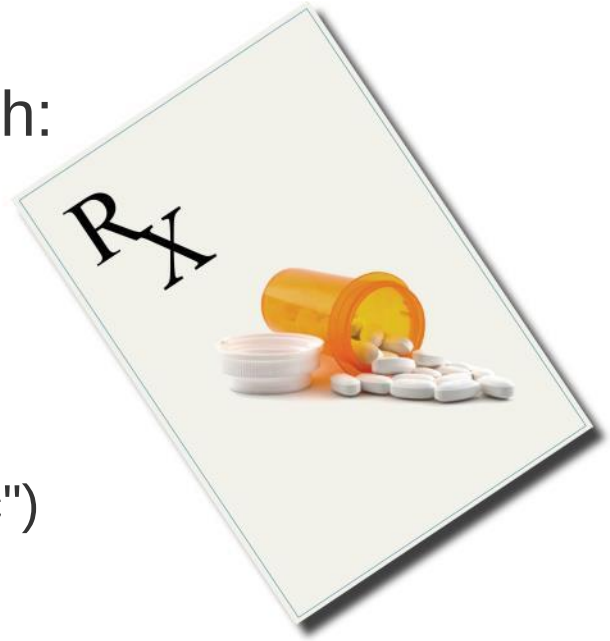
Pivotal Milestones in Treatment

Year	Milestone
1970 1973	Methadone is approved by the FDA for *detoxification* Methadone is approved by the FDA for *maintenance*
1974	Opioid Treatment Programs (OTP's) able to dispense Methadone for maintenance treatment
1984	Oral Naltrexone is approved by the FDA
2000	Drug Addiction Treatment Act of 2000 (DATA 2000) allowed qualified physicians to offer Office Based Opioid Treatment (OBOT)
2002	Buprenorphine is approved by the FDA
2010	Extended-release injectable naltrexone is approved by the FDA
2016	Comprehensive Addiction and Recovery Act (CARA) - Allows Nurse Practitioners and Physician Assistants to become eligible to prescribe buprenorphine for treatment of opioid use disorder

Drug Addiction Treatment Act (DATA 2000)

Permitted physicians who met certain qualifications to treat opioid addiction with:

- Schedule III, IV, and V narcotic medications that had been specifically approved by the FDA for that indication
- In treatment settings other than the traditional Opioid Treatment Program ("methadone clinic") settings



DATA 2000 – Practitioners Requirements

- ✓ Licensed provider with DEA Registration
- ✓ Subspecialty training in addictions or completion of an 8-hour course for MDs
  - 2016 CARA update: PA/APRNs – 24 hrs
- ✓ Registration with SAMHSA and DEA
- ✓ Must affirm the capacity to refer patients for appropriate counseling and ancillary services
- ✓ Must adhere to patient panel size limits
  - 30 during the first year
  - 100 during the second year
  - 275 during the third year

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Treatment Gap for Substance Use Disorders

- Approximately 22 million individuals aged 12 or older needed substance use treatment in 2015
- 10% of those diagnosed with SUDs received any type of specialty treatment
- Although increasing, currently a minority of all providers are trained to provide MOUD
- We see many patients with untreated OUD in the ED – We have the opportunity to link patients to treatment!

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Jones et al., 2015
SAMHSA, 2017

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Treatment Goals

- Range of treatment goals

Minimization of harms from ongoing use

Sustained recovery with abstinence from all substances

- Treatment Options
  - FDA approved treatment Medications for OUD (MOUD) include:
    - Buprenorphine: Partial Agonist at the mu-receptor
    - Methadone: Agonist at the mu-receptor
    - Naltrexone/Naloxone: Antagonists at the mu-receptor
  - Behaviorally-Oriented Treatment
- Ultimate Goal: Maintain long-term recovery with *or* without medication

Evidence Based Counseling for OUD

- Although some patients may benefit from additional counseling, for many patients with opioid use disorder, medication & medical management is the key!
- Do not let the inability to refer or provide counseling limit the initiation of buprenorphine for the treatment of OUD
- A Cochrane review of 35 studies with >4,000 patients found that overall, there was no clear benefit of additional specific counseling over the counseling received as part of the MOUD medical management (methadone or buprenorphine).

Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004147

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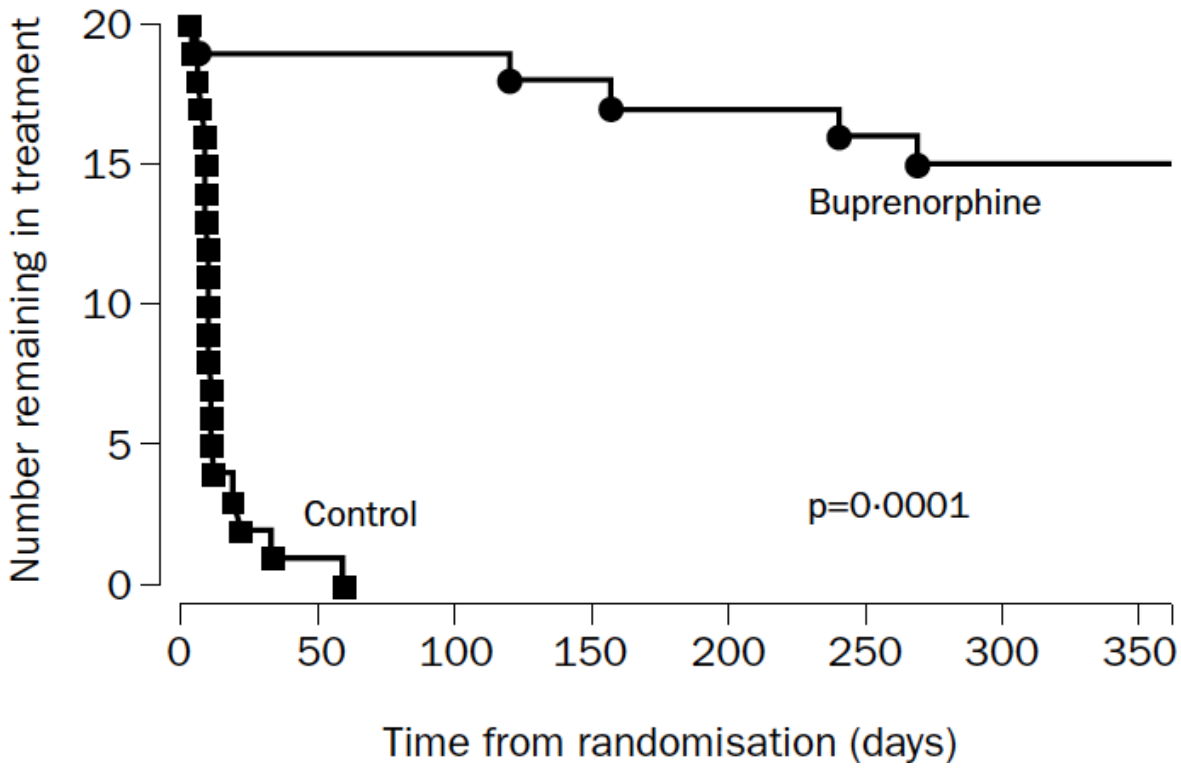
MEDICATIONS FOR ADDICTION TREATMENT is the MOST EFFECTIVE Treatment for OUD

- Opioid use disorder does not respond to the same treatments as alcohol use disorder.
- Abstinence based therapies generally DO NOT WORK: ~80 – 90+% annual relapse rate.
- One small study found 75% retention at 1 year for patients on buprenorphine compared to 0% for those who only received a 6 day taper.
- Twelve Step programs alone, without medications have a LOW rate of patient retention and sobriety at one year, when treating OUD (possibly <10%).*
- Retention rates in MOUD programs vary broadly, dependent upon multiple factors, with 1 year sobriety of ~10 to 80%, but average ~40-50%.

*Poor data collection from most of these programs.
Kakko, 2003

Taper vs. Ongoing Treatment



Deaths: Taper – 4/20 Buprenorphine – 0/20

Kakko, Lancet, 2003

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Heroin overdose deaths during expansion of methadone and buprenorphine in Baltimore, 1995-2009

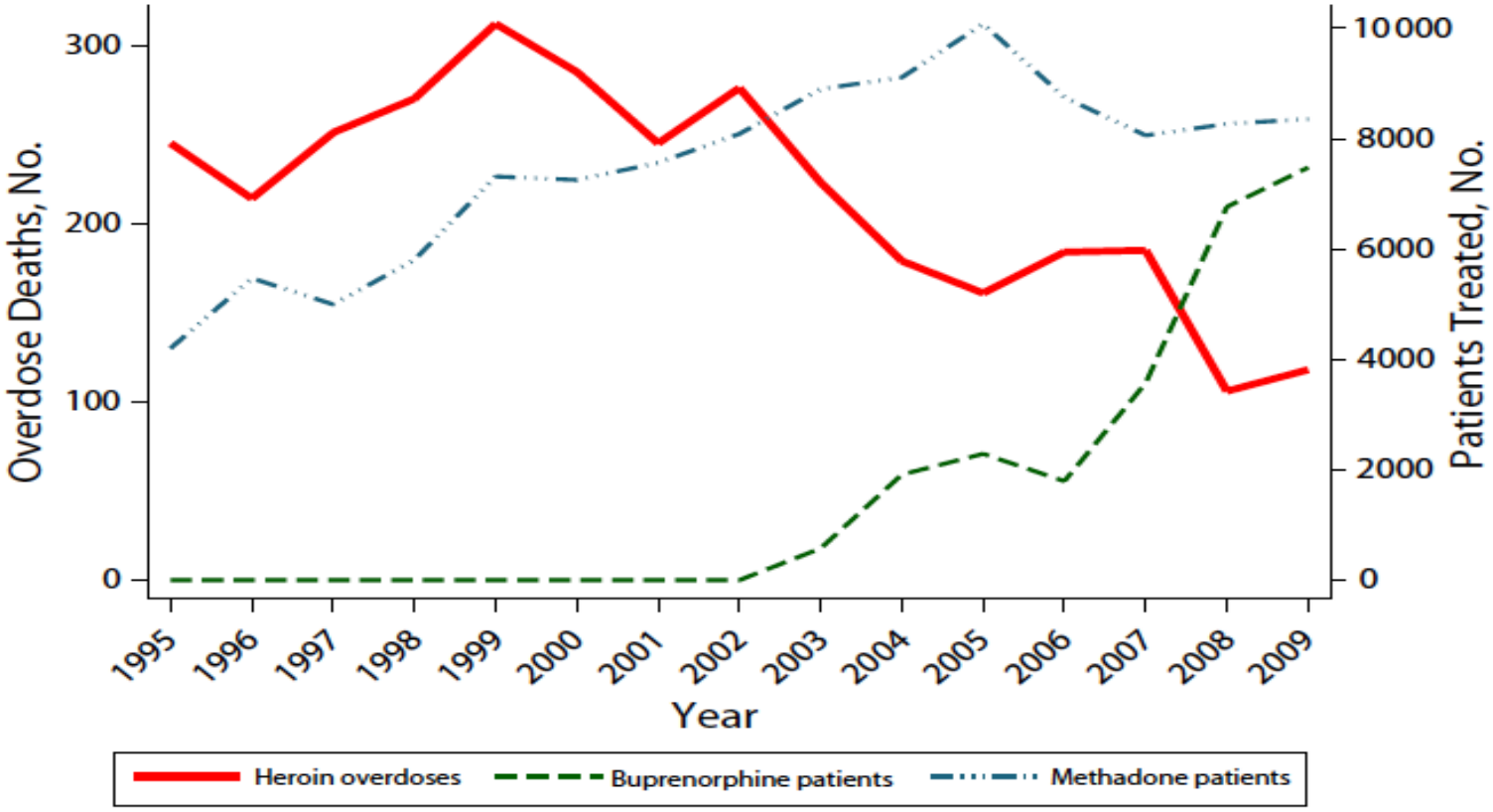

FIGURE 1—Heroin overdose deaths and opioid agonist treatment: Baltimore, MD, 1995–2009.

Schwartz, AJPH, 2013

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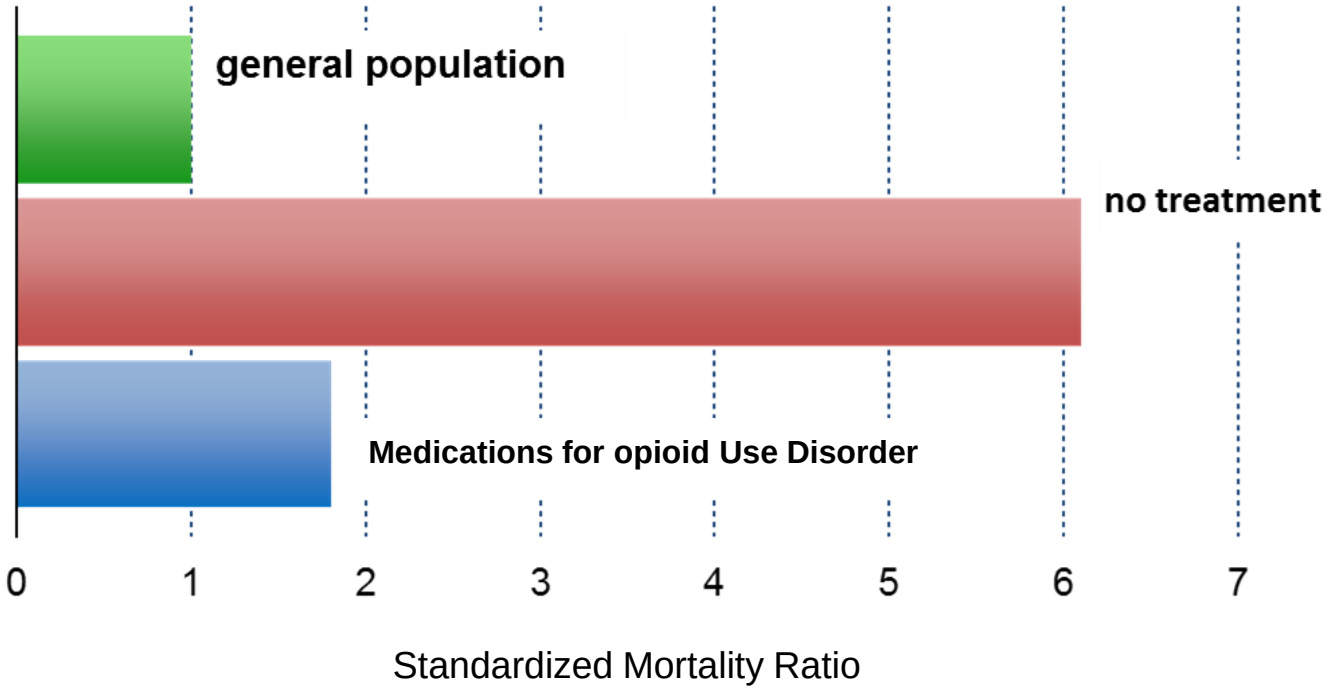
Benefits of Medications for OUD: Decreased Mortality

Death rates:



Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017

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Advantages of Opioid Agonist Treatment

- Decreases:
- Opioid use
- Opioid overdose deaths
- Legal consequences
- Infectious disease transmission

- Increases:
- Social functioning
- Retention in treatment

Mattick et al, 2008
Volkow et al., 2019

Opioid Agonist Treatment After ED Visit For Nonfatal Overdose Reduces Mortality

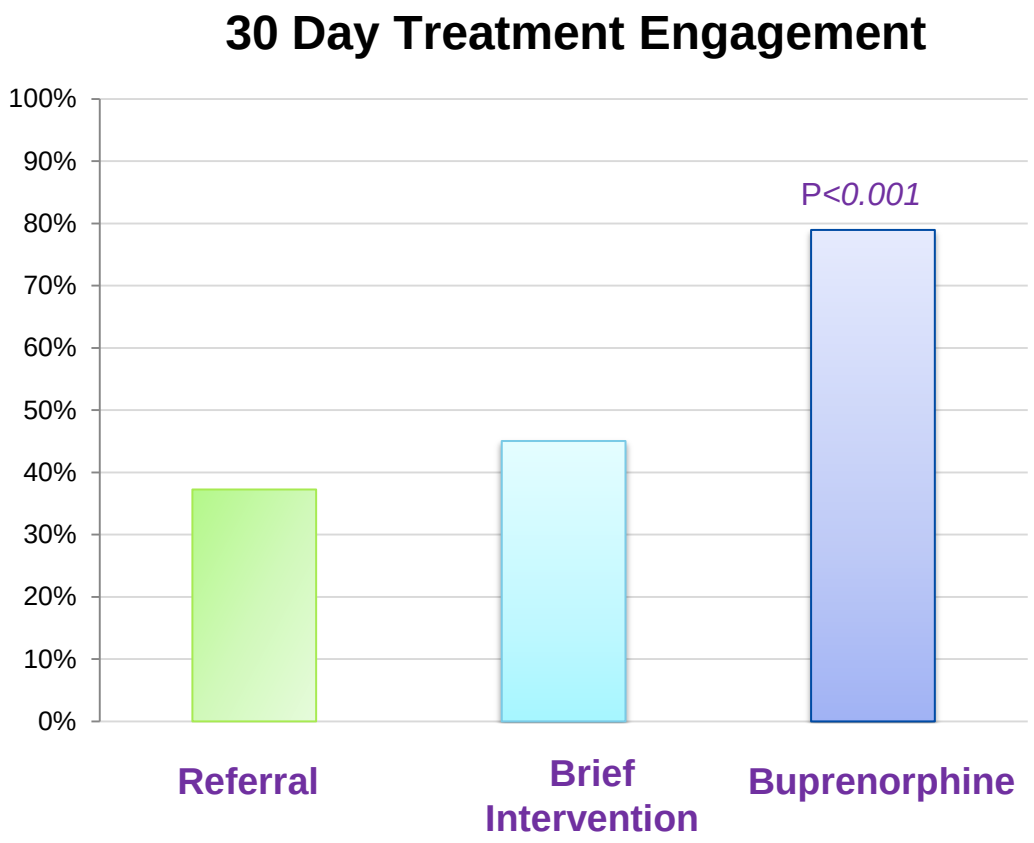
Analysis of >17K ED patients with nonfatal overdose

- 4.7% 1-year annual mortality
- Only 1/3s received MOUD in the year following ED visit for non-fatal OD
- All cause and opioid related mortality decreased 59% in patients who receive either buprenorphine or methadone in subsequent year

Larochelle et al., 2018

Emergency Department Initiated Buprenorphine

- Treatment trial of 329 ED patients with mod/severe OUD randomized to:
  - Standard Referral
  - Brief Intervention (BI) with facilitated referral
  - BI with ED-initiated buprenorphine with primary care follow-up



D'Onofrio et al, 2015

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Words Matter

VIEWPOINT

Changing the Language of Addiction

Michael P. Botticelli, MEd
White House Office of National Drug Control Policy, Washington, DC.

Howard K. Koh, MD, MPH
Harvard T.H. Chan School of Public Health, Boston, Massachusetts; and Harvard Kennedy School, Cambridge, Massachusetts.

Words matter. In the scientific arena, the routine vocabulary of health care professionals and researchers frames illness[1] and shapes medical judgments. When these terms then enter the public arena, they convey social norms and attitudes. As part of their professional duty, clinicians strive to use language that accurately reflects science, promotes evidence-based treatment, and demonstrates respect for patients.

However, history has also demonstrated how language can cloud understanding and perpetuate societal bias. For example, in the past, people with mental illness were derided as "lunatics" and segregated to "insane asylums." In the early days of human immunodeficiency virus, patients were labeled as having "gay-related immune deficiency," with public discourse dominated by moral judgments. Other examples apply to disability and some infectious diseases. In all of these cases, stigma and discrimination can arise when patients are labeled, linked to undesirable characteristics, or placed in categories to separate "us" from "them."

Today, these complex themes have special relevance for addiction. Scientific evidence shows that addiction to alcohol or drugs is a chronic brain disorder with potential for recurrence. However, as with many other chronic conditions, people with substance use disor-

Stigma isolates people, discourages people from coming forward for treatment, and leads some clinicians, knowingly or unknowingly, to resist delivering evidence-based treatment services. The 2014 National Survey on Drug Use and Health[4] estimates that of the 22.5 million people (aged ≥12 years) who need specialty treatment for a problem with alcohol or illicit drug use, only an estimated 2.6 million received treatment in the past year; of the 7.9 million specifically needing specialty treatment for illicit drug use, only 1.6 million received treatment. The survey noted that reasons for not seeking treatment included fears that receiving it would adversely affect the individual's job or the opinion of neighbors or other community members. Lack of insurance coverage, cost concerns, and not perceiving a need for treatment also contributed. Among health care professionals, negative attitudes regarding people with SUDs have led to diminished feelings of empowerment among patients, lower levels of empathy and engagement among health care professionals, and poorer outcomes.[5] Not surprisingly, medication-assisted treatment remains isolated within SUD treatment systems, which in turn have historically been separated from the rest of health care.

To help address these concerns, the American Medical Association has called on physicians across

Botticelli & Koh, 2016

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Words Matter

Words are powerful... They can contribute to stigma and create barriers to accessing effective treatment

Use person-first language; focus on the person, not the disorder

When Discussing Opioid or Other Substance Use Disorders...

Avoid These Terms:	Use These Instead:
Addict, user, drug abuser, junkie	Person with opioid use disorder or person with opioid addiction, patient
Addicted baby	Baby born with neonatal abstinence syndrome
Opioid abuse or opioid dependence	Opioid use disorder
Problem	Disease
Habit	Drug addiction
Clean or dirty urine test	Negative or positive urine drug test
Opioid substitution or replacement therapy	Opioid agonist treatment
Relapse	Return to use
Treatment failure	Treatment attempt
Being clean	Being in remission or recovery

Adapted from National Council Behavioral Health

MAT vs MOUD

- Addiction is a chronic relapsing remitting medical disorder that affects behavior and decision making
- Methadone, buprenorphine and Naltrexone have previously been referred to collectively as Medication-Assisted Treatment
- A broad evidence base supporting the benefits of medications as the treatment for OUD, similar to the treatment of diabetes with insulin or oral hypoglycemics.
- While many behavioral therapies may be beneficial similar to weight reduction and nutritional counseling for diabetes, they are important adjuncts to treatment, but NOT the definitive treatment.
- Thus, the evolving language from the National Institute of Health of Medications for Opioid Use Disorder (MOUD) more accurately reflects the role of medications in the treatment for OUD.

Wakeman 2017
Volkow 2019

Summary

- Rates of overdose deaths from opioids continue at alarming rates
- The ED is often the point of entry for individuals with opioid use disorder and represents an opportunity for initiation of treatment and access to care, narrowing the treatment gap.
- Addiction is a chronic relapsing, remitting medical condition that affects behavior and decision making.
- MOUD reduces opioid use, overdose, mortality and infectious disease transmission, and increases retention in treatment and social functioning.

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Neurobiology of Addiction

Objectives

1. **Describe the physiologic effects of opioids and the receptors involved**
2. Describe the effects of opioids on the positive and negative reinforcement pathways of the brain
3. Describe the effects of Agonists, Antagonists, and Partial Agonists on the mu receptor
4. Describe and recognize manifestations of opioid tolerance, intoxication, overdose, and withdrawal

Definitions

- 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

Stein, 2016

Opioid Receptors and Physiology

- 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

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

- Most of the clinically significant effects of prescribed and illicit opioids are attributed to activity at the mu receptor

Stein, 2016

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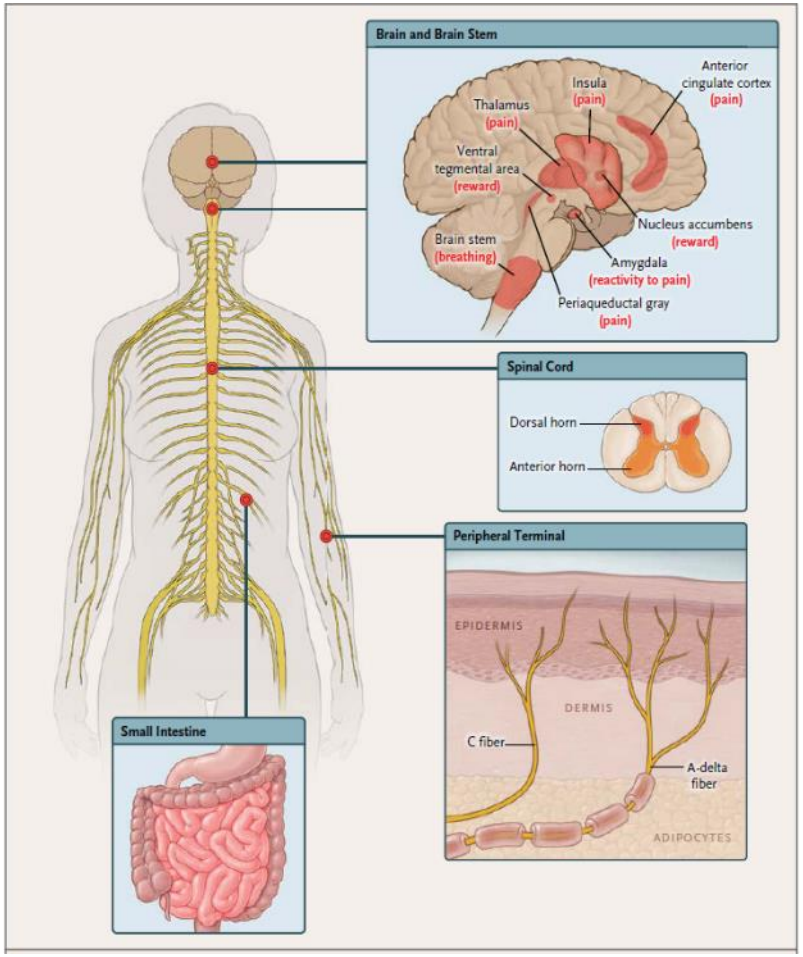
Opioids Receptor Locations

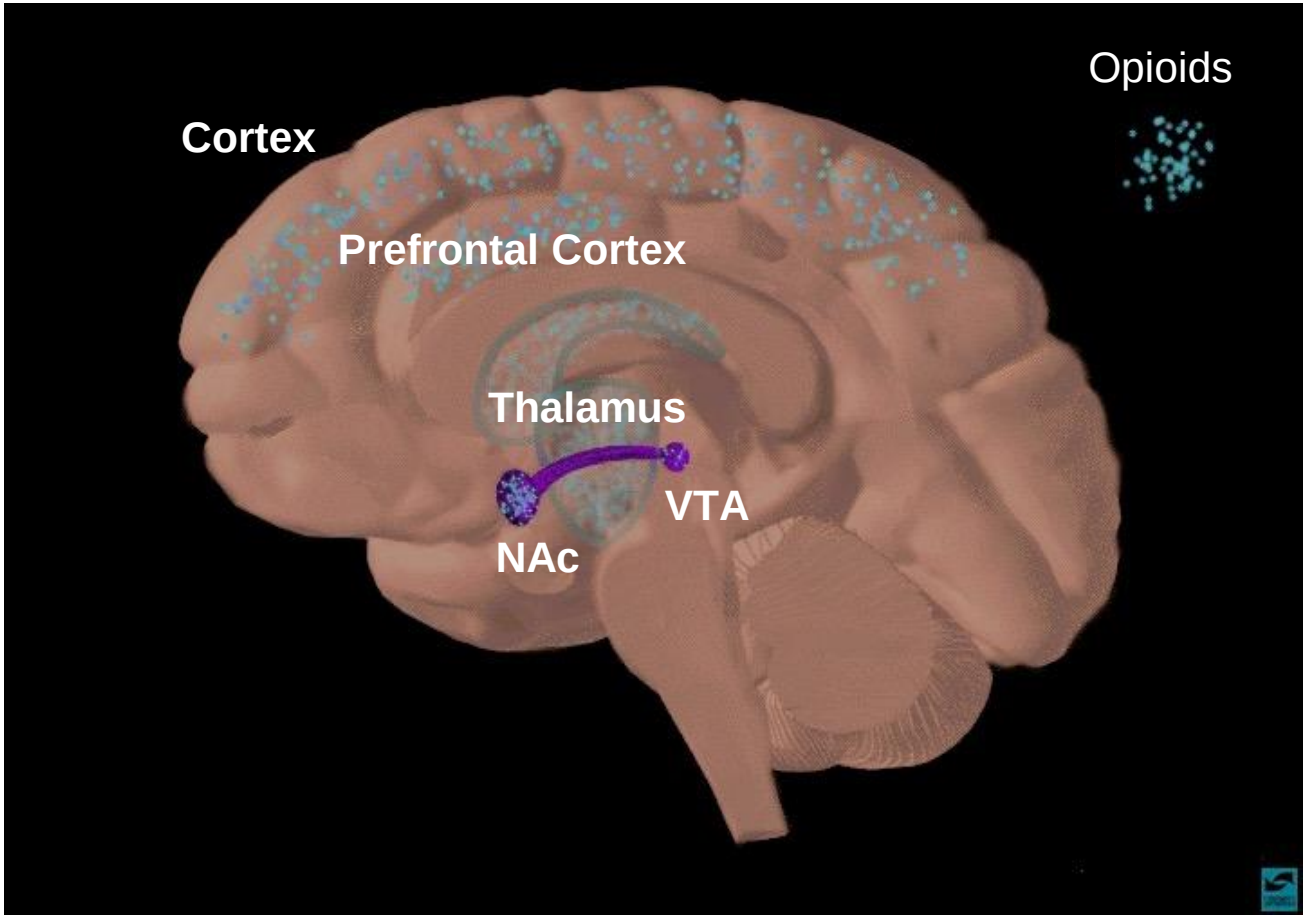
- Main target for Opioids are Mu Receptors

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



Volkow and McLellan, 2016

Opioid Binding



NIDA, 2007

Physiologic Effects of Opioids

- Activation of **mu** receptors in the central nervous system causes effects including:
  - analgesia
  - sedation
  - euphoria
  - pupil constriction
  - decreased respiration → **potentially lethal in overdose**
  - 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

SAMHSA, 2018
Stein, 2016

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Biology of Motivation

Positive reinforcement

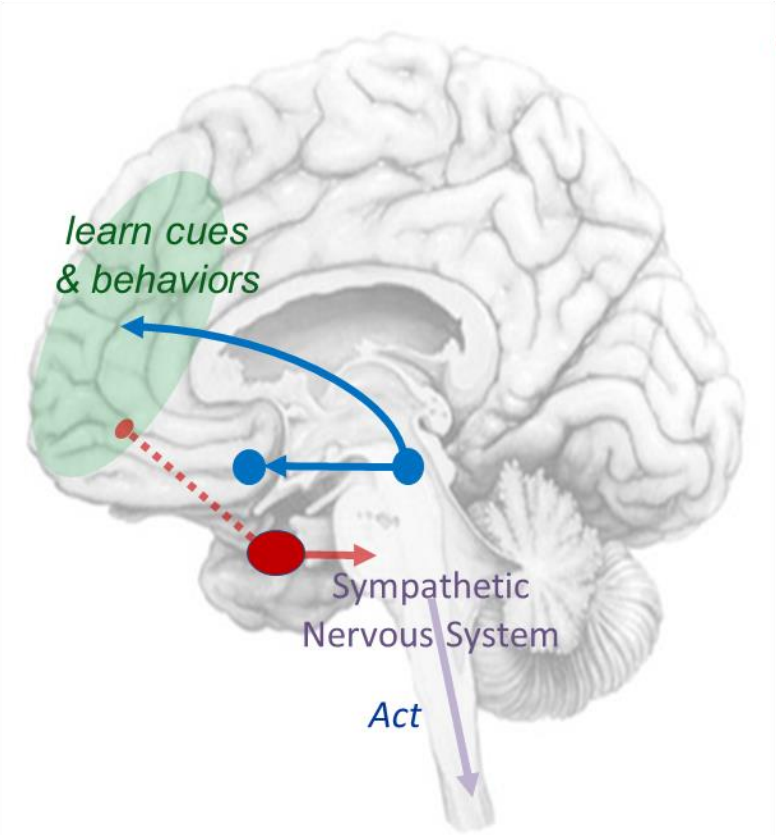
cells in the brainstem release **dopamine** in the **nucleus accumbens**

↓

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**

Volkow et al., 2016
Wise and Koob, 2014

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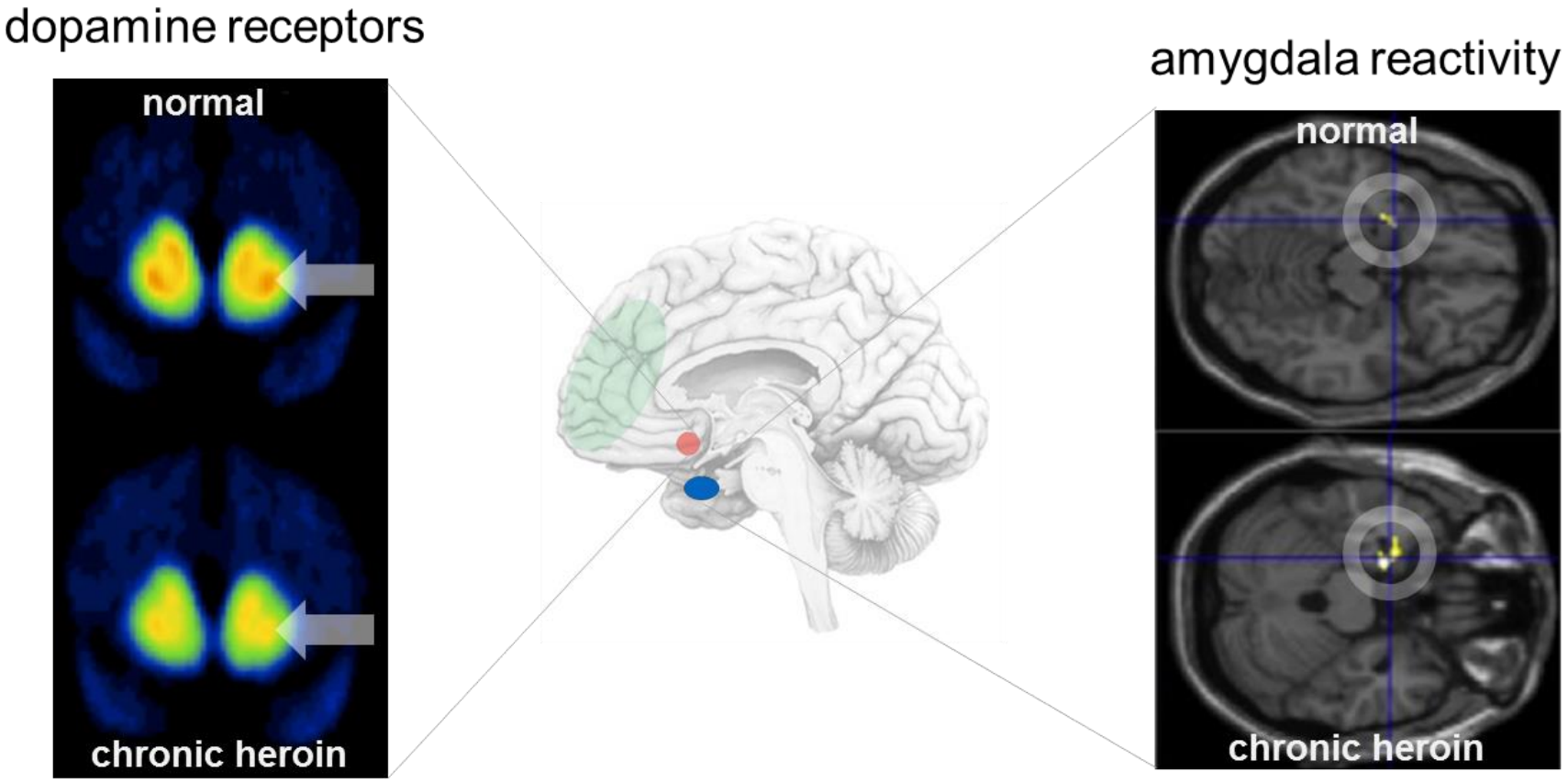
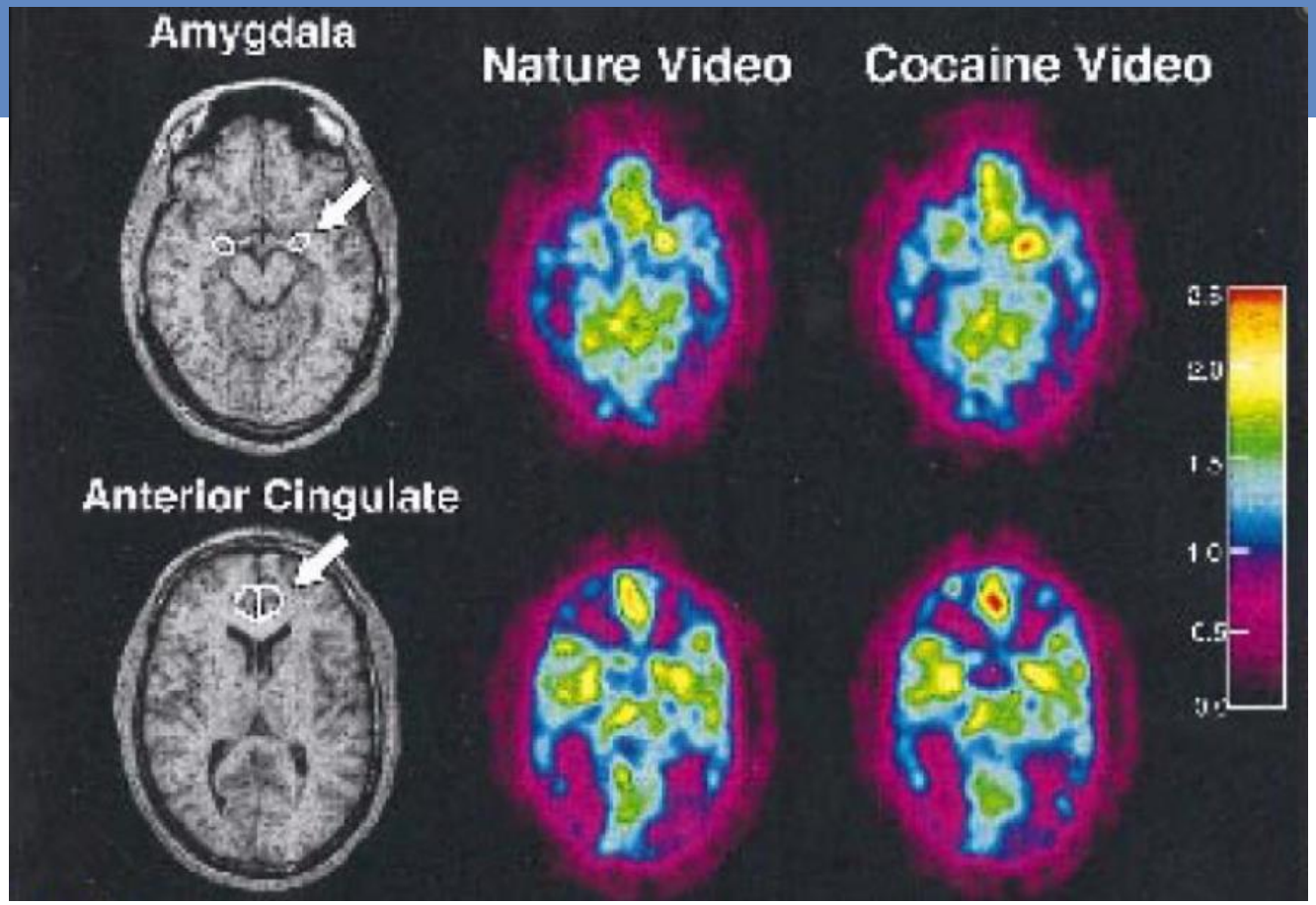
PET Imaging of Addiction



Martinez et al., 2012
Schmidt et al., 2014

Drug Cues Stimulate Craving



- Showing patients with addiction pictures of things that remind them of drugs (eg, syringes, white powder,) dramatically increases blood flow in the amygdala.
- In addition to the striatum, the amygdala is important to the genesis of addiction

Childress et al., *Am J Psychiatry*. 1999; 156(1):11.

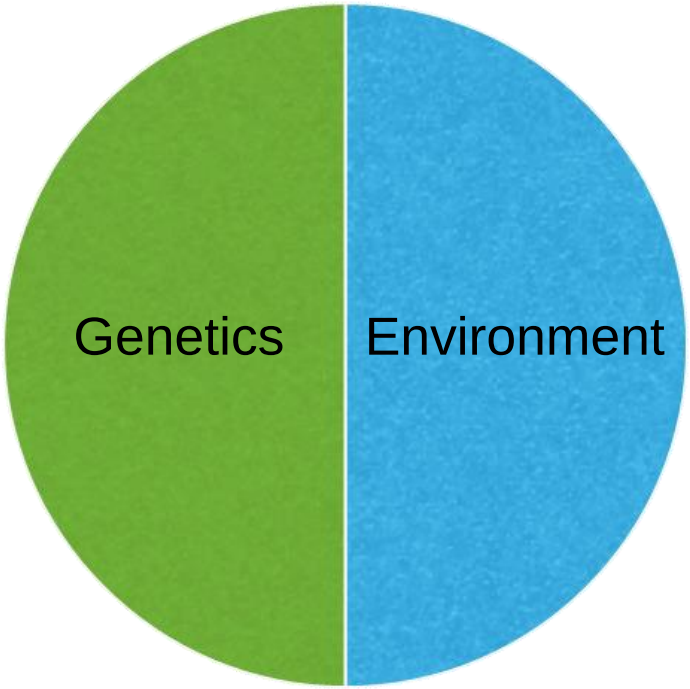
Addiction is NOT a moral failing

It is a chronic relapsing, remitting medical condition that affects behavior and decision making

Vulnerability to SUDs

- opioid receptors
- dopamine
- other transmitters
- intracellular signals

- novelty seeking
- harm avoidance
- impulsivity
- psychiatric disorders



- parents
- siblings
- friends

- Adverse Childhood Experiences (ACEs)
- psychiatric disorders
- stressors
- lack of positive experiences

- illicit sources
- prescription
- family and friends

Anokhin et al., 2015
Milivojevic et al., 2012
Reed et al., 2014
Volkow et al., 2016

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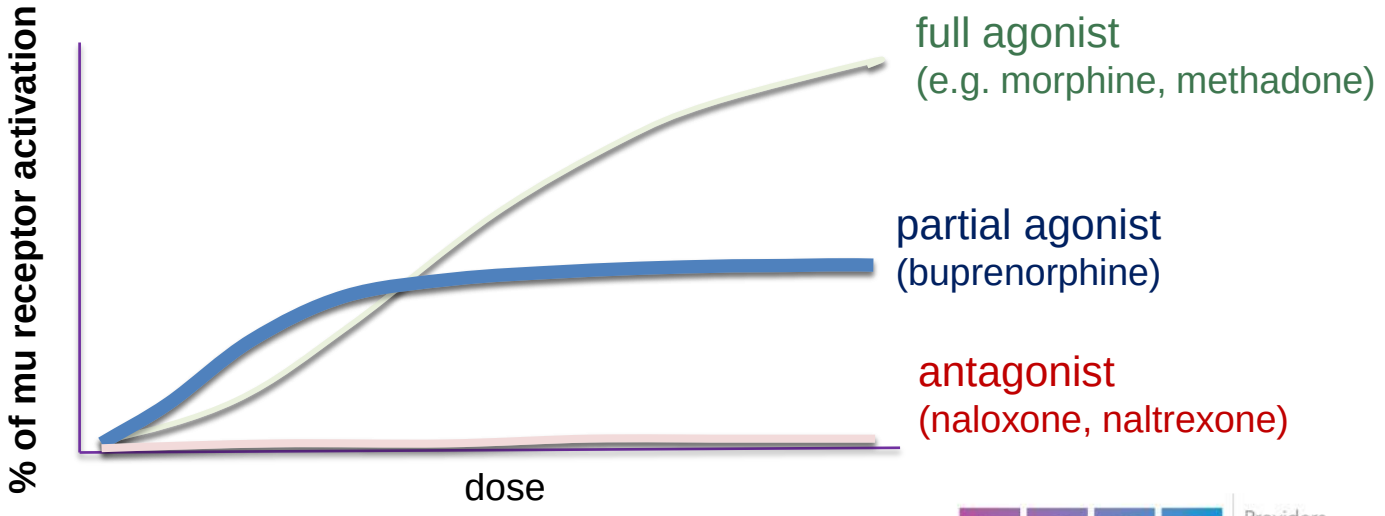
Opioid Partial Agonist Therapy

- The partial agonist **buprenorphine** prevents withdrawal and maintains a steady level of opioid activity like methadone, but like naltrexone also blocks the effects of other opioids
  - Unlike full agonists, buprenorphine is **schedule III** and therefore eligible under DATA 2000 to be prescribed in office-based treatment.
- Because of its partial agonism it is *unlikely* to lead to fatal respiratory suppression even at at high doses



SAMHSA, 2018
Orman & Keating, 2009

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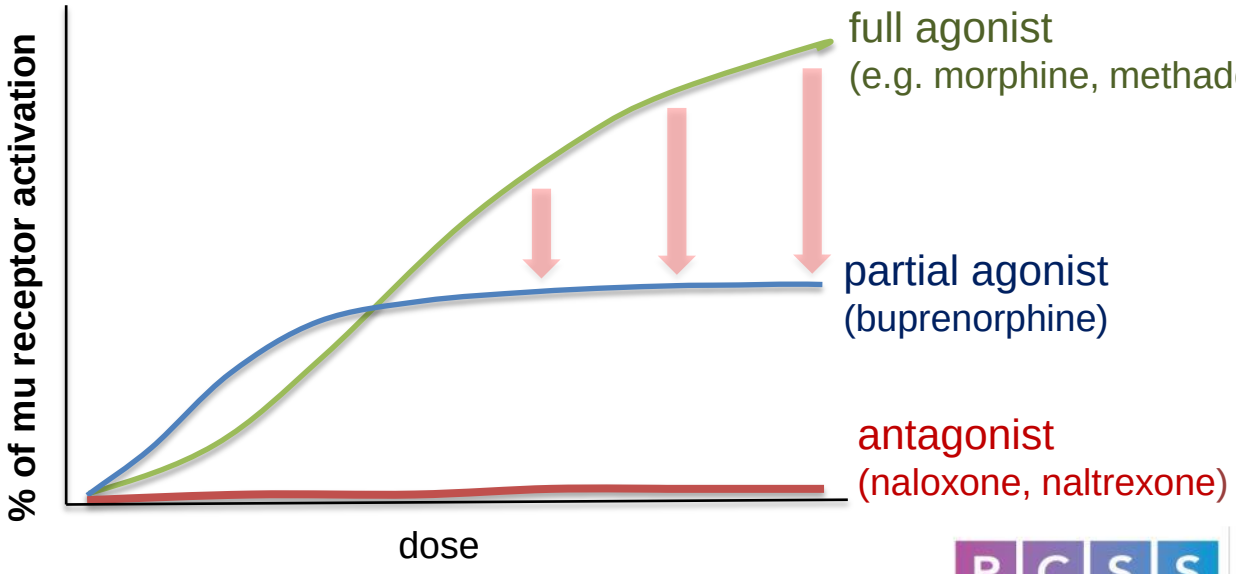
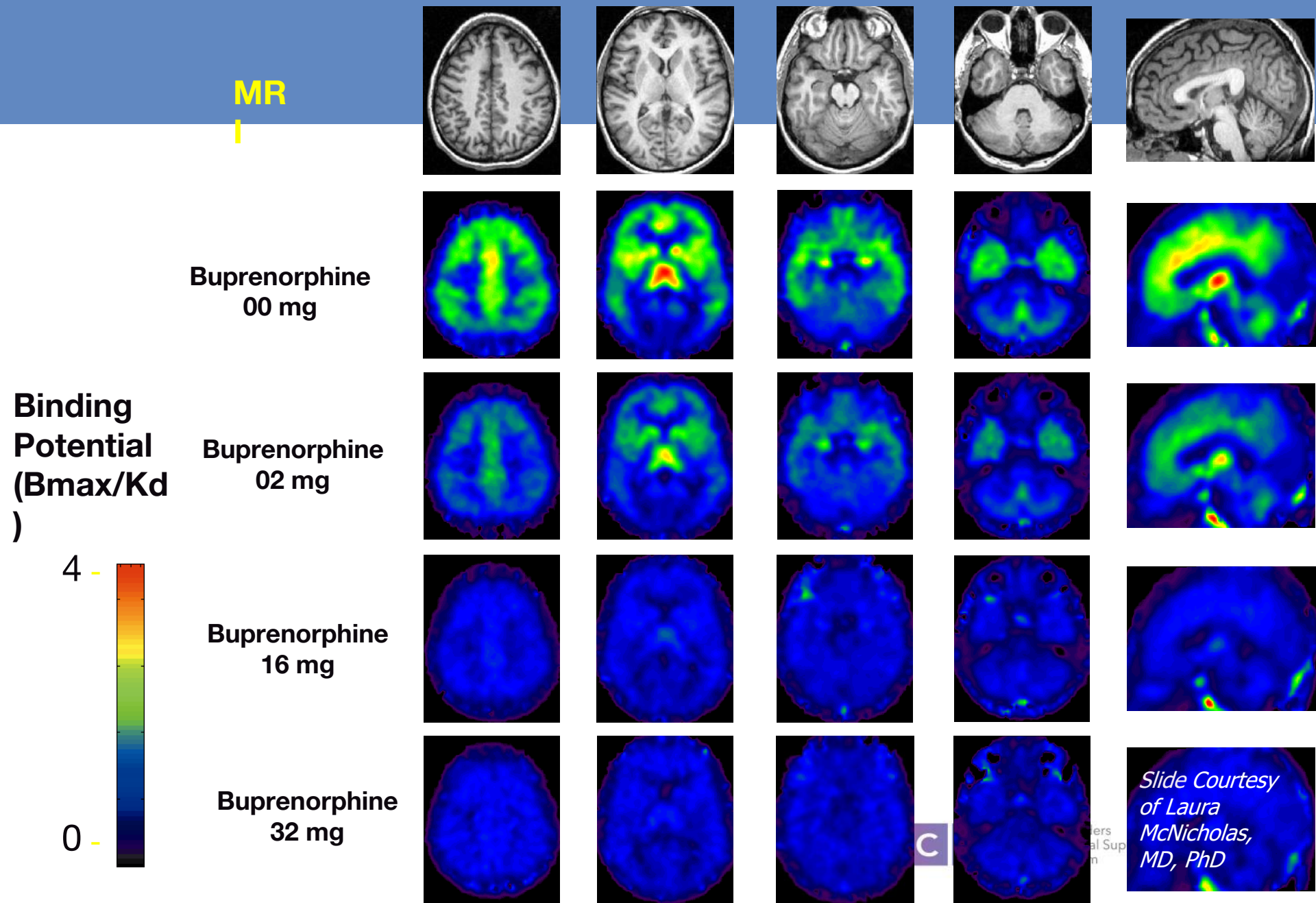
Precipitated Withdrawal

- Because of its high affinity for mu opioid receptors, buprenorphine can displace other agonists (such as heroin, methadone) that are already present
- The sudden drop from full-agonist to partial-agonist stimulation of opioid receptors can cause sudden and severe withdrawal symptoms, a condition known as ***precipitated withdrawal***



SAMHSA, 2018
Orman & Keating, 2009

Effects of Buprenorphine Dose on μ-Opioid Receptor Availability in a Representative Subject



Objectives

1. Describe the physiologic effects of opioids and the receptors involved
2. Describe the effects of opioids on the positive and negative reinforcement pathways of the brain
3. Describe the effects of Agonists, Antagonists, and Partial Agonists on the mu receptor
4. **Describe and recognize manifestations of opioid tolerance, intoxication, overdose, and withdrawal**

Tolerance to Opioid Effects

- With repeated exposure to opioids, tolerance (needing more to produce the same effect) develops
- Tolerance 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)

Stein, 2016

Opioid Intoxication

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

SAMHSA, 2018

Opioid Overdose

- 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

SAMHSA, 2018

Opioid Withdrawal Signs and Symptoms

- **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 Withdrawal Timing of Symptoms

- All opioids produce similar withdrawal symptoms when stopped abruptly
  - Severity varies with the amount and duration of use
- Timing of withdrawal symptoms depends on the opioid:
  - With longer-acting opioids, symptoms usually begin later and last longer:

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

SAMHSA, 2018

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Summary

- The main target for opioids are mu receptors which have multiple effects including analgesia, euphoria, sedation and decreased respiration and heart rate.
- Opioids take over the positive reinforcement (which causes individuals to seek out and use more opioids) and negative reinforcement (which impels individuals to avoid not having opioids which can then result in fear, anxiety and distress) pathways.
- Agonists (e.g. Methadone), Antagonists (e.g. Naltrexone, naloxone), and Partial Agonists (e.g. Buprenorphine) have distinct effects on the mu receptor. Because of its partial agonism buprenorphine is unlikely to lead to fatal respiratory suppression even at high doses.
- Opioid withdrawal and overdose have distinct symptoms and can be treated successful with opioid agonist treatment.

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Buprenorphine Pharmacology

Buprenorphine Pharmacology: Objectives

1. Understand receptor full agonism vs. partial agonism vs. antagonism
2. Understand receptor affinity
3. Understand how buprenorphine's partial agonism, high receptor affinity and slow dissociation make it uniquely suited to deter misuse and treat opioid addiction
4. Understand how buprenorphine can precipitate opioid withdrawal in dependent patients

Buprenorphine Pharmacology

Buprenorphine was developed in 1969 by British pharmacologists looking for a morphine alternative

Goal: retain analgesic effects of morphine without adverse effects (e.g. respiratory depression) and without addictive potential

Buprenorphine does not fully satisfy this goal, and the quest for such a compound continues today

However, buprenorphine has a unique pharmacology that makes it particularly well suited to treat opioid use disorder

Therapeutic use for pain and opioid addiction began in late 70's and early 80's

Buprenorphine Pharmacology

#1. Buprenorphine is a **partial mu receptor agonist**

- **Full agonists:** All pathways activated – analgesia, sedation, euphoria, respiratory depression, etc.
- **Partial agonist:** Pathways activated disproportionately – (example: **analgesia↑↑↑ stop withdrawal and cravings:↑↑↑**, but euphoria: ↑, sedation: ↑, respiratory depression: ↑ – much less
- **Antagonist:** Receptor, and thus pathways blocked -- no pathways activated.

Buprenorphine Pharmacology

#2. Buprenorphine has a **higher mu receptor affinity** than nearly every other opioid

Buprenorphine pushes almost everything else off the mu receptor – binds very competitively.

Not easily pushed off the mu receptor

Buprenorphine Pharmacology

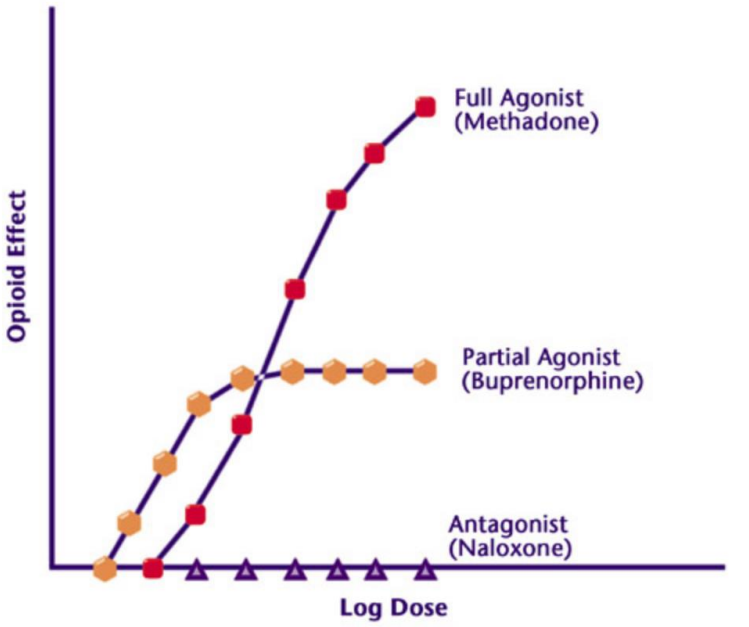
#3. Buprenorphine, administered SL, has a slower onset of action than opioids administered IV or IN. It also dissociates from the mu receptor very **slowly**

Long duration of action

(which is also the key property of methadone)

Buprenorphine Pharmacology

Partial agonism provides comparative **safety – ceiling effect on respiratory depression**



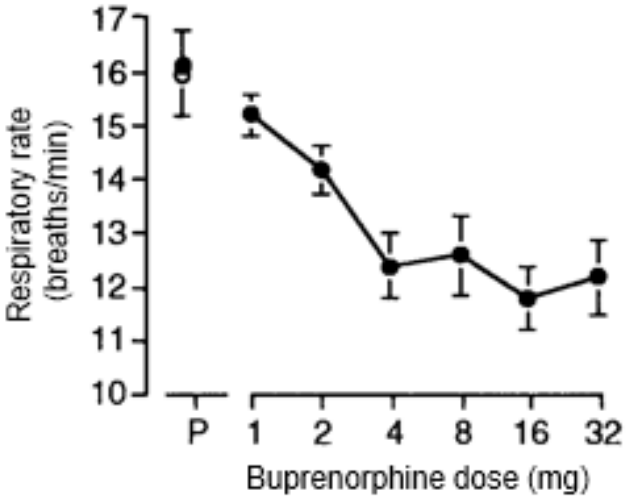
Respiratory depression incurred at 16mg =~ 32mg = ~64mg*

Dangerous overdose still possible, especially in children or with sedative/respiratory depressant co-ingestants, but buprenorphine is much safer than full agonists (e.g. methadone, heroin, oxycodone)

*Ahmadi, et al. 2018

Buprenorphine Pharmacology

Partial agonism provides <u>comparative</u> **safety -- ceiling effect on respiratory depression**



However, beware of potential for severe respiratory depression in certain populations

Buprenorphine behaves more like a full agonist in infants and toddlers. Also, should be cautious in the elderly, particularly those with COPD, or other chronic respiratory illness, or if taking other potentially respiratory depressing medications.

Hakkinen et al., 2012
Walsh et al., 1994

Buprenorphine Pharmacology

Partial agonism + high affinity = potential for **buprenorphine-precipitated withdrawal**

Opioid-dependent person who has full agonist on board (i.e. not in withdrawal or in only mild withdrawal) will have full agonist replaced with partial agonist

Withdrawal occurs during period of competition at the receptors – when receptors are not bound by either drug.

In these cases, buprenorphine behaves as a *functional antagonist*, until the buprenorphine binds to the receptors.

Buprenorphine Pharmacology

Partial agonism + high affinity = potential for **buprenorphine-precipitated withdrawal**

buprenorphine is fabulous for **treating** opioid withdrawal, but if an opioid-dependent person is not in withdrawal (from a full agonist), buprenorphine can precipitate opioid withdrawal

Buprenorphine Pharmacology

Partial agonism + high affinity = potential for **buprenorphine-precipitated withdrawal (BPW)**

BPW although treatable, can range from mild to intense – better to avoid if possible.

Before treating patient with buprenorphine, ensure the patient either:

- is adequately withdrawing, OR
- has completed acute physiologic withdrawal before treating with buprenorphine.

Buprenorphine Pharmacology

Partial agonism + relatively slow on/very slow off means buprenorphine is **less euphoric** than most full agonists (particularly with SL administration).

While some euphoria is achieved with injecting buprenorphine, it is much less misuse-prone than full agonist opioids

Buprenorphine Pharmacology

Partial agonism + high affinity means that most full agonists are **blocked** from exerting their effects.

- Person with Opioid Use Disorder who is therapeutic on buprenorphine is less likely to misuse other opioids because they will have much reduced psychoactive effect.

- This reduced effect (and thus the reduced reward from, reduced craving for, and reduced use of, full agonists) **protects the patient from overdose** by full agonists

Buprenorphine Pharmacology

Partial agonism + slow dissociation allows for **safety in high doses to prolong the dosing interval**

- Potential boon to emergency department-based buprenorphine initiation,
- but clinical data on high-dose (>16 mg) buprenorphine still evolving

Buprenorphine Pharmacology

Buprenorphine has less potential for misuse than full agonist opioids but is more euphoriant when it is crushed and injected.

The preferred preparation of buprenorphine when used to treat opioid use disorder (OUD) is to **combine buprenorphine with naloxone (nx) – bup/nx**

Buprenorphine Pharmacology

Bup/nx is designed to be sublingual

Buprenorphine has moderate (~30% to <50%) bioavailability SL.

Naloxone has negligible bioavailability SL, but low (although measurable) bioavailability if swallowed.

However, the small amount of naloxone which is absorbed, if swallowed, is known to contribute to headaches (which some patients get from buprenorphine SL as well).

The naloxone in bup/nx has a negligible effect when bup/nx is taken SL as intended.

Buprenorphine Pharmacology

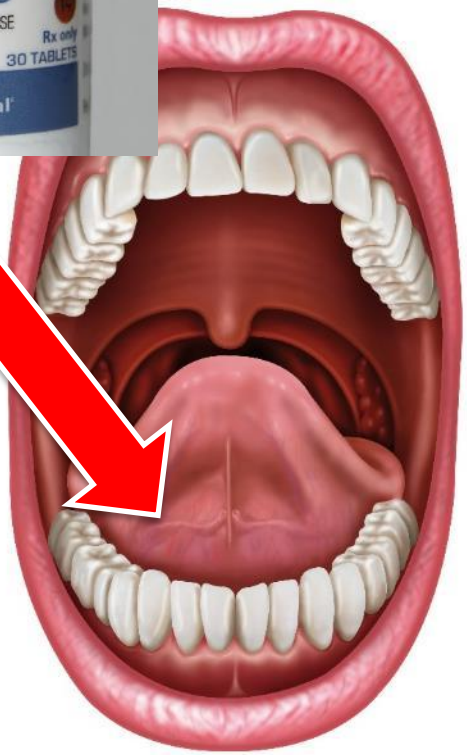
Many patients (and providers) believe that Buprenorphine Precipitated Withdrawal (BPW) is related to the naloxone in bup/nx:

- However, BPW is an effect of the buprenorphine itself.
- The naloxone in bup/nx only functions to prevent misuse by crushing/injecting.
- The efficacy of bup/nx as a deterrent is variable, patient dependent, effective for many patients, but not uniformly effective.

Mammen, K 2009
Webster, L. 2015

Buprenorphine Pharmacology

Thus, there are multiple reasons to be sure to educate your patients about benefits of taking the medication properly, and adverse effects of taking improperly



Buprenorphine has low bioavailability when ingested (and undergoes first pass metabolism as well). Thus dosing likely to be subtherapeutic. Patients should not swallow sublingual tab/strip.

Buprenorphine Pharmacology

Long-acting forms of buprenorphine exist and more are being developed

- 6 month implantable “rods,” and a monthly depot subcutaneous injections are on the market for OUD maintenance.
- Additional monthly and weekly injectable forms have been developed for induction and maintenance, but await FDA approval.
- Potential for emergency providers to initiate long-acting buprenorphine to be determined.

Summary

- Buprenorphine is a slow-dissociating, partial mu receptor agonist with higher receptor affinity than nearly all other opioids
- Buprenorphine is therefore safer in overdose and less prone to misuse than full agonist opioids, and while therapeutic on buprenorphine patients are protected from overdose, withdrawal, and cravings
- Buprenorphine can precipitate opioid withdrawal if administered to a dependent person who still has sufficient full agonists on board
- Buprenorphine has more misuse potential when crushed/injected, so the preferred preparation for outpatient prescription management is combined with naloxone

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Receptor Affinity Comparison Table

Drug	Human K_i (nM) [35]	Marmoset K_i (nM) [38]	Guinea Pig K_i (nM) [13]	Average Docking Score (ADS)	Standard Deviation in Score	Predicted Conc. Regime
N-methyl fentanyl*			18000 ± 3000	-7.89	0.21	> 100 nM
(1R,2R)Tramadol	12,500			-7.85	0.06	> 100 nM
(1S,2S) Tramadol	12,500			-7.97	0.20	> 100 nM
Meperidine	450			-7.77	0.07	> 100 nM
Propoxyphene	120			-9.56	0.08	0–100 nM
N-Methyl carfentanil*			42 ± 6	-8.53	0.07	0–100 nM
Diphenoxylate	12.4			-10.1	0.47	Sub nM
Alfentanil	7.39	14.4 ± 4.2		-10.5	0.56	Sub nM
R-Methadone	3.38			-8.69	0.12	0–100 nM
S-Methadone	3.38			-8.63	0.07	0–100 nM
Fentanyl	1.35	1.32 ± 0.35	1.2 ± 0.2	-9.43	0.38	0–100 nM
Sufentanil	0.138	0.24 ± 0.05		-9.89	0.23	Sub nM
Carfentanil^		0.22 ± 0.08	0.024 ± 0.004	-10.8	0.30	Sub nM
Lofentanil^		0.055 ± 0.006	0.023 ± 0.004	-10.8	0.50	Sub nM
R30490*			0.09 ± 0.01	-10.3	0.31	Sub nM
Codeine	734			-8.23	0.16	> 100 nM
(+)-Pentazocine	118			-7.77	0.12	> 100 nM
Oxycodone	25.9			-8.78	0.27	0–100 nM
Nalbuphine	2.12			-8.47	0.29	0–100 nM
Morphine	1.14			-7.76	0.14	> 100 nM
Oxymorphone	0.406			-8.40	0.18	0–100 nM
Hydromorphone	0.365			-7.94	0.26	> 100 nM
Buprenorphine	0.216			-9.76	0.48	0–100 nM

*Experimental data from guinea pig whole brain membranes.

^Experimental data from marmoset brain homogenates.

https://doi.org/10.1371/journal.pone.0197734.t001

ED-Initiated Buprenorphine

ED-Initiated Buprenorphine

- Overall goal:
  - To describe the components of buprenorphine initiation in the ED
  - To describe key differences between ED and office-based initiation
- Specific goals:
  - Identify eligible patients with moderate/severe Opioid Use Disorder (OUD)
  - Assess degree of withdrawal
  - Initiate Buprenorphine
    - Administer dose(s) in the ED
    - Prescribe for home induction
  - Provide patient education
  - Provide prescription & referral for ongoing treatment

SAMHSA, 2004

How do I start buprenorphine in the ED?

Obtain History of Substance Use

To determine safety of prescribing buprenorphine from the ED, and the dose to prescribe, strive to obtain the following information:

- 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)
  - Injection use? Smoking?
- 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 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
- Assess COWS and document mild, moderate or severe withdrawal:
  - 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

https://medicine.yale.edu/edbup/

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ASSESS FOR OPIOID USE DISORDER

DSM V Criteria: Opioid Use Disorder

- 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 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.
- Severity is related by the number of symptoms.

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

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Questions based on DSM-5 for diagnosis of Opioid Use Disorder

Severity
Presence of Symptoms
Mild: 2-3
Moderate: 4-5
Severe: ≥6

- [x] 1. Have you found that once you started using opioids you ended up taking more than you intended
- [x] 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?
- [x] 4. Have you had a strong desire or urge to use opioids?
- [ ] 5. Have you missed work or school or often arrived late because your were intoxicated, high, or recovering from the night before?
- [ ] 6. Have your use of opioids caused other problems with other people such as family members, friends or people at work?
- [x] 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?
- [x] 9. Have you continued to use even though you knew that opioids caused you problems like making you depressed anxious or irritable?
- [x] 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 cut down or stopped using?

At least 2 criteria must be met within a 12 month period

ED patients often meet several DSM-V Criteria

Without going through the full DSM-V criteria/questionnaire with the patient, many red flags may check off several boxes:

- Did the patient present with an opioid overdose?
- If the patient is using Rx opioids, is the patient smoking or injecting them?
- Is the patient using heroin?
- Did the patient present with complications of heroin use? Injection drug use abscess?
  - Heroin use, particularly with heroin use related complications, can probably meet criteria #1-4, and #10 & 11, as well.
  - Patients with regular heroin use generally have at least a moderate opioid use disorder.

ASSESS FOR OPIOID WITHDRAWAL

Clinical Opioid Withdrawal Scale (COWS)

Resting Pulse Rate			
80 or below (0)	81-100 (1)	101-120 (2)	>120 (4)

Restlessness			
Sits still (0)	Difficulty siting still (1)	Frequently shifting limbs (3)	Unable to sit still (5)

Anxiety or irritability			
None (0)	Increasing (1)	irritable/ anxious (2)	Cannot participate (4)

Yawning			
None (0)	1-2 times (1)	3 or 4 times (2)	Several per/min (4)

Pupil Size			
Normal (0)	Possibly larger (1)	Moderately dilated (2)	Only rim of iris visible (5)

Runny Nose or Tearing			
Not present (0)	Stuffiness/ moist eyes (1)	Nose running/ tearing (2)	Constant running/ tears streaming (4)

Tremor			
No tremor (0)	Felt-not observed (1)	Slight tremor observable (2)	Gross tremor/ Twitching (4)

Sweating				
No report (0)	Subjective report (1)	Flushed/ observable (2)	Beads of sweat (3)	Streaming down face (4)

Gooseflesh Skin		
Skin is smooth (0)	Piloerection (3)	Prominent piloerection (5)

Bone or Joint pain			
None (0)	Mild (1)	Severe (2)	Unable to sit still due to pain (4)

GI upset				
None (0)	Stomach cramps (1)	Nausea or loose stool (2)	Vomiting or diarrhea (5)	Multiple episodes (5)

Score:
5-12= Mild
13-24= Moderate
25-36= Moderately Severe

If considering initiating buprenorphine in the ED, complete the COWS if there is any doubt that the patient is in at least moderate withdrawal.

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LABORATORY TESTING

Laboratory Testing

- Pregnancy testing for women in reproductive years
  - NOT an exclusion criteria but should 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

Do not delay buprenorphine for laboratory testing, if the patient is obviously in at least moderate withdrawal.

PROVIDE BUPRENORPHINE

Treat Opioid Withdrawal with Buprenorphine

72-hour rule

Title 21, Code of Federal Regulations, Part 1306.07(b)

Allows to administer (but not prescribe) narcotic drugs for the purpose of relieving acute withdrawal symptoms while arranging for the patient's referral for treatment

- Not more than 1-day's medication may be administered or given to a patient at one time
- Patient must return to ED each day for no more than 72 hours
- This 72-hour period cannot be renewed or extended

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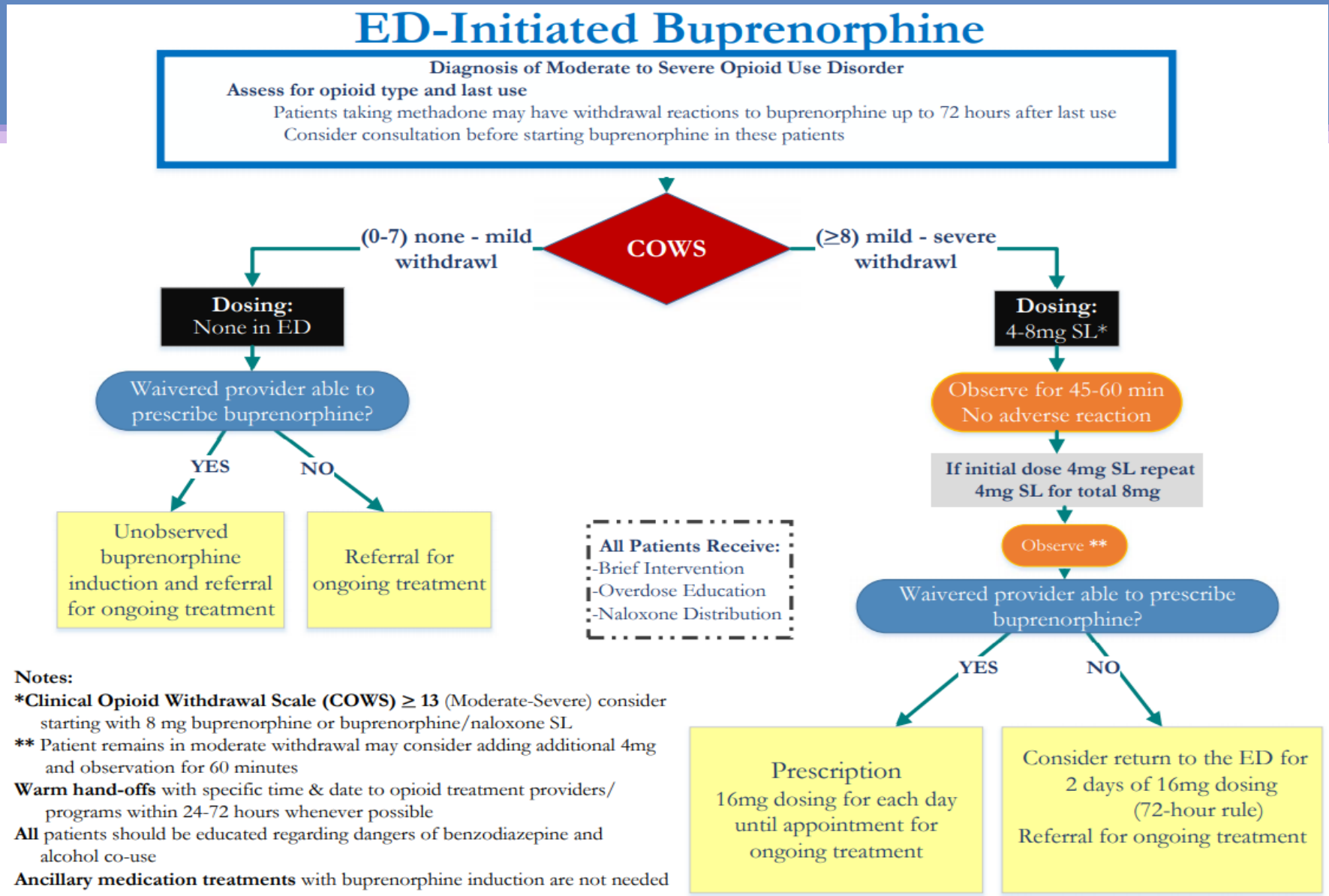
A Common Treatment Algorithm



Yale ED buprenorphine Website
Tintinalli 2019

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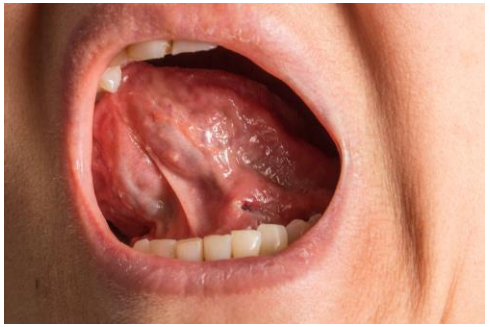
TIPS: Initiating Buprenorphine in the ED

- Warm hand-off to outpatient opioid treatment with specific time and date:
  - Preferably within 72 hours (although that may not be realistic for many EDs)
  - If a longer delay, may need to provide a longer buprenorphine prescription
  - Consider arrangement with a clinic that has designated days open to ED follow up
- All patients should be counseled regarding risks associated with alcohol and sedative co-use.
- Ancillary medication to treat withdrawal (i.e. anti-emetics, etc) in addition to buprenorphine are usually not needed (if the patient is adequately dosed with buprenorphine).
  - Although the actively vomiting patient may benefit from a single dose of an anti-emetic (e.g. orally dissolving ondansetron) with the first dose of buprenorphine.

Buprenorphine Initiation
Patient Education

- 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

Complicated ED Buprenorphine Induction

- Usually ED buprenorphine induction proceeds smoothly, and within 30 minutes withdrawal symptoms are abating.
- However, sometimes, opioid withdrawal does not initially improve, or may worsen with the first dose of buprenorphine.

  Potential contributing factors:
  - Overestimation of withdrawal severity (e.g. due to other co-occurring condition – anxiety disorder, stimulant toxicity, other substance withdrawal, acute viral illness, etc.).
  - Mixed opioid use (particularly with street opioids, “heroin” may be a mixture of heroin, fentanyl, methadone, etc.)
  - Very high opioid tolerance (consider with regular fentanyl use).
  - Inaccurate history
  - Incorrect buprenorphine administration method

Complicated ED Buprenorphine Induction Management

- Begin with an effective dose of buprenorphine.
  - If no contraindication, usually begin with 8mg SL
- If worsening, or not improving at 30 minutes, *repeat the dose*.
- *Repeat the dose again* as necessary.
- Review Differential Dx (something missing?)
- Anticipatory guidance/patient education very helpful!
  - Advise the patient before the first dose that if symptoms worsen, may need to repeat buprenorphine (preferably promptly).
  - If not informed in advance, the patient may be fearful or reluctant to take another dose of buprenorphine.

ED Buprenorphine Initiation

If patient is not currently in opioid withdrawal or recent naloxone reversal (not in naloxone precipitated withdrawal):

- Consider unobserved home induction
  - Prescribe up to 12 mg day on day one*
    - *Official FDA guideline for patients prescribed buprenorphine new to the medication.
    - Many will be experienced with buprenorphine, and may begin/resume at 16mg day one.
    - Some experienced with buprenorphine may want to resume a lower dose which was effective for them in the past.
    - Some patients with OUD, who use lower doses of opioids, may need less than 12-16mg/day.
  - The majority of ED patients should be prescribed up to 16 mg daily until follow-up appointment.

Photo by: Wouterhagens

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Initiating Buprenorphine in the ED

If patient is not currently in opioid withdrawal or recent naloxone reversal:

- Provide instructions:
  - Key instruction is to wait at least 12 hours since last opioid usage to avoid precipitating withdrawal.
    - Stress the importance of this delay.
  - May help to designate a time on the clock for the patient.

Photo by: Wouterhagens

PROVIDE INSTRUCTIONS FOR STARTING BUPRENORPHINE AT HOME

Initiating Buprenorphine at Home

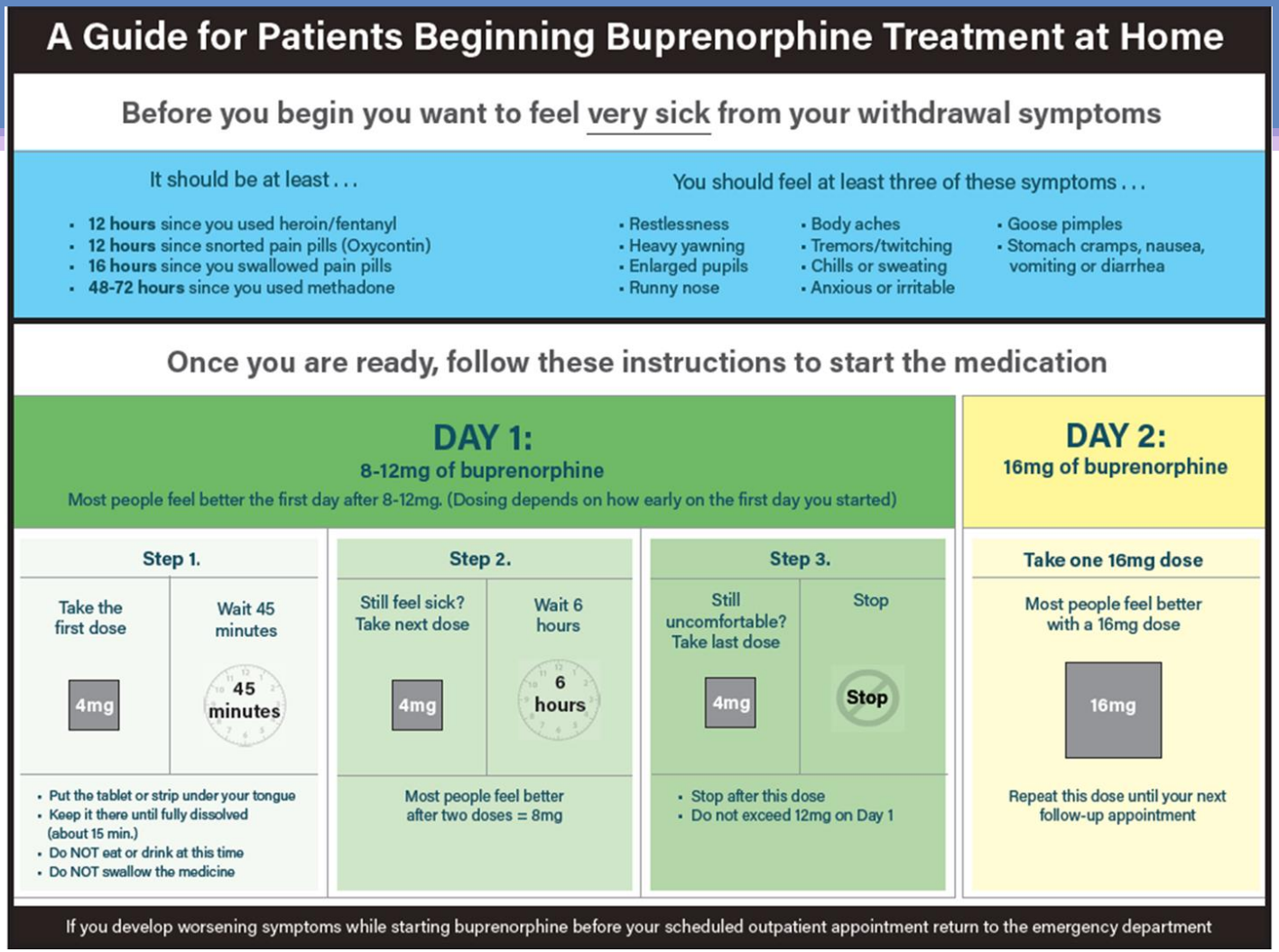
- Observed and home induction have similar safety and efficacy outcomes
- In 2007, 42% of primary care doctors primarily used unobserved induction
- 50% of patients in the original ED trial of buprenorphine initiation received unobserved home induction
- Traditional Process:
  - Educate patient about buprenorphine pharmacology and absorption
  - Review withdrawal symptoms and instruct patient to:
    - Assess withdrawal symptoms
    - Self administer 4 mg buprenorphine when feeling “very sick” (maybe safer to set the clock)
    - Assess after first 4mg use: If still with symptoms and not feeling worse, self administer another 4 mg dose
      - (Although if patient precipitates withdrawal -- may advise not to delay the next 4mg).
    - Repeat until a maximum of 12mg the first day

Lee et al, 2009; D’Onofrio et al, 2015

Initiating Buprenorphine at Home

- However, for patients experienced with buprenorphine:
  - (Many ED patients are familiar with buprenorphine, from either previous prescription treatment or from self-managing their OUD with illicitly gained buprenorphine)
    - In addition to advising a clock time, assess withdrawal symptoms.
    - At the designated time, if the patient is feeling at least moderately ill (but before the patient develops significant nausea), begin the first 4mg (as per the previous slide).
    - Or resume the previous dosing schedule which was effective for the patient previously.

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

It should be at least . . .

- **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

You should feel at least three of these symptoms . . .

- 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

Once you are ready, follow these instructions to start the medication

DAY 1:
8-12mg of buprenorphine

Most people feel better the first day after 8-12mg. (Dosing depends on how early on the first day you started)

Step 1.

Take the first dose — 4mg

Wait 45 minutes — 45 minutes

- 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

Step 2.

Still feel sick? Take next dose — 4mg

Wait 6 hours — 6 hours

Most people feel better after two doses = 8mg

Step 3.

Still uncomfortable? Take last dose — 4mg

Stop — Stop

- Stop after this dose
- Do not exceed 12mg on Day 1

DAY 2:
16mg of buprenorphine

Take one 16mg dose

Most people feel better with a 16mg dose

16mg

Repeat this dose until your next follow-up appointment

If you develop worsening symptoms while starting buprenorphine before your scheduled outpatient appointment return to the emergency department

https://medicine.yale.edu/edbup/

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PROVIDE HARM REDUCTION AND OVERDOSE PREVENTION COUNSELING

Opioid Overdose Prevention Education

- Capitalize on the opportunity to provide education on overdose prevention and treatment to all patients who are at risk for experiencing or witnessing an opioid overdose, including those who are initiating treatment for OUD.

Surgeon General's Advisory on Naloxone and Opioid Overdose

I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, ***knowing how to use naloxone and keeping it within reach can save a life.***

BE PREPARED. GET NALOXONE. SAVE A LIFE.

www.surgeongeneral.gov/

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Take Home Naloxone

- Some EDs have naloxone to distribute to patients, friends & families of those at risk for overdose
  - often grant funded or through local DPH
- Prescription is another model, but filling can be problematic
- Non-judgemental conversations, including those focused on harm reduction, can go a long way to establishing a therapeutic relationship (and increasing patient willingness to discuss treatment for OUD)

Opioid Overdose

- 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
- Treatment:
  - Naloxone:
    - NARCAN® Nasal Spray
    - EVIZIO® prefilled auto-injection device
    - Generic Injectable products for nasal atomizer, intravenous, intramuscular, or subcutaneous use

SAMHSA, 2018

PROVIDE REFERRAL TO ONGOING TREATMENT

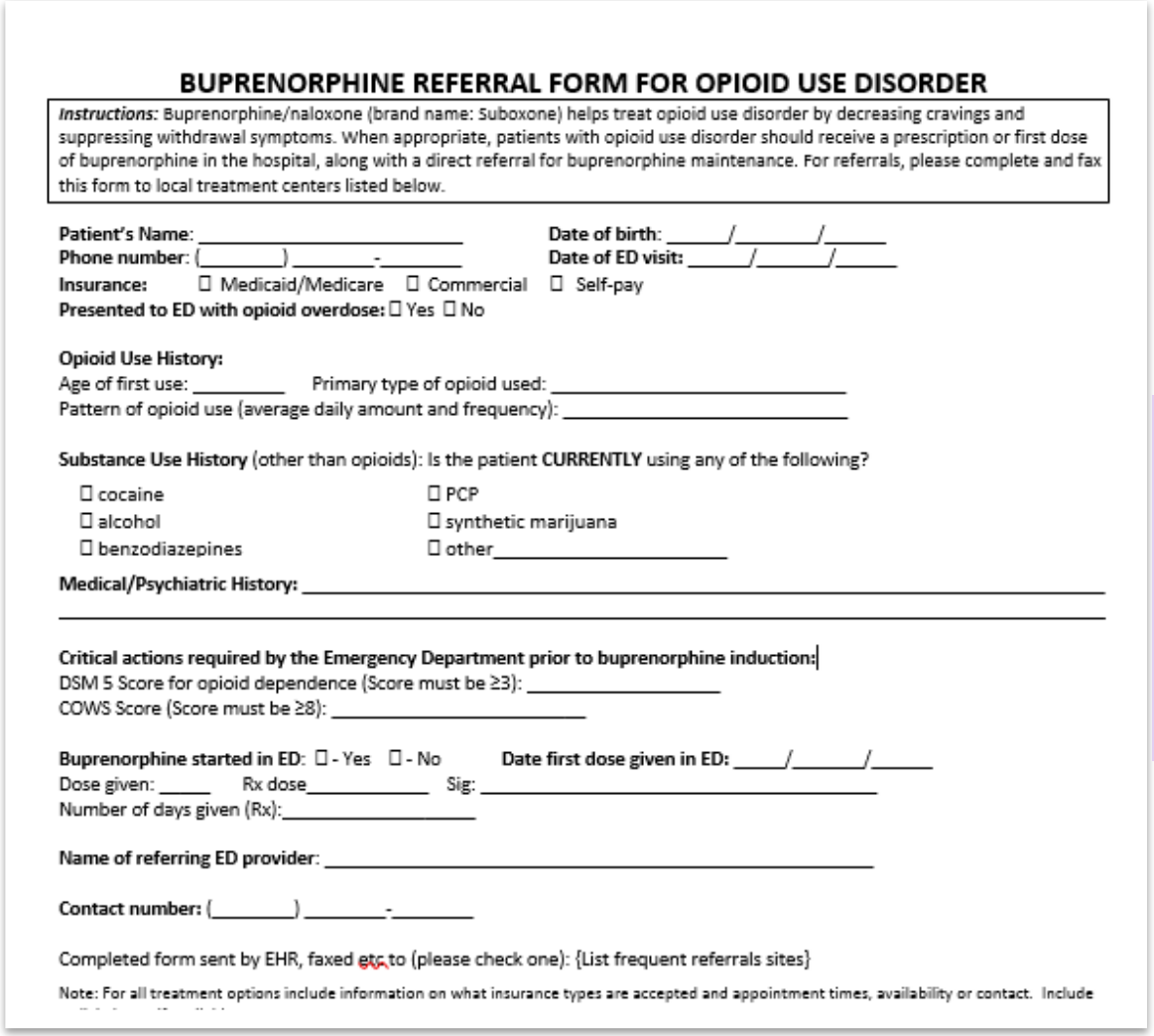
Standardize the Referral Process

- Establish clear follow-up agreements with community sites to ensure a direct linkage
  - Including date, time and place or a commitment to a walk-in policy
- Discuss expectations with the patient
  - That he/she may need to wait for several hours
  - They should expect to receive medication and a prescription that day
  - That the dose or medication type may be moderated based on

Standardize the Referral Process

- Arrange communication strategy with each provider regarding notification method, such as EHR fax, phone call and what information should be available.
- Common data elements to include in the referral, if requested by community treatment provider (some info may be collected at initial visit):
  - Patient identifiers (Name/DOB)
  - Insurance
  - Co-occurring SUD, mental heath and medical diagnoses
  - ED management – including dose of buprenorphine given in ED and prescribed (including dose & quantity)
  - Patient contact information (Be sure that phone numbers are correct in the EHR)
  - Testing information completed
  - Plan for patient follow-up, date and time

Standardized Referral Process Can Improve Communication and Follow Up Attendance



BUPRENORPHINE REFERRAL FORM FOR OPIOID USE DISORDER

Instructions: Buprenorphine/naloxone (brand name: Suboxone) helps treat opioid use disorder by decreasing cravings and suppressing withdrawal symptoms. When appropriate, patients with opioid use disorder should receive a prescription or first dose of buprenorphine in the hospital, along with a direct referral for buprenorphine maintenance. For referrals, please complete and fax this form to local treatment centers listed below.

Patient's Name: _____ **Date of birth:** _____/_____/_____
Phone number: (_____) _____-_____ **Date of ED visit:** _____/_____/_____
Insurance: ☐ Medicaid/Medicare ☐ Commercial ☐ Self-pay
Presented to ED with opioid overdose: ☐ Yes ☐ No

Opioid Use History:
Age of first use: _____ Primary type of opioid used: _____
Pattern of opioid use (average daily amount and frequency): _____

Substance Use History (other than opioids): Is the patient **CURRENTLY** using any of the following?

☐ cocaine ☐ PCP
☐ alcohol ☐ synthetic marijuana
☐ benzodiazepines ☐ other_____

Medical/Psychiatric History: _____
_____

Critical actions required by the Emergency Department prior to buprenorphine induction:
DSM 5 Score for opioid dependence (Score must be ≥3): _____
COWS Score (Score must be ≥8): _____

Buprenorphine started in ED: ☐ - Yes ☐ - No **Date first dose given in ED:** _____/_____/_____
Dose given: _____ Rx dose_____ Sig: _____
Number of days given (Rx):_____

Name of referring ED provider: _____

Contact number: (_____) _____-_____

Completed form sent by EHR, faxed etc to (please check one): {List frequent referrals sites}

Note: For all treatment options include information on what insurance types are accepted and appointment times, availability or contact. Include

Buprenorphine referral form

(optional)

Standardized forms can include referral criteria for multiple sites, drop in/office hours, directions for placing referral with each outpatient site, additional resources.

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Feedback and Quality Improvement

- ED-initiated buprenorphine depends on successful implementation strategies
- ED providers often see only the treatment failures
- Arranging a feedback process so that providers know if a referred patient is in treatment is very satisfying and promotes further treatment and referral
- A quality improvement project that assesses the treatment and referral processes of patients presenting with OUD is helpful if shared with the providers
- Developing critical actions and their evaluations are essential

ED-Buprenorphine Initiation Review

- Assess for opioid use disorder
- Assess for withdrawal symptoms
- Administer first dose 4-8 mg SL buprenorphine/naloxone if appropriate
  - Relief of opioid withdrawal symptoms should begin within 20-45 minutes after the first dose.
  - Consider other diagnoses if you do not see some relief of withdrawal symptoms after 8 mg.
    - However, some patients will need additional buprenorphine (vomited or swallowed first dose, severe withdrawal, very high tolerance, etc.)
- Provide prescription and instructions for home initiation if patient not in sufficient withdrawal at the time of the ED visit
- Arrange for warm handoff is essential for to optimize success (an ED navigator is ideal).
- All patients with OUD should receive overdose education and naloxone

Office Based Buprenorphine Initiation (for those who still do this)

- Similar to ED- initiation with regard to
  - Patient selection (moderate/severe OUD)
  - Need for withdrawal prior to medication initiation (COWS >8)
  - Need for X-waiver to prescribe
  - Need to establish clear follow-up plan

Office-Based Buprenorphine Initiation (for those who still do this)

Key Differences:

- Consideration of office based workflow and hours
  - Some offices prefer initiations earlier in the week – and avoid Fridays
  - If doing office based initiation, consider scheduling earlier in the day
- Set expectations for ongoing care with patient, including urine toxicology testing
- Traditionally started with lower dosing 2-4 mg and titrated up
- For office based initiation, patient fills prescription and brings medication to the office where it will be administered
- Home/unobserved initiation is increasingly the norm.

More resources: www.pcssNOW.org

Lee et al, 2009

SPECIAL CONSIDERATIONS: ADOLESCENTS AND PREGNANCY

Adolescents

- Age:
  - DATA 2000 authorizes treatment of individuals age 16 and older
    - Buprenorphine is approved for individuals **at least** 16 years of age
    - Methadone is approved for individuals **at least** 18 years of age
  - 42 CFR § 8.12 – offers an exception for methadone in patients aged 16 and 17 who have a documented history of:
    - At least two prior unsuccessful withdrawal management attempts and have parental consent
  - Age of consent for medication varies from state to state:
    - Be familiar with the relevant state statutes
- Pregnancy:
  - Recommended to assess ALL female adolescent patients prior to starting buprenorphine to discuss treatment options

CFR 42, 2017
DATA, 2000

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Adolescents

- ***American Academy of Pediatrics***:
  - Recommends that pediatricians consider offering MOUD to their adolescent and young adult patients with severe opioid use disorders or discuss referrals to other providers for this service

- ***FDA Approved Medication Options:***
  - Buprenorphine (approved for patients>16yo)
    - Often considered to be the first choice
    - Significantly decreased use of opioids and cocaine
    - Much better treatment retention in comparison to no medication
    - Decreased injecting
    - Decreased need for additional treatment while on medication
  - Methadone
  - Naltrexone ER (approved for patients>18yo)

- ***Psychosocial Treatment Options:***
  - Family Intervention Approaches
  - Vocational support
  - Behavioral interventions

If state law allows, if appropriate, may initiate buprenorphine Tx for OUD for adolescents in the ED.

AAP, 2016; Fishman et al., 2010; Kampman et al., 2015; Woody et al., 2008

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Opioid Use Disorder and Pregnancy

- Epidemiology:
  - ~21,000 pregnant women aged 15 to 44 misused opioids in the past month
  - Prevalence of opioid use among women who gave birth increased in the United States from:
    - 1.19 to 5.63 per 1,000 hospital births per year between 2000 and 2009
- American College of Obstetrics and Gynecology (ACOG) and ASAM:
  - Recommends screening for substance use as part of comprehensive obstetric care and should be done at first prenatal visit
- Key point for the ED: Opioid withdrawal → fetal distress and ↑ risks of complications. Do not delay treating opioid withdrawal in pregnant patients.
- Patients can be maintained on buprenorphine or switched to methadone.

ACOG/ASAM 2017

Use of Buprenorphine With or Without Naloxone in the Pregnant Patient

- Buprenorphine/Naloxone:
  - The FDA labels naloxone as Pregnancy Category B (however the combination of buprenorphine-naloxone is Category C):
    - No known teratogenic effects in animals, however,
    - Controlled studies have not been conducted in humans
  - Increasing evidence that Buprenorphine/Naloxone may be safe in pregnancy
  - However, Buprenorphine *without* naloxone is still recommended for pregnant, opioid-dependent women, as the first option.
  - Misuse of Buprenorphine mono-product may be an indication for Bup/Nx in pregnancy.

- Mother can breastfeed while taking buprenorphine or methadone.

Lund et al., 2013

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Opioid Withdrawal Management

Objectives

1. List typical opioid withdrawal signs and symptoms
2. List non-opioid treatments for opioid withdrawal
3. Describe the limitations of non-opioid treatments for opioid withdrawal
4. Recognize the value of opioid agonists in the treatment of opioid withdrawal
5. Describe strategies for managing naloxone-precipitated withdrawal
6. Describe strategies for managing buprenorphine-precipitated withdrawal

Opioid Withdrawal

Typical opioid withdrawal case

- 28 y/o female, no significant past medical history, visiting from out of town
- Admits to daily fentanyl use (“a lot”)
- Presents 1 day after last fentanyl use in severe acute opioid withdrawal, with severe body aches, restlessness, vomiting, and diarrhea

Opioid Withdrawal

Typical opioid withdrawal case

- 4 IV start attempts over 30 minutes
- Substantial verbal conflict with nurses and other staff
- Over 12 hours in the ED:
  - Ondansetron 8mg IV x2: 16mg IV total
  - Promethazine 25mg IVPB x2: 50mg IV total
  - Clonidine 0.2mg PO x 4 doses: 0.8mg PO
  - Lorazepam 2mg IV x 3 doses: 6mg IV
  - Haloperidol 5mg IV x 2 doses: 10mg IV
  - Normal Saline 2 liters IV
- Eventually discharged with promethazine and clonidine prescriptions

Opioid Withdrawal

Typical opioid withdrawal case

- Returns the next day with severe body aches, restlessness, vomiting, diarrhea. Now she is also intermittently drowsy and lightheaded/pre-syncopal.
- After multiple IV attempts:
  - Ondansetron 8mg IV x1: 8mg IV
  - Promethazine 25mg IVPB x2: 50mg IV
  - Clonidine 0.2mg PO x 3 doses: 0.6mg PO
  - Lorazepam 2mg IV x 3 doses: 6mg IV
  - Haloperidol 5mg IV x 1 doses: 5mg IV
  - Ketamine 10mg IV (0.2mg/kg) x 2 doses: 20mg IV
  - Normal Saline 3 liters IV
- After 8 hours in the ED, again discharged with promethazine and clonidine prescriptions

Opioid Withdrawal

Typical opioid withdrawal case

- Returns the next day, this is visit #3 in 3 days
- Severe body aches, restlessness, vomiting and diarrhea
- Very emotionally distraught, demanding IV fluids and medications
- The nursing staff are frustrated and exasperated before even attempting the first IV start.

What now?

Opioid Withdrawal

As discussed in the neurobiology section, because of the broad distribution of mu receptors in the CNS, GI tract, dermis, etc., multiple systems are affected:

diffuse pain, myalgias, arthralgias, vomiting, diarrhea, abdominal cramping

… along with a severe **hyperalgesia**, which makes the IV attempt so difficult to tolerate.

Opioid Withdrawal

Further exacerbating the physiologic manifestations are the potentially severe emotional symptoms of:

- Anxiety
- Irritability
- Restlessness
- Agitation
- Dysphoria
- Depression
- Hopelessness

Opioid Withdrawal

Autonomic dysfunction:

- Sweating
- Tremor
- ↑HR/BP
- Rhinorrhea
- Lacrimation
  Mydriasis
- Yawning
- Piloerection

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Opioid Withdrawal

Opioid withdrawal as "Hell on Earth."

Lay press patient quotes:

- "It feels like the worst flu you ever had, the sickest you've ever been, at times suicidal thoughts and complete and total confidence that you are never, ever, ever going to feel better."
- "For days, I shook uncontrollably. I sweat through my sheets."
- "I wanted to tear my hair out of my skull and scratch the skin off off my body."
- "It feels like the day your wife left, and your kitten died, and there were no more rainbows anywhere, and never will be again."

Cosmopolitan Magazine
Vice Magazine

Opioid Withdrawal

Non-opioid treatments:

Dysautonomia/Anxiety: clonidine (or dexmedetomidine or lofexidine)

Pain: NSAIDs, acetaminophen, gabapentin, baclofen, tizanidine

GI distress: ondansetron, phenothiazines, antihistamines, loperamide, dicyclomine, octreotide

Agitation: antipsychotics, ketamine.
Benzodiazepines are often used, but should be avoided.

These all should be considered “adjuncts” now.

Opioid Withdrawal

Non-opioid treatments of opioid withdrawal do not address the underlying problem and are therefore relatively **ineffective.**

Because non-opioid treatments of opioid withdrawal are relatively ineffective, the patient's ED course is often **difficult** and **protracted.**

Opioid Withdrawal

Non-opioid treatments do not address **cravings** and **dysphoria**, which leave the patient much more vulnerable to self-treating with street drugs, which are more lethal than ever before.

Treating withdrawal with non-opioids misses the opportunity to **move the patient to recovery** with **MOUD**

Opioid Withdrawal

Opioid withdrawal treatment with **methadone**

- 10 mg IM or 20 mg PO will suppress physical withdrawal symptoms regardless of maintenance dose
- Cannot be prescribed by emergency providers (for OUD) but can be administered in the ED
- Potential full agonist disadvantages: respiratory depression, potential for misuse

Opioid Withdrawal

Opioid withdrawal treatment with **buprenorphine**

- Partial agonist + high receptor affinity = much less likely to cause respiratory depression and blocks activity of other opioids.
- Administered sublingually. No IV required.
- Relief may begin in ~ 15 minutes. If no relief beginning at 30 minutes, may administer a 2nd dose.
- Usually complete abatement of withdrawal symptoms can be achieved in 45-60 minutes.
- **Additional medications, "adjuncts," are rarely needed.**

Case Resolution

- On third visit, our patient was treated with ondansetron 8mg ODT and buprenorphine 8 mg SL. After 30 minutes had only mild improvement. Another 8 mg was given, and 30 minutes later had complete resolution of symptoms.
- She was then comfortable for the first time in days and was able to have a very engaged conversation about starting treatment with buprenorphine.
- Discharged with buprenorphine prescription and arranged follow up with outpatient addiction treatment.
- Thirty days later, the patient was still in outpatient treatment, and in recovery.

Case Resolution

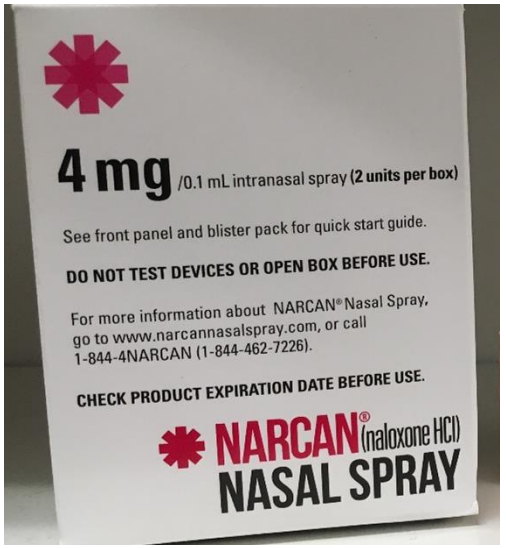
The patient's interaction with the nursing staff was no longer antagonistic.

No IV was necessary, ED visit 2 hours including discussion with a peer recovery coach/addiction counselor/social worker.

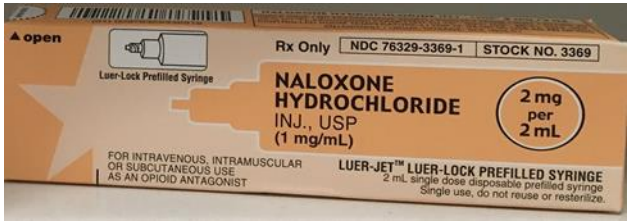
Naloxone Precipitated Withdrawal (NPW)

Can be severe, particularly if an overdose is reversed with a large dose of naloxone:

- Cartridge actuated nasal spray, which delivers a fixed dose of **4mg.**
- Standard 2mg dose – common Fire/BLS kit



Usually relatively short-lived -- less than 2 hours (limited by half-life of naloxone).

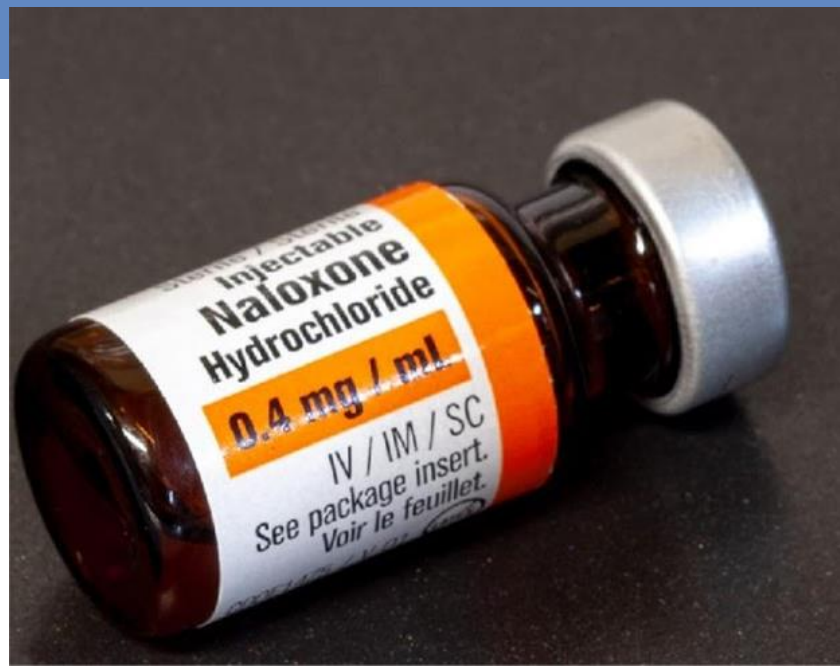


However, depending on the underlying opioid (and other substances), dangerous opioid intoxication may return after naloxone is metabolized.

Naloxone Precipitated Withdrawal (NPW)

When possible (in the ED or an ALS environment), safer to gently resuscitate the patient, to avoid NPW, to avoid the patient leaving AMA, etc.

But how best to treat NPW?



Whenever possible, identify which opioid the patient overdosed on. Short acting? Oxycodone? Heroin?

Is the patient on other long-acting opioids?

Is the patient in a methadone treatment program?

Naloxone Precipitated Withdrawal (NPW)

Treating NPW with traditional adjuncts (e.g. clonidine, anti-emetics, etc.) with observation until naloxone metabolized is always an option.

However, adjunctive treatment does not move the patient toward effective OUD treatment.

Treatment of NPW from short half-life opioids (heroin, oxycodone) not well studied, but the limited data (consistent with the experience of most experts) suggests buprenorphine is effective.

Once withdrawal symptoms abate, patient able to discuss continuing ongoing treatment with buprenorphine after leaving the ED.

Jain, K, 2011
Zamani M, 2015
Herring A. 2019

Naloxone Precipitated Withdrawal (NPW)

Notes of Caution:

- Recommend informed consent of patient:
  - Patients in moderate to severe NPW may consent more readily.
  - Some patients with OUD have intense fear of buprenorphine.
- May need higher doses of buprenorphine than when treating usual opioid withdrawal:
  - Must overcome naloxone – which has a high mu receptor binding affinity.
- Recommend observation through duration of naloxone (~ 2 hours), and peak of buprenorphine (~ 1 hour).

Naloxone Precipitated Withdrawal (NPW)

Notes of Caution:

- If patient intends to continue chronic treatment with long half-life opioids (e.g. pt will maintain treatment in methadone clinic):
  - Safer to treat NPW with traditional adjunctive treatment (e.g. clonidine, anti-emetics, etc.), and observe pt until naloxone metabolized, and methadone peaks
  - Treating NPW from long-half opioids, may require multiple doses of buprenorphine to abate NPW symptoms:
  - Recommend a longer observation period
  - Must watch for respiratory depression until last dose of buprenorphine has peaked in effect

Buprenorphine after Naloxone

Naloxone rescue from overdose, but without NPW:

- Again, with gentle administration, patients can be rescued from an opioid overdose, without precipitating withdrawal.

- Opportunity for discussion about starting treatment with buprenorphine.

- Patient may be candidate for buprenorphine home induction.

Buprenorphine Precipitated Withdrawal (BPW)

As buprenorphine, due to its high mu receptor affinity, competes at the mu receptors with other opioids (which had been occupying those receptors), and overall receptor binding decreases, withdrawal symptoms develop.

[The reason to wait for the patient to enter opioid withdrawal naturally is to avoid BPW]

As the effects of buprenorphine are relatively rapid, BPW can develop quickly – over several minutes, can be severe, and can last for several hours (longer than NPW).

It is the experience of BPW, and the fear of BPW, which keeps some patients with OUD from trying buprenorphine treatment.

BPW is better avoided than treated.

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Buprenorphine Precipitated Withdrawal (BPW)

The best strategy for treatment of BPW is **additional dosing of buprenorphine** as higher levels of buprenorphine, with its high mu receptor binding affinity, will displace lower affinity opioids, and saturate the receptors.

May require rapidly escalating buprenorphine doses (4 > 8 > 16 mg or more.)

Buprenorphine's partial agonist effect, limits respiratory depression during the process.

If additional buprenorphine dosing is not desired, or is ineffective, may require aggressive treatment with adjunctive medications, including sedating non-opioids.

Summary

- Opioid withdrawal syndrome is an extremely debilitating condition that can cause severe somatic and emotional symptoms.
- Non-opioid treatments of opioid withdrawal can improve symptoms but are comparatively ineffective and do not address the underlying cravings that will cause patients to continue to use opioids.
- Opioid agonist treatment of opioid withdrawal is effective and also offers the opportunity to move opioid misuse patients to recovery with medication-assisted therapy.

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Pain Management for Patients with OUD

Objectives

For patients taking buprenorphine, methadone, and naltrexone:

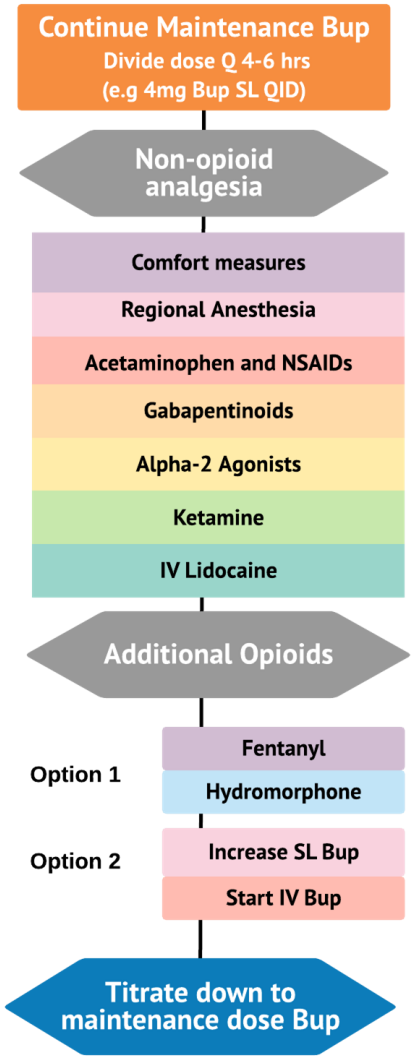
- Describe the principles of:
  - Acute pain management
  - Perioperative pain management
- Understand fundamentals of chronic pain management

ED Acute Pain Management

Just as you would for patients without OUD -- consider the etiology of the acute pain

- If the condition should not usually be treated with opioids (and the patient is not actively in opioid withdrawal) then don't consider an opioid
  - Example: Migraine headache in patient with OUD on methadone or buprenorphine
  - Just as for patients who do not have OUD, migraine headaches should not be treated with opioids

ED Acute Pain Management



Use the column on the left as a guide.

Always consider, as applicable:

- Standard non-opioid treatment, including:
  - Ice, immobilization, and relaxation techniques as appropriate
  - Acetaminophen and NSAIDS
- Alternatives To Opioids ("ALTO"), such as:
  - Trigger point injections
  - Lidocaine IV and lidocaine patches
  - Gabapentinoids
  - Regional nerve blocks (e.g. for rib fractures)
  - Hematoma blocks

Liu B, 2017

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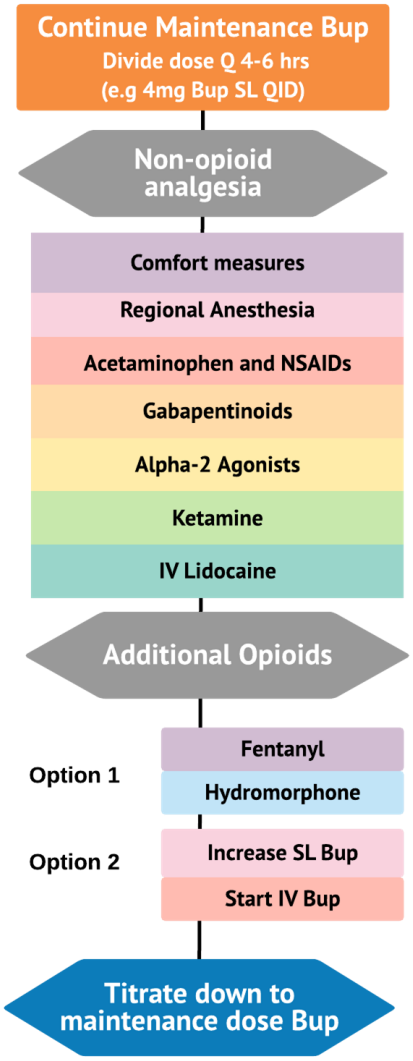
ED Acute Pain Management



Continuing with the column on the left:

More advanced regional nerve blocks:

- Serratus Anterior plane block
- Femoral nerve block
- Fascia Iliaca block

Sub-dissociative ketamine

IV push doses

Continuous IV infusions (drips)

Alpha-2 Adrenoceptor agonists:

- Clonidine
- Dexmedetomidine

Khalil A, 2017
Khan Z, 1999

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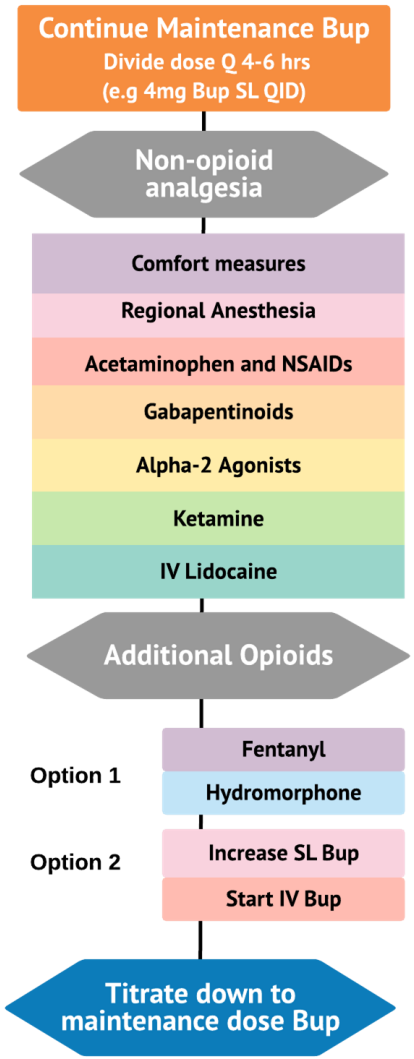
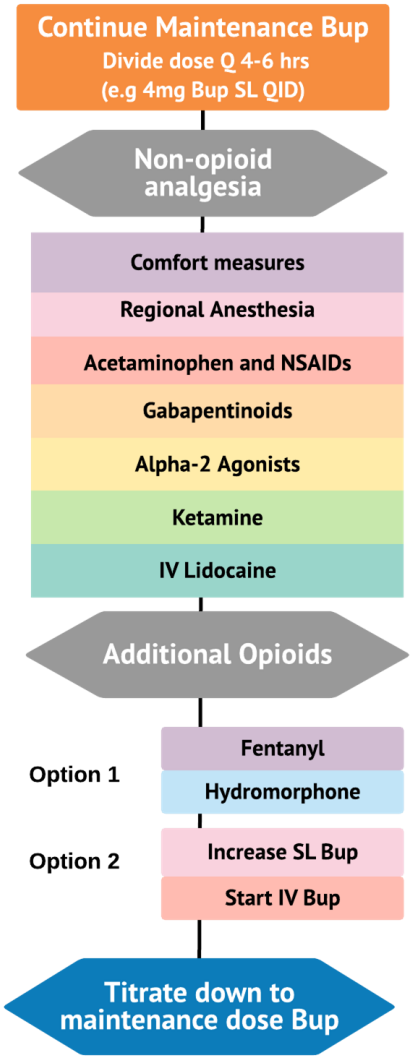
ED Acute Pain Management



Mastering non-opioid techniques of pain management is particularly important in patients on MOUD

- Patients on MOUD have a high opioid tolerance
- Naltrexone has a very high mu receptor binding affinity - pain difficult to treat with most opioids
- Buprenorphine has a high binding affinity – requires strategy with applying additional opioids
- Methadone is long half-life full mu agonist

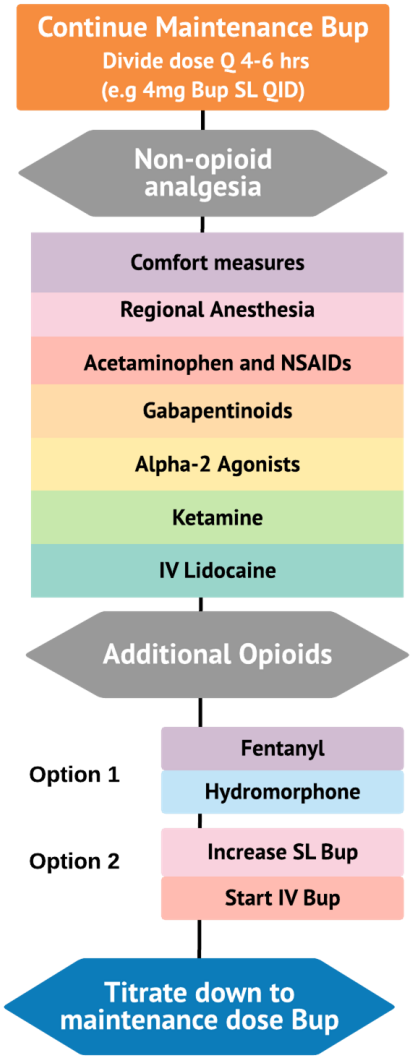
ED Acute Pain Management



Acute pain management for patients on **naltrexone** (particularly depot IM naltrexone):

- Employ all non-opioid techniques
- When it comes necessary to add an opioid, select an opioid with a high mu receptor binding affinity:
  - **Fentanyl:** high affinity, titratable, short-acting (but still may need very high doses to overcome naltrexone
  - **Dilaudid:** higher binding affinity than fentanyl, longer acting (and less titratable)
  - **? Buprenorphine ?**

ED Acute Pain Management

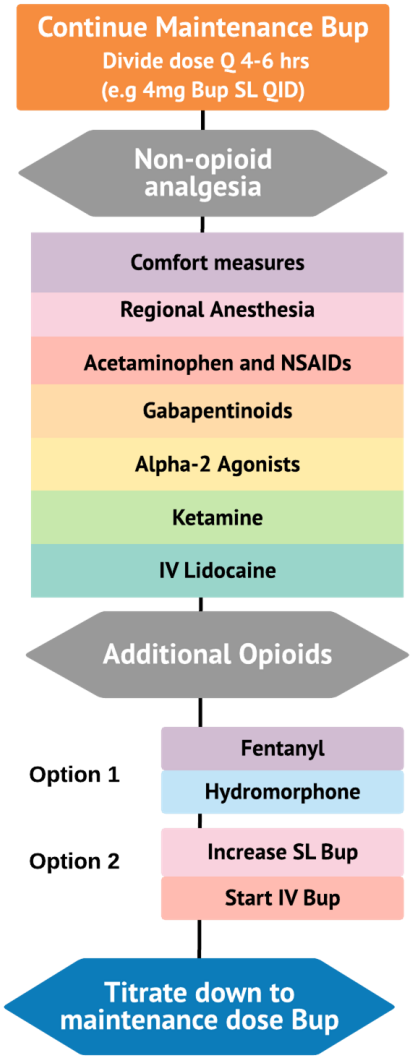


For patients on **Methadone:**

<u>Employ all non-opioid techniques</u>.

- Do NOT administer buprenorphine or butorphanol (“Stadol”) – both are high affinity partial agonists – may precipitate withdrawal
- For sustained pain relief, to reduce the need for additional opioids, adjust/divide methadone dosing to TID or BID
  - Methadone has a short half-life as an analgesic (~ 8 hours)
- May add other full mu agonists (temporarily)
- May increase total daily methadone dose (gradually)
- May want to consult an expert

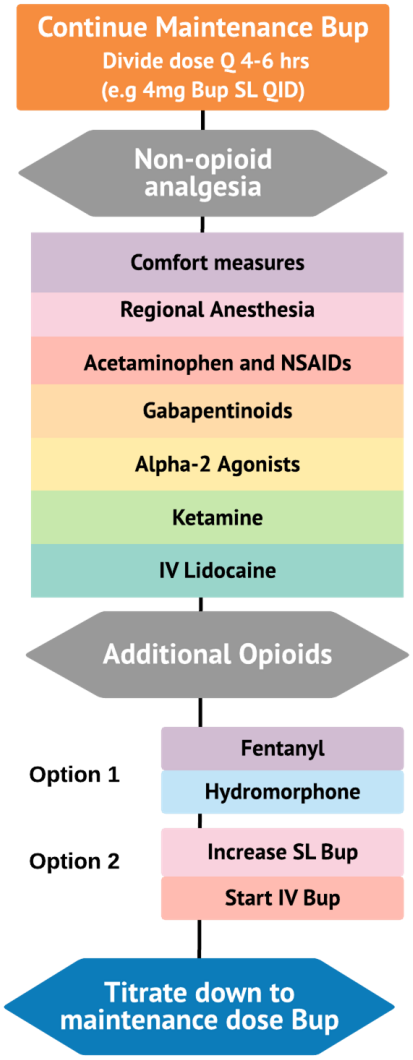
ED Acute Pain Management



Acute pain management for patients on **buprenorphine**:

- Employ non-opioid techniques (as applicable)
- First adjust buprenorphine dosing intervals:
- Divide dose to TID or QID if on daily dosing:
  - e.g. adjust 12mg daily to 4mg TID
  - e.g. adjust 16mg daily to 4mg QID
- May increase the dose of buprenorphine temporarily (examples):
  - e.g. increase from 8mg BID to 8mg TID
  - May increase to even shorter intervals (particularly if in the hospital)
  - Consider IV buprenorphine

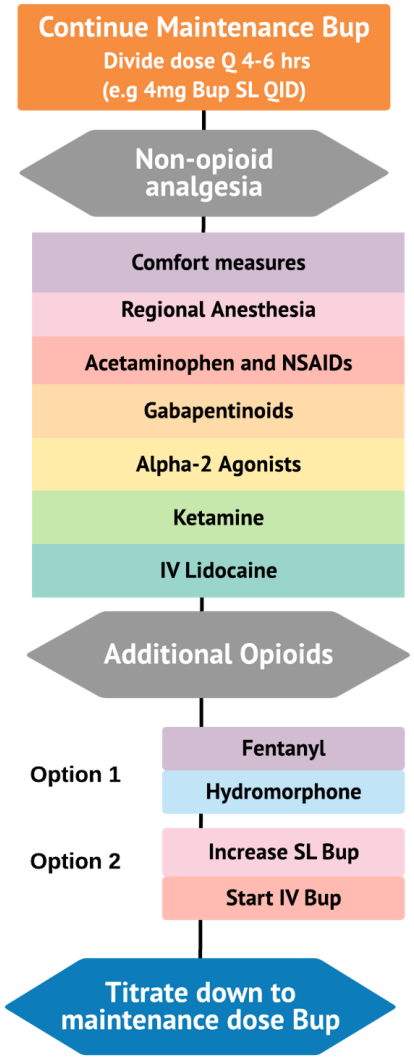
ED Acute Pain Management



Acute pain management for patients on **buprenorphine**:

- Employ all non-opioid techniques.
- When it becomes necessary to add an opioid, as with naltrexone, select an opioid with a high mu receptor binding affinity:
  - **Fentanyl:** high affinity, titratable, short-acting (may need relatively high doses)
  - **Dilaudid:** higher binding affinity than fentanyl, longer acting (and less titratable)

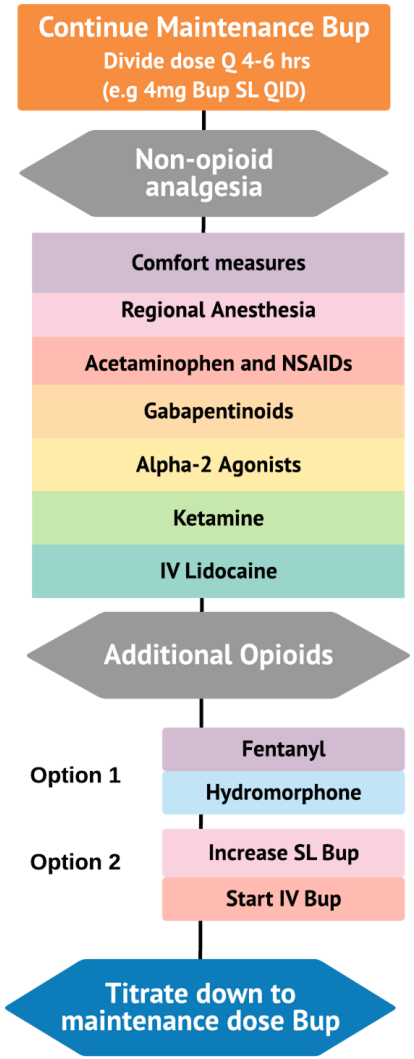
Pre-op Acute Pain Management



- Current evidence does not support the practice of routinely discontinuing Buprenorphine before surgery
- Buprenorphine is a powerful analgesic that can be combined synergistically with other opioids
  - **Buprenorphine onboard first, and maintained**

Harrison, T., 2018.
Quaye, A., 2018
Lembke, A., 2018

Buprenorphine for Acute & Chronic Pain Management



- Potent Mu agonist analgesic
- Synergistic additive analgesia when combined with full agonist opioids
- Potent anti-hyperalgesia via Kappa antagonism
- Increases Mu opioid receptor expression on the cell surface
- Blocks morphine induced receptor desensitization
- Reduced opioid tolerance
- Longer half-life (6-8 hours IV)
- Ceiling on respiratory depression
- Reduced constipation
- Reduced gonadal suppression
- Reduced immune suppression
- Reduced pancreatic and biliary duct tone

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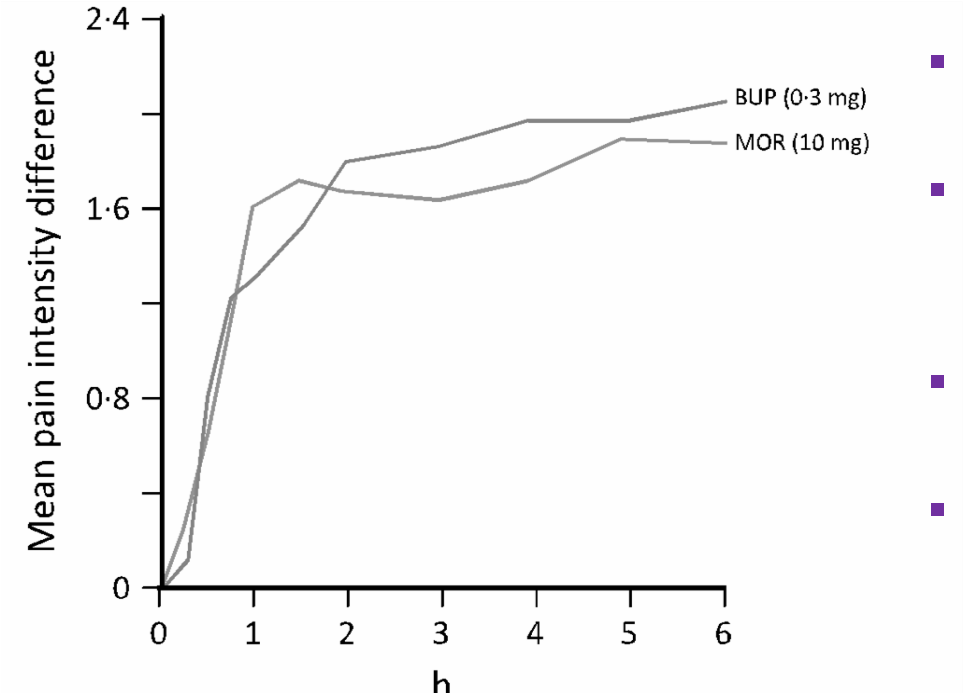
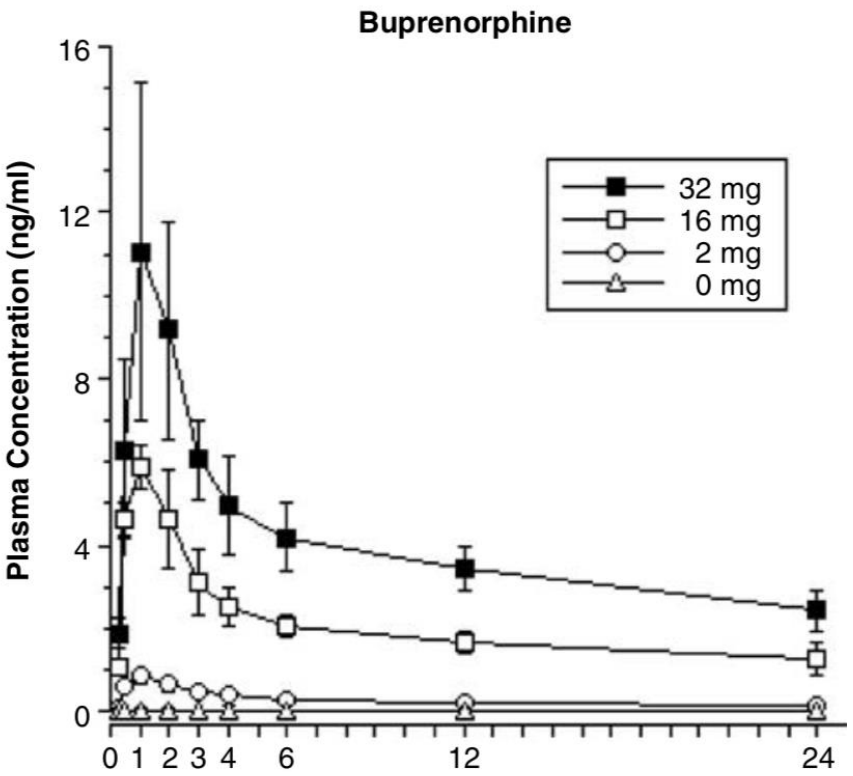
Pain Dosed Buprenorphine



White, L., 2018
Raffa, R., 2014.

- Buprenorphine is **30 to 40 times** more potent than morphine
- Clinically significant analgesia begins at 5-10% receptor occupancy
- Analgesic effect seen over the 0.1 to 10 mg range IV
- Reduced Side effects:
  - Hypotension
  - Respiratory depression
  - Sedation
  - Pruritis

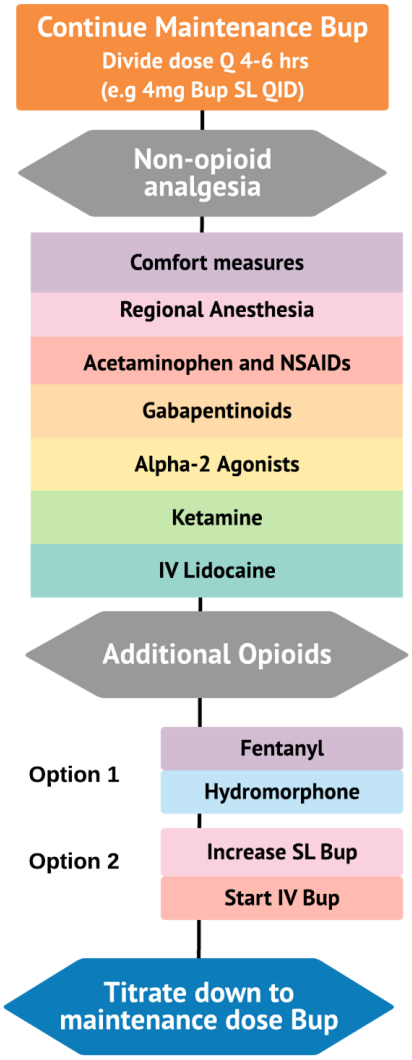
Pain Dosed Buprenorphine



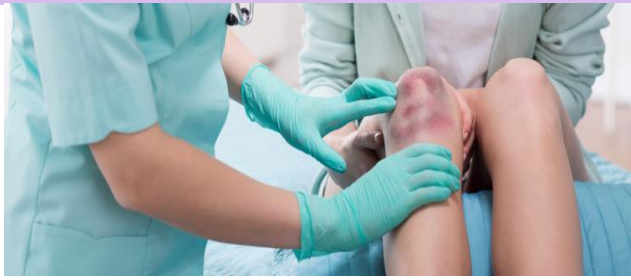
Greenwald, M. 2003

- **Increased frequency** of dosing
- Buprenorphine's analgesic duration is only a few hours
- **Increased total dose**
  - No clinical ceiling on analgesic effect

Acute Pain Management in Buprenorphine Maintained Patients



Recap:



- Use multimodal analgesia:
  - Regional anesthesia
  - Acetaminophen, NSAIDs
  - Ketamine, Magnesium Alpha-2 Agonists—clonidine
  - Gabapentinoids
  - IV lidocaine
- May continue same buprenorphine maintenance dose but add non-opioid analgesics
- May first divide current dose of buprenorphine into more frequent small supplemental doses of sublingual buprenorphine - Buprenorphine's analgesic duration is only a few hours
- May also increase the total daily dose of buprenorphine
- Combine high affinity (fentanyl or hydromorphone) full agonist therapy with maintenance Buprenorphine

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Perioperative Management

- General:
  - Patients fear mistreatment, Providers fear deception
  - Lack of consensus in the field – often based on the preference of the surgical/ anesthesia teams

- Pre-Op:
  - Confirm Multi-Party Consent and Coordination of care with providers
  - In general buprenorphine should not be discontinued. Some clinicians may lower the dose to 8-16mg SL per day in divided doses during the perioperative period

Harrison, T. K. 2018,
Quaye, A., 2018.
Lembke, A, 2018.

Chronic Pain Patients

- Consider consulting a pain medicine specialist
- Consider Multidisciplinary Team Approach
- Try non-opioid and adjuvant analgesics
- Consider non-pharmacologic therapies
- For patients maintained on chronic opioids, consider transition to buprenorphine:
  - Safer
  - Fewer adverse effects than other opioids

Summary

- Patients with OUD treated with naltrexone, buprenorphine, and methadone, each present different challenges and opportunities for acute pain management
- Emergency physicians should develop a competency with multiple forms of non-opioid acute pain management techniques, nerve blocks, and non-opioid forms of analgesia
- Peri-operative pain management practices for patients with OUD are variable and require close coordination with surgical team
- Patients on buprenorphine can be maintained on buprenorphine through acute pain management, including peri-operative management

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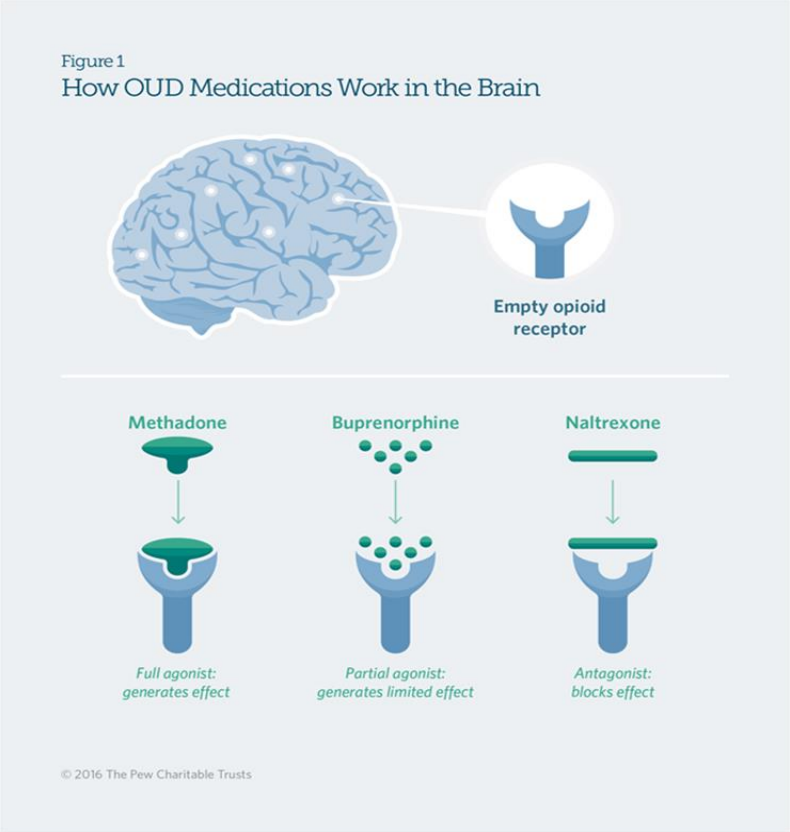
PCSS Providers Clinical Support System

Methadone and Naltrexone

Objectives

1. Contrast the pharmacologic features of methadone and naltrexone
2. Describe the efficacy and adverse side-effects of methadone and naltrexone
3. Identify substances with potentially dangerous interactions with methadone and naltrexone
4. Differentiate patient selection criteria for methadone vs. naltrexone
5. Apply dosing models of methadone and naltrexone
6. Recognize how methadone treatment is disconnected from state PDMP reporting

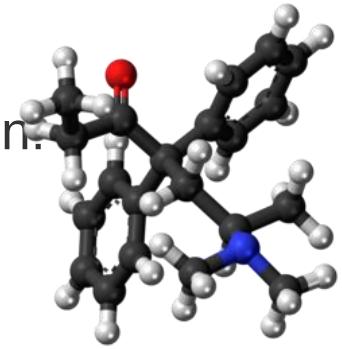
Methadone and Naltrexone



Methadone and Naltrexone

Methadone

- Synthetic opioid that occurs in R- and S-enantiomeric forms with *all its activity due to R-methadone*
- Discovered in 1937 (Germany). Received FDA approval in:
  - 1947 for treating pain and coughing
  - 1970 for medically supervised withdrawal ("Detoxification")
  - 1973 for maintenance therapy



- Metabolized in the liver and by intestinal cytochrome: CYP3A4
- Most methadone is ultimately excreted into the biliary tract, but small fractions enter the urine and are detectable in urine drug tests
- Oral bioavailability when swallowed: 36% -100%

CSAT, 2005

Major Features of Methadone

***Full Agonist* at mu receptor**

Long acting

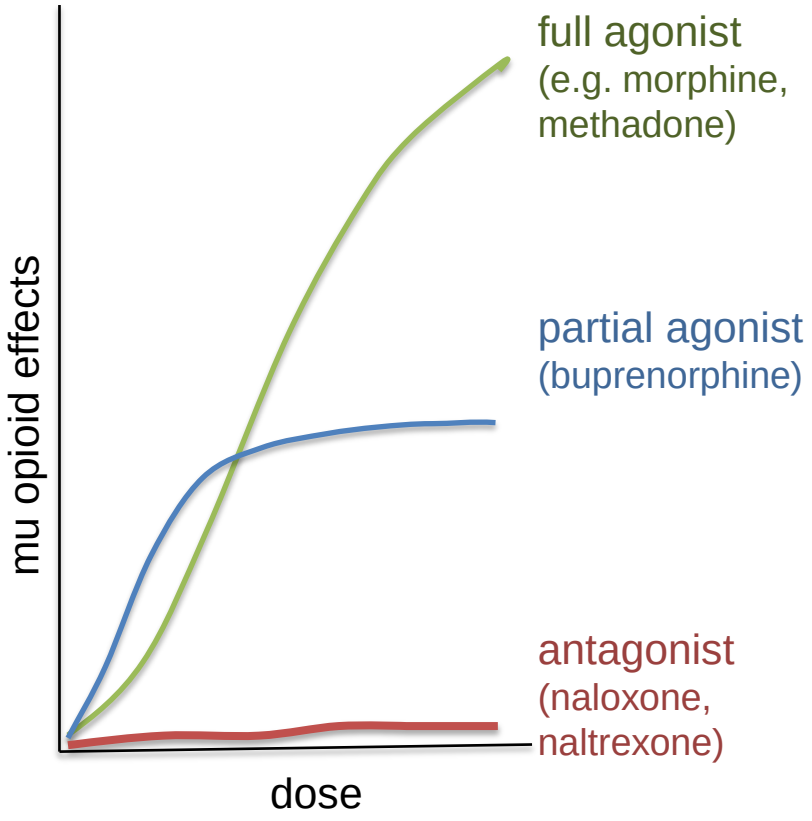
- Half-life ~ 15-60 Hours (avg ~ 24 hrs)

Weak affinity for mu receptor

- *Can be displaced by partial agonists (e,g. burprenorphine) and antagonists (e.g.naloxone, naltrexone),* which can both precipitate withdrawal

Monitoring

- Significant respiratory suppression and potential respiratory arrest in overdose
- QT prolongation



Methadone

Very Effective Medication for Opioid Use Disorder:

- Methadone can be an effective 1st line treatment.
- However, some regard methadone as 2nd line medication – for patients who fail office-based buprenorphine treatment.
- Nearly all methadone clinics use liquid methadone (to deter diversion).
- Most diverted methadone is in the tablet form (the prescription form).

Methadone

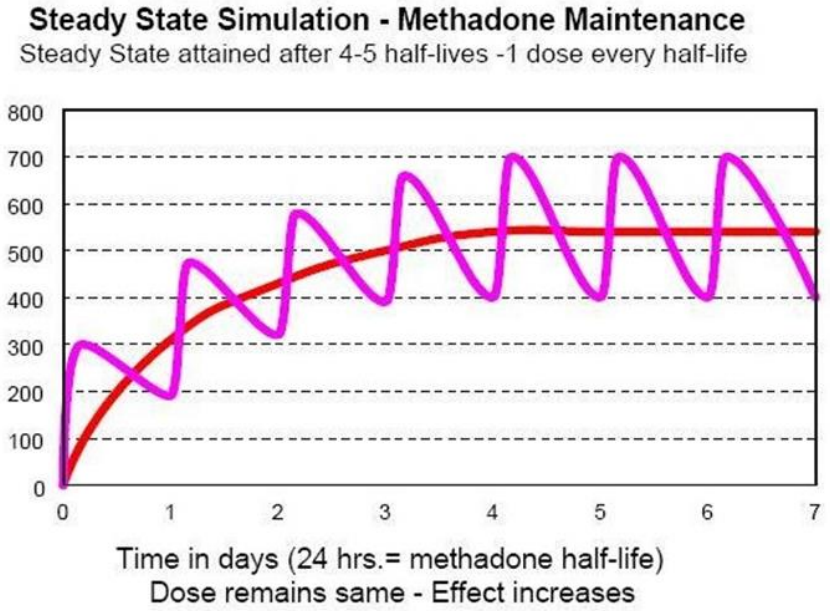
- Methadone is NOT "prescribed" for OUD.
- It is only administered and dispensed in licensed, specialized clinics.

- **The dosing is very patient specific!**
- The dose is gradually adjusted to reach the most effective dose for the individual patient.
- Traditional teaching: "80-120mg/day"
- However:
  - Patients are dosed from <10mg/day to >250mg/day.
  - The vast majority of patients are dosed at <200mg/day.
  - Prior opioid use (heroin, oxy, etc.) daily total volume/dose is the main predictor of therapeutic methadone dose.

Methadone

Methadone Is Effective When Patients Dose Consistently, And Maintain A Steady State

- The daily dose is gradually titrated up to therapeutic dose for that patient.
- **Highest (and most common) starting dose is 30mg/day**
- **NOT increased by > 10mg/day.**
- Increased slowly for safety!
- Therapeutic dose:
  - Patient is not craving or withdrawing;
  - Patient does not feel sedated, and able to achieve a normal sleep/wake cycle.
- **Titrating too slowly, leads to high rates of patient drop out, and encourages ongoing illicit opioid use.**



In the graph above the wavy line represents the blood levels of methadone as well as the "effect" it has on the individual patient.

PCSS Providers Clinical Support System

Methadone

Well managed clinics have high rates of sobriety.

- HOWEVER:
- Requires daily travel to the clinic.
- May not be available in suburban & rural areas.
- Inconvenient for many occupations -- daily dosing at a clinic.
- Dosing at the methadone clinic means congregating with other patients with OUD.

Methadone

Advantages:

- Provides structure
- On-site medication monitoring, testing
- Behavioral health services

Challenges:

- May require daily travel to the clinic - Inconvenient for many occupations or for patients with limited transportation options
- Frequently not available in suburban & rural areas

Prescribing Methadone for pain – Avoid if at all possible.

PRESCRIPTION FORM – very RISKY!

- **High risk drug for treating chronic (or acute) pain by prescription.**
- 24 hr ½ life for dependency, but only ~ 8 hr ½ life for pain relief.
- Slow onset ~ 3-4 hours to peak.
- 24 hr ½ life for potential effects of respiratory depression.
- The surge in methadone deaths in the 2000's was from treatment for pain by Rx, or diverted use, rather than in an addiction clinics.

QTc Interval Prolongation & Medication Interactions

Methadone can prolong the QTc Interval:

- Increased risk of Torsades de Pointes
- Increased risk:
  - At high doses
  - Underlying native prolonged QT
  - When combined with other QTc prolonging medications.
    - Screening – AATOD Policy and Guidance Statement (2012)
- **Methadone Metabolism Can be inhibited and Induced by other prescriptions.**
- Multiple drug interactions. CYP3AK metabolism affected
- e.g. ciprofloxacin – metabolism inhibitor – increases serum methadone levels.

Interactions Involving Methadone

Medication Type and Examples	Action with Methadone	Recommended Treatment Response
SSRIs (fluvoxamine, fluoxetine, sertraline)	Some SSRI's 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

CSAT, 2005

Methadone

Methadone Dosing is NOT reported to state PDMPs:

- Methadone treatment for OUD is not by prescription, it is administered and dispensed in the clinic
- Only Rx filled in pharmacies are reported to state PDMPs.

Verifying a methadone patient's dose requires contact with the patient's clinic (can be challenging after hours).

- Due to the standard of privacy required of addiction treatment centers (CFR 42 Part 2), written consent for release of information by the patient may be required. EDs exempted.
- Replacing a full missed methadone dose in the ED should NOT be done (nor should dosing be provided during hospitalization) unless the patient's dosing history can be verified by the patient's clinic.
  - DO treat opioid withdrawal with up to 30 mg methadone daily if unable to verify.

Methadone Summary

- VERY EFFECTIVE for treating OUD!
- Full Mu Agonist
  - **Increased Risk of Respiratory Depression and overdose when combined with other sedating medications.**
- Multiple drug interactions
- Dosing is carefully titrated

The ED is NOT the place to initiate methadone treatment

Major Features of Naltrexone

Full Antagonist at mu receptor

- Very competitive binding at mu receptor

Long acting

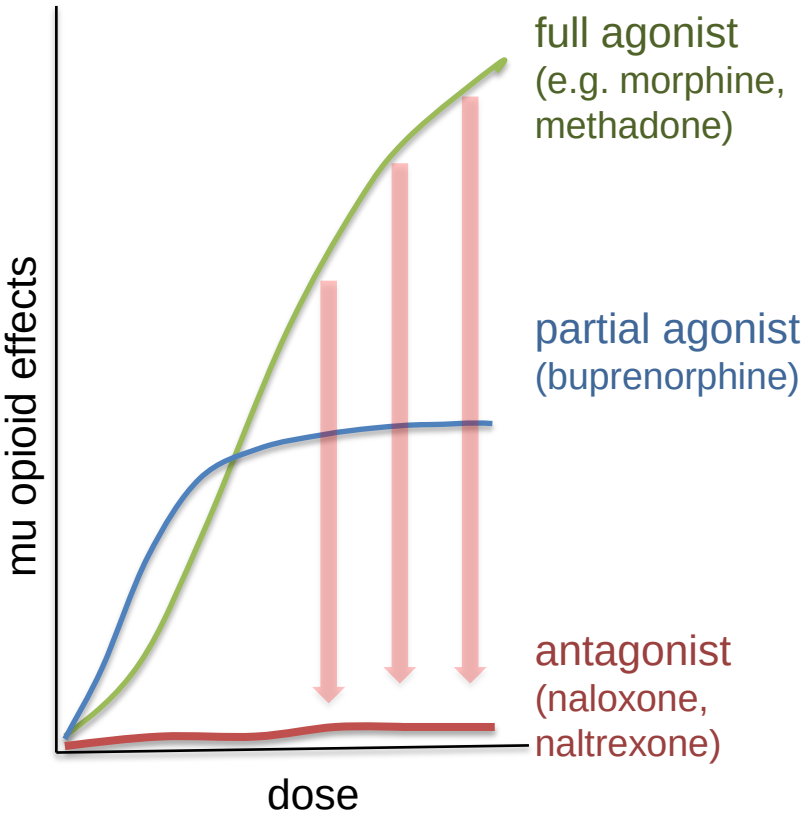
- Half-life:
  - Oral ~ 4 Hours
  - IM ~ 5-10 days

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids
  - Can precipitate withdrawal

Formulations

- *Tablets: Revia®: FDA approved in 1984*
- *Extended-Release intramuscular injection: Vivitrol®: FDA approved in 2010*



SAMHSA, 2018

Naltrexone (NTX)

NTX is intended to prevent any reward from opioid use, and thus gradually reduce cravings.

Medication Assisted ABSTINENCE

Treatment option for patients who want to be opioid free.

Increasing use in correctional facilities and residential programs.

Some patients opt for NTX:

- After “detoxing” acutely,
- After completion of an abstinence program,
- Or after a slow weaning process from methadone or bupe Tx.
- Certain occupations that prohibit any use of any prescription opioids.

Overall outpatient numbers are still low.

PCSS Providers Clinical Support System

Naltrexone

Also effective in Tx of alcohol use disorder – acts as an antagonist to reduce ethanol cravings.

- But when treating alcoholism, must screen for OUD, and check urine screen – to avoid precipitating withdrawal.

NTX daily ORAL doses of 25mg and 50mg tablets.

- Not often used to treat OUD at home (poor daily adherence).
- More often used in “Detox” or other residential programs for OUD.

Monthly 380mg Injection (depot NTX) – “Vivitrol” brand name.

- Much better compliance!

PCSS Providers Clinical Support System

Naltrexone Treatment

- NTX: Active metabolite (6-β-naltrexol) which is <u>also an antagonist</u>
- In sufficient plasma concentrations (>2 ng/ml) naltrexone fully blocks all opioid effects

- Injection site upper outer quadrant of buttock.

Naltrexone

Patients should be opioid free for 7-10 days, and should have a urine drug screen negative for opioids (including bupe) before receiving NTX.

- Challenging to endure d/w Sx.
- Non-opioid Tx – clonidine.

Patient usually are tested first on oral NTX, before receiving IM depot naltrexone: 25mg then 50mg.

NTX precipitated withdrawal can be severe!!

For patients taking naltrexone, managing ACUTE PAIN with opioids is VERY DIFFICULT, as the mu receptors are blocked.

NTX is NOT a medication to be initiated in the E.D.

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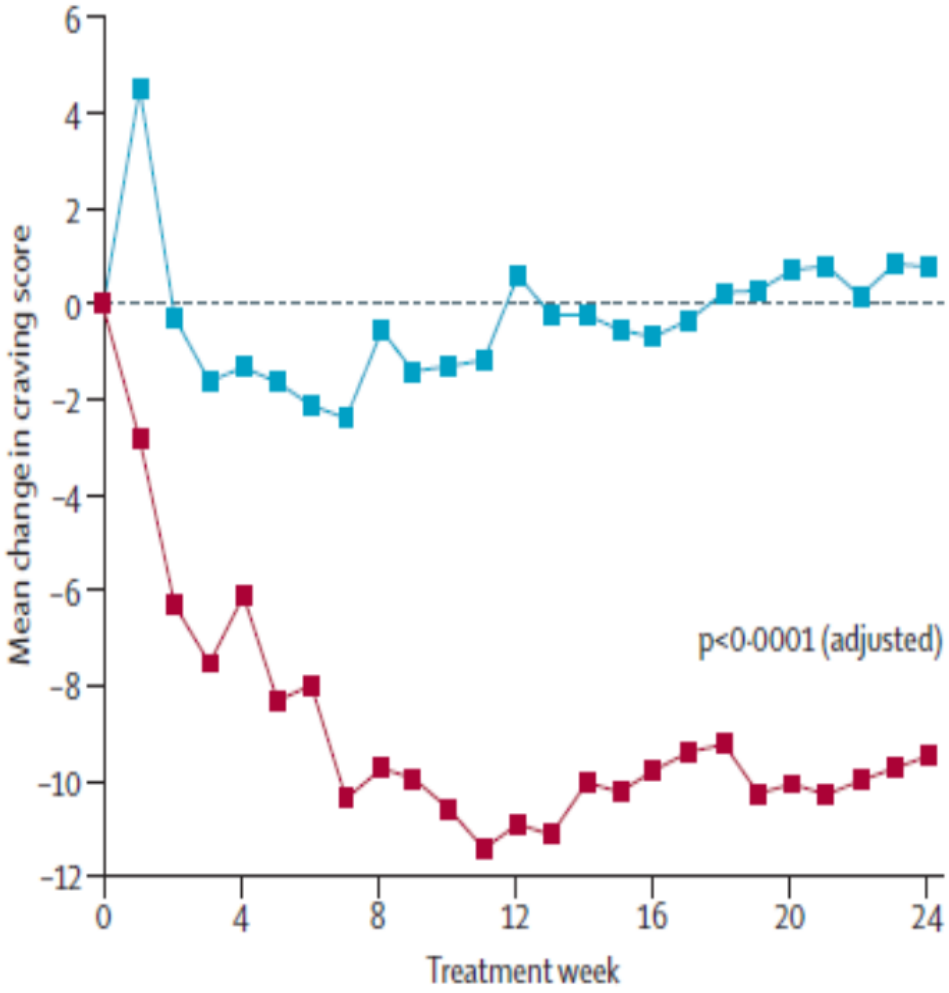
Naltrexone: Craving



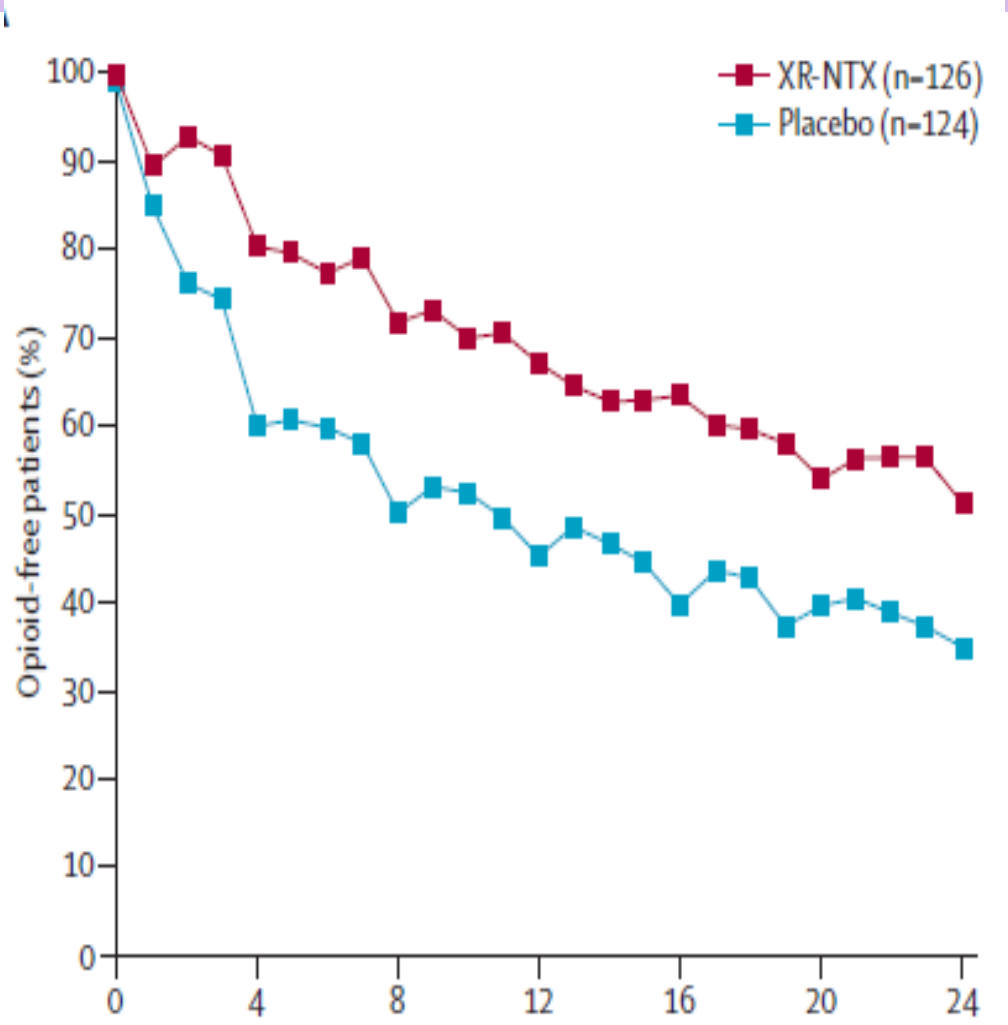
Cravings at weeks of Treatment

XR-NTX

Placebo

Krupitsky et al., 2011

Naltrexone: Efficacy



Percentage of patients opioid free at weeks of treatment

XR-NTX

Placebo

Krupitsky et al., 2011

Naltrexone Considerations: Adherence

- Treatment adherence is better with long acting injectable formulation
  - The treatment plan should include **counseling, anticipatory guidance, motivational techniques** and emphasis on adherence with ongoing counseling supports
  - Involvement of a significant other may be helpful to support adherence with monthly injections
  - Some patients experience subacute withdrawal symptoms after the first naltrexone injection,
    --Typically resolves after one or two weeks and does not recur after subsequent monthly injections
  - Other than soreness at injection site, few other side effects
  - Main safety concern is risk of relapse when injections are discontinued

Naltrexone Treatment: Mechanism

Mechanism Theory (psychiatrist language):

- **Behavioral mechanism:** blockade of the reinforcing effects of heroin leads to gradual extinction of drug seeking and craving
  - Patients who use opioids while on naltrexone experience no effect of exogenous opioids and often stop using them.
  - However, requires several months of repeated injections to achieve lasting craving reduction (probably at least 6 months, but perhaps a year or more).
  - In general: the longer the course of Tx, the better odds of remaining opioid free after cessation of NTX Tx.

- **Pharmacological mechanism:** naltrexone decreases reactivity to drug-conditioned cues and decreases craving thereby minimizing pathological responses contributing to relapse
  - Patients on naltrexone often have decreased urges to use opioids.

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Drug Testing in the ED in the patient with OUD

General Goals of Drug Testing in Office-Based Treatment

- Urine testing should be viewed as a means for helping the provider to help the patient
- Testing is not meant to "catch" the patient
  - Concerning tests offer an opportunity to change the treatment plan
- The utility of the test in the ED vs clinic are different
- Language regarding the results of the test is important

Words Do Matter

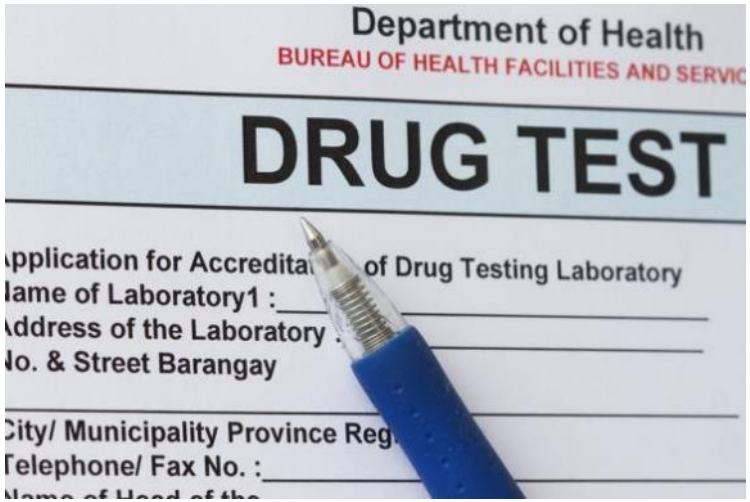
Language is Important

Try to Avoid Calling Test Results Clean or Dirty

Refer to Patients as Patients with an Opioid Use Disorder

Drug Testing in Office-Based Treatment Specifics

- In the office, testing offers several advantages
  - Screening
  - Treatment planning
  - Monitoring adherence
  - Helps determine if treatment is working
- Optimal testing is random and urine collection is observed
  - [Not always practical.]
- In the ED, the information obtained, and the environment are different



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Screening and Confirmatory Tests

Screening Tests

- Rapid and inexpensive
- Generally immunoassay based on the NIDA panel
- Can be done at bedside or sent to a lab
- Can have false positives and false negatives
- Result as yes or no but actually have cutoffs

Confirmatory Tests

- Slower and more expensive
- Requires more expertise to perform
- Some combination of chromatography and mass spectrometry
- Must be done in a specialized lab
- Do not expect false positives, i.e., high specificity
- May result as yes or no but can obtain quantitative information if asked

Moeller et al., 2017
SAMHSA, 2012

Screening and Confirmatory Tests The ED vs The Clinic

- In the clinic, confirmatory testing:
  - Avoids false positives which can negatively impact the patient/physician interaction
  - May not be necessary if patients admits to use

- In the ED, screening testing is obtained
  - Confirmatory testing is not practical
  - If following up at a different facility, unlikely that confirmatory results will be reviewed

Immunoassay Testing

- Each immunoassay is different but does come with a package insert with this information
- Some commonly-used screening tests include:
  - Opiates : morphine, codeine, and heroin
  - Benzodiazepines : oxazepam, diazepam, chlordiazepoxide
  - Cannabinoids: tetrahydrocannabinol
  - Amphetamines : methamphetamine, amphetamine
  - Cocaine metabolite : benzoylecgonine
  - *Alcohol* metabolite: In *urine: ethyl glucuronide or ethyl sulfite*
- Tests for “designer” synthetic cannabinoids and cathinones are available, but limited by the rapid development of new molecules

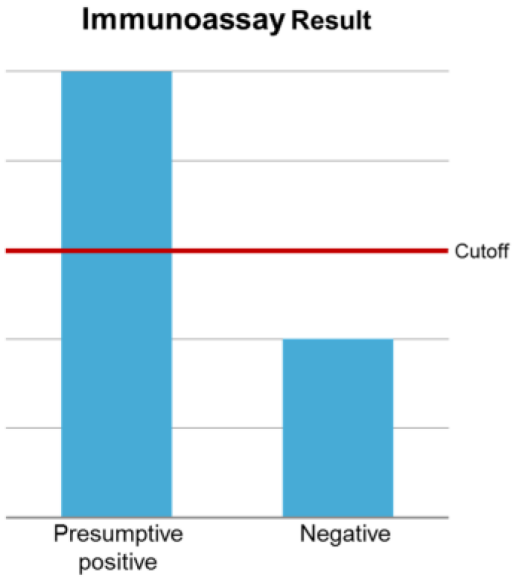
Moeller et al., 2017

Interpretation of a True Positive Opiate Screen

- Patient is compliant
  - Uses an opioid (but unclear which opioid)
- Patient is non-compliant
  - May have taken one dose just before collection
  - Added drug to urine after collection
- Patient likes bagels (i.e., poppy seeds)
- However:
  - Does not correlate with effectiveness or impairment
  - Does not indicate route of administration
  - Cannot tell time of use or amount used

Interpretation of a True Negative Opiate Screen

- Patient is not compliant
  - Or is not using as directed
    - Concentration below the cut
  - Or is diverting
- Wrong assay used
  - e.g.: Opiate assay for oxycodon
- Collection/Lab error



Specimen validity testing may be helpful for both positive and negative results.

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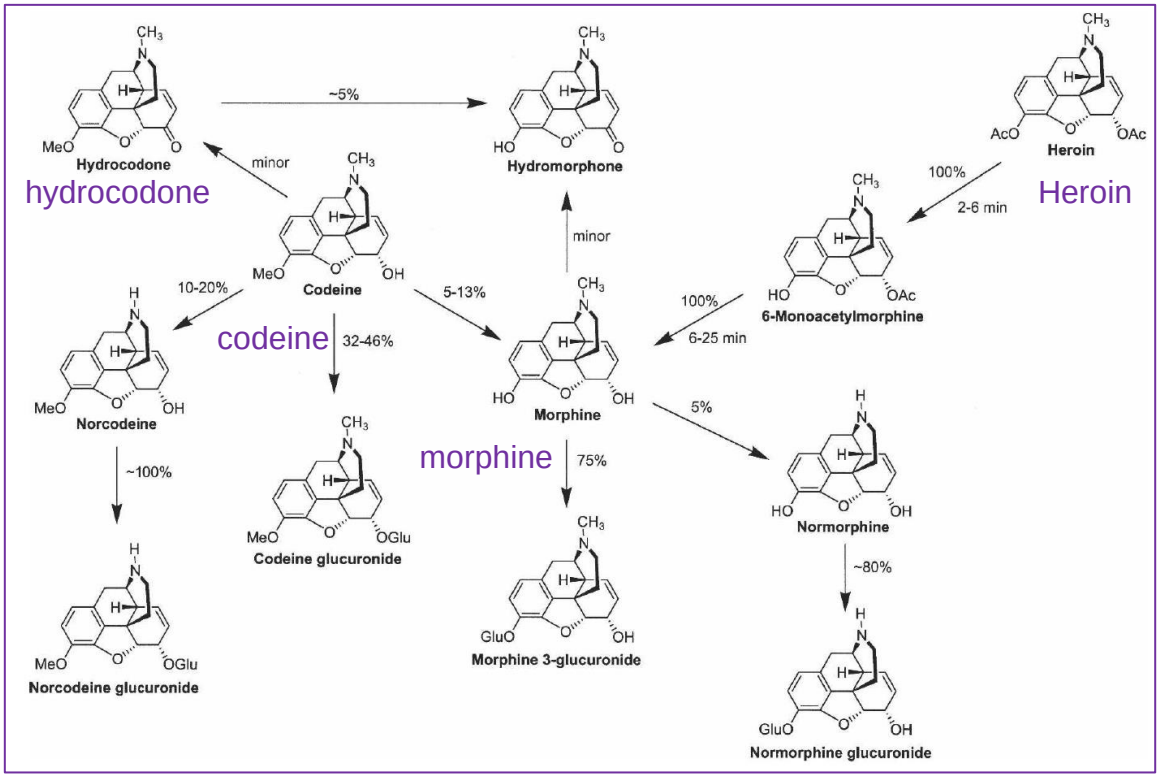
Limitations of an Immunoassay

- A “morphine” assay does NOT detect other opioids
  - Methadone
  - Buprenorphine
  - Fentanyl
  - Oxycodone
  - Hydrocodone (in some cases)
- Some benzodiazepine assays do NOT detect these common benzos:
  - Alprazolam
  - Lorazepam
  - Clonazepam
- Can obtain specific immunoassays for some of these drugs.
- Learn the limitations of the assays at your institution.

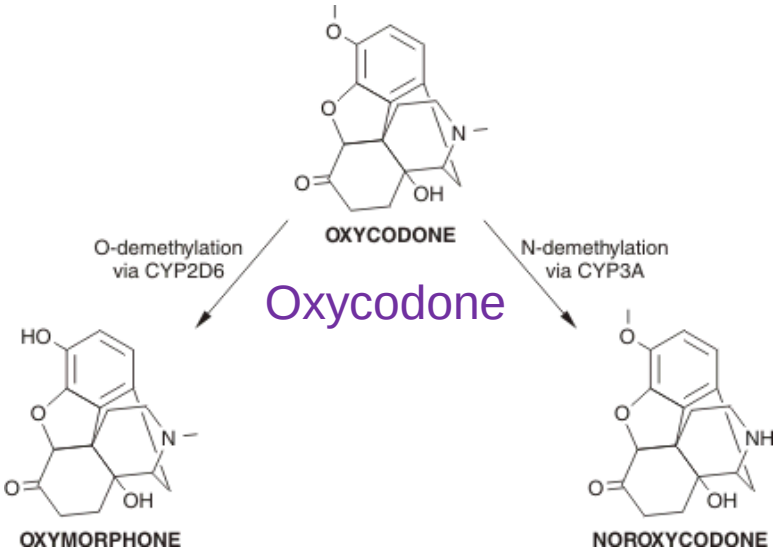
Limitations of an Immunoassay

- Most “opiate” urine immunoassays screen for morphine, codeine, and heroin metabolites, which may or may not include hydrocodone.
- The diagram shows the related metabolic pathways.

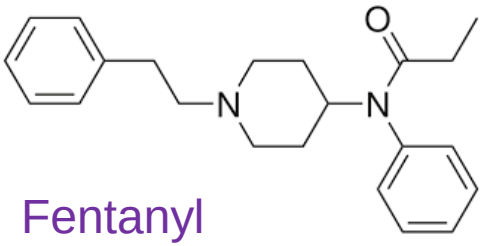


Other Opioids

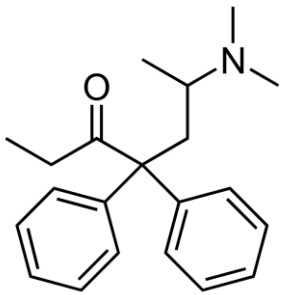
- Oxycodone is outside of the morphine metabolic pathway.
- Fentanyl, methadone, buprenorphine have structures very dissimilar from the morphine family compounds



Oxycodone



Fentanyl



Methadone

Must confirm if your “opioid” test includes an oxycodone assay.

The Rest of the ‘Typical’ UDS

- False positives can occur
  - Very rare with cocaine and cannabinoids
  - Can be seen with the amphetamine screen
- Amphetamine screen
  - Tests for amphetamine
  - Methamphetamine is metabolized to amphetamine
  - May have false positives (e.g. pseudoephedrine)

THE TESTS ONLY CONFIRMS POSSIBLE EXPOSURE
NOT INTOXICATION

Today's New Street Drugs

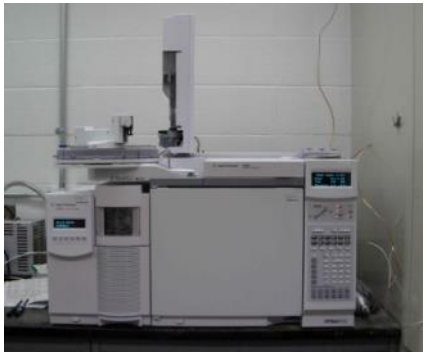
Assume that none of the newer synthetic opioids
(e.g. fentanyl and analogs) will turn the immunoassay positive

Same for synthetic cannabinoids (K2, spice, etc.)
And the synthetic cathinones (bath salts)

Confirmatory testing (GC/MS or equivalent) generally needs to be able to match substance so may not be helpful

The Gold Standards for Confirmation

- Gas Chromatography/Mass Spectrometry
  - Gold standard for confirmation
  - Chemical “fingerprint” of drugs
  - Sensitive and specific
  - Legally defensible



- Liquid Chromatography/Tandem Mass Spectrometry (LC/MS)
  - Emerging standard for confirmation
  - Less sample preparation

- Most office-based programs will only rarely utilize confirmatory testing.

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Testing for Buprenorphine What and Why They Do It In Clinic

- Assists in monitoring treatment and prevents diversion
- Not part of standard drug screens (i.e. the UDS obtained in the ED)
- Important to also test metabolites and not just for buprenorphine
  - If taken appropriately, large amounts of norbuprenorphine (metabolite)
  - If place buprenorphine in urine, very little norbuprenorphine
- Metabolite concentrations also can assist with titration
  - Rapid CYP3A4 metabolizers as well as inducers/inhibitors

Sethi & Petrakis, 2013
Hull et al., 2008

Window of Detection

- Amphetamines
  - 2 - 3 Days
- Cocaine
  - 2 - 4 Days
- “Opiates”
  - 3 - 4 Days
- PCP (phencyclidine)
  - 5 – 8 Days
- THC
  - About a week for most recreational users
  - Up to 8 weeks in heavy/chronic users

Inconsistent Test Results in Clinic

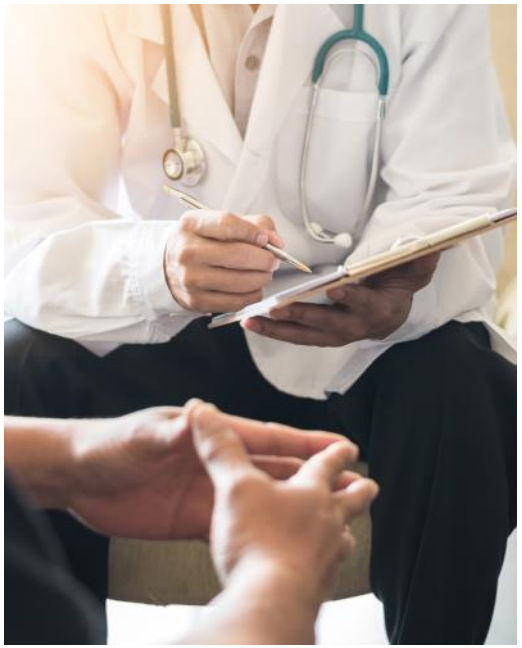
- Adulterated urine suggests need to review treatment plan
- Clinic policy:
  - Develop in advance
  - Purpose is not to kick patient out of clinic (i.e. is not punitive)
- Review dosing, counseling, intensity of treatment
- Review goals of care including take home dosing

Other Testing in the ED DON'T HOLD BUPRENORPHINE TO GET TESTING!!

- Checking LFTs is usually NOT required
  - Buprenorphine can elevate LFTs
  - Clinics may check
- HIV
- Hepatitis C
  - Can be obtained at follow up
- STI testing?
- EKG is not necessary
- Pregnancy Test

Summary

- Purpose of testing in the ED is very different than in clinic
- Testing is never meant to be punitive
- In ED screening tests are obtained
- The laboratory director can assist with becoming familiar with the nuances of your hospital's drug screen



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Providers Clinical Support System

Developing an ED-initiated Buprenorphine Program

Educational Objectives

- At the conclusion of this activity participants will be able to:
  - Describe how EDs can promote access to buprenorphine treatment for patients with OUD.
  - Describe ED and community components needed to implement successful buprenorphine treatment programs.
  - Develop community referral specifics for continued treatment.

ED Contributions to Systems of Care for Patients with OUD

EDs are ideally positioned to fill gaps in care for opioid use disorders, providing:

- Access to care 24/7/365 regardless of ability to pay
- Treatment for acute life-threatening complications and other associated illnesses and injuries related to OUD
- Treatment initiation for OUD
- Linkage for ongoing treatment in the community

- Develop **proactive, inviting, de-stigmatizing** systems of care that actively reach out to bring patients into care

Build a Proactive System to "Pull" Individuals into Care for OUD

Principles of system development

- Build the system to most optimally meet the needs of the person with an OUD seeking help.
- Evaluate success from the perspective of the individual with an OUD seeking help.
- Multiple, diverse, redundant, low-barrier access points to care for use disorders promotes engagement and retention in treatment (ED, bridge clinics, office-based practices).

The Solution: Establishing a Culture of "Treatment Starts Here" in the ED

- The ED can improve care for patients with OUD by:
  - Initiating patients who are not in treatment on buprenorphine
  - Preventing treatment interruptions by providing stop-gap treatment
  - Re-starting medication treatment after relapse

Components of an ED-initiated Buprenorphine Treatment Program

- ED Staff Training
- Clinical care pathway
- IT/clinical decision support
- Medication accessibility
- Other support staff such as social work, counselors
- Partnerships with community providers and treatment programs
- Integration into ED flow minimizing ED length of stay

Staff Training

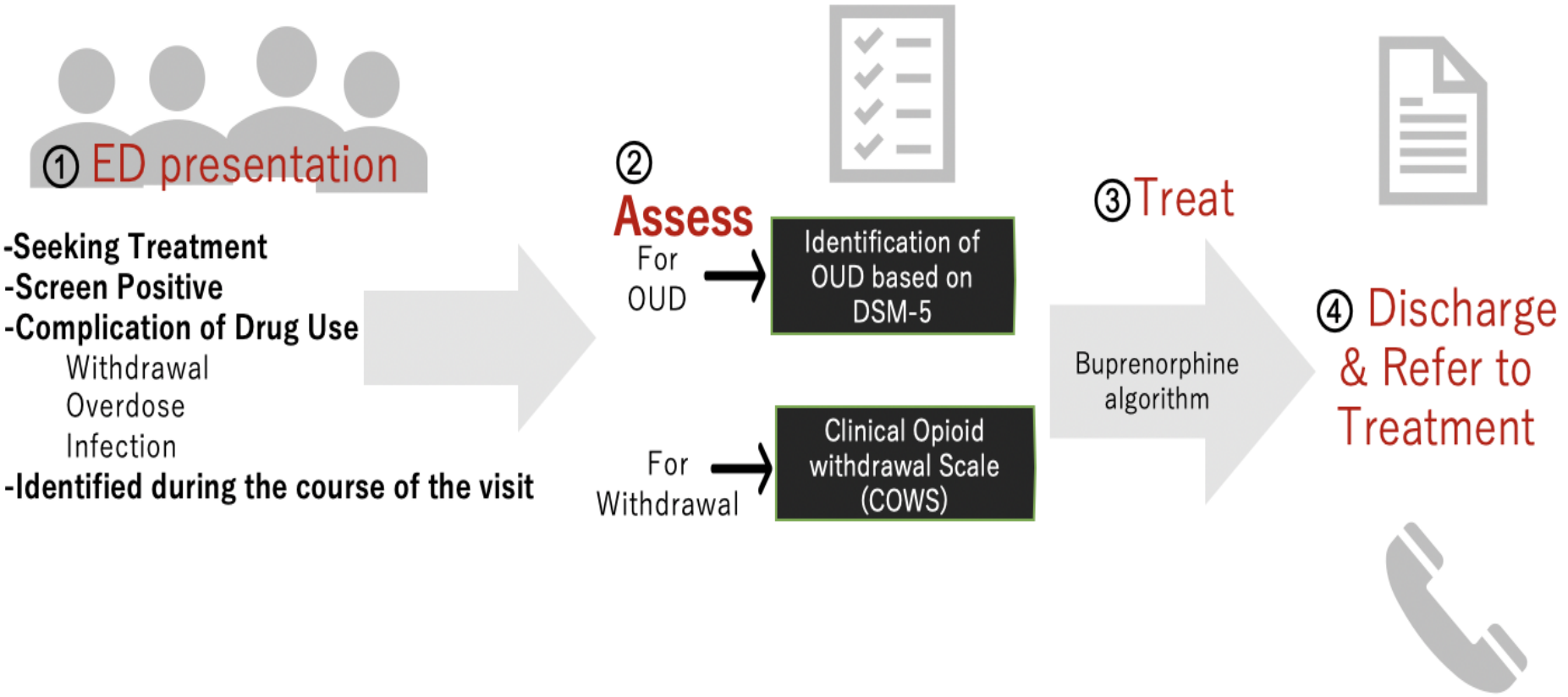
- Staff training can involve a combination of
  - Grand Rounds/Lecture
  - Online Webinars (PCSS, ACEP)
  - Journal Clubs
  - Education about pathways and protocols
  - X-waiver trainings
  - Nursing huddles
  - Hospital/ED pharmacists

Include your Advanced Practice Practitioners and pharmacists, as they can often enhance program development!

Develop a Clinical Care Pathway

- Each ED needs to develop a clear protocol and clinical care pathway tailored to their ED.
- Components to consider include:
  - Patient Identification
  - Patient Assessment
  - Medication Dispensation
  - Care Transition/Referral

Example Buprenorphine Integration Pathway



https://medicine.yale.edu/edbup/overview/

IT and Clinical Decision Support

- IT solutions can help streamline care and increase uptake of practice change.
- An optimized Electronic Health Record (EHR) can:
  - Include order sets and clinical decision support
  - Include default prescribing doses; often matching patient insurance to preferred buprenorphine formulation (film vs. tablets) and naloxone
  - Auto-populate x-waiver numbers to electronic Rx
  - Include discharge instructions on medication use, home induction, referrals, overdose prevention
  - Communicate referrals to community providers

Easy-to-Access Medication

Buprenorphine or Buprenorphine/ Naloxone should be readily available for prompt administration when indicated.

- Buprenorphine should be on your hospital formulary.
- It should be readily available <u>in the ED</u> automated medication dispensing systems.

Role of Support Staff

- EDs may often benefit from the integration of patient navigators, case managers, health promotion advocates, recovery coaches or social workers assisting with:
  - Enhancing patient's motivation to start treatment
  - Patient navigation
  - Patient education
  - Direct linkage to referrals
  - Offering feedback to ED staff regarding successes in linkages to treatment

Support staff can be helpful but are not absolutely necessary. Don't let their absence deter you from developing a program!

Components of a Successful System

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Identify ED, Hospital and Community Champions

- ED physicians
- Residents
- Nurses
- Advanced Practice Practitioners
- Pharmacists
- Social workers and Care Managers
- Counselors
- Hospital and Clinic Administrators
- Community Opioid Treatment Providers and Programs
- Community Opioid Related Coalitions

Obtain Leadership Buy-In

- ED physician leadership
- ED nurse and advanced practice practitioner leadership
- Hospital administrators
- Pharmacists
- Community office-based treatment providers
- Opioid Treatment Programs

Key Points

- "This medication saves lives and should not be withheld "
- Discuss potential benefits relevant to each stakeholder

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Create ED/Community Partnerships

- Build relationships with outpatient providers
- Many treatment centers WANT your buprenorphine patients!
- Visit treatment center(s)
  - Best for at least one ED person (a “champion”) to have a robust understanding of what happens there
- Agree on a streamlined referral process
- Build in a feedback mechanism for problem solving and troubleshooting for
  - Patients
  - ED providers
  - Community Providers

Develop System Protocols and Referrals

- Protocols need to be integrated into the ED flow and EHR
- Buprenorphine should be readily available in the ED
- Discharge plans should be SIMPLE and RELIABLE
- Minimize the contingent steps required to secure a follow appointment with a clinician who can continue to prescribe buprenorphine.
- Maximize the capacity to establish a set time and date for follow-up before discharge.
- Set clear expectations for patients and programs
- Establish relationships with nearby pharmacies for obtaining medication

Care Transitions

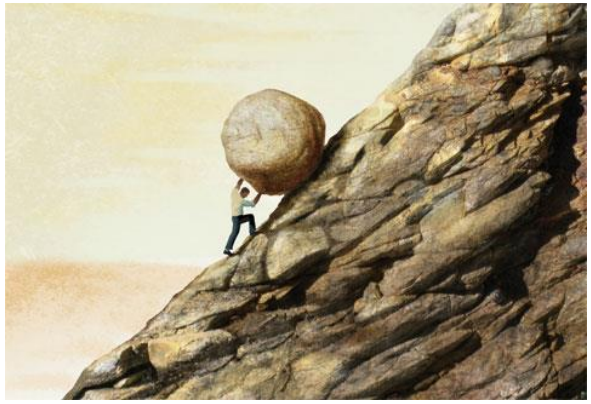
The priority is maintaining access to buprenorphine pharmacotherapy after discharge.

- Any lapse in buprenorphine dose access increases risk for a return to illicit use.

Patient motivation is often quite high

- Complex healthcare systems create barriers to filling a prescription after discharge even for the highly organized and motivated.

Anticipating Challenges and Offer Solutions



- Anticipate resistance, particularly around ANY increased workload. How can you offload some of the work?
- What motivates different key players?
  - Reducing repeat ED visits
  - Promotion of staff safety
  - Reduction in length of stay
  - Increased patient satisfaction
  - Success in engaging patients with OUD into treatment
  - Improving access to care!

Providers often need assistance the first time they prescribe so develop a support call system

Important Caveats

- Engaging stakeholders helps change culture
- It will not happen overnight
- Perfect is the enemy of good
  - **Do not wait for a perfect protocol or system!**
- The easier it is for providers and patients, the higher likelihood of success
- Feedback to providers is essential for continued success

Share Success Stories

- ED providers often do not get to see the downstream outcome of their work. They often see only the patients with return to use. Thus:
  - Hearing that a patient that was referred to treatment is currently in treatment is highly motivating to providers
  - Sharing success stories at staff meetings, or along with other ED metrics can enhance uptake of ED-initiated buprenorphine across staff

References

- ED Initated Buprenorphine Website, Yale University. https://medicine.yale.edu/edbup/
- ED Bridge: Emergency Buprenorphine Treatment. https://ed-bridge.org

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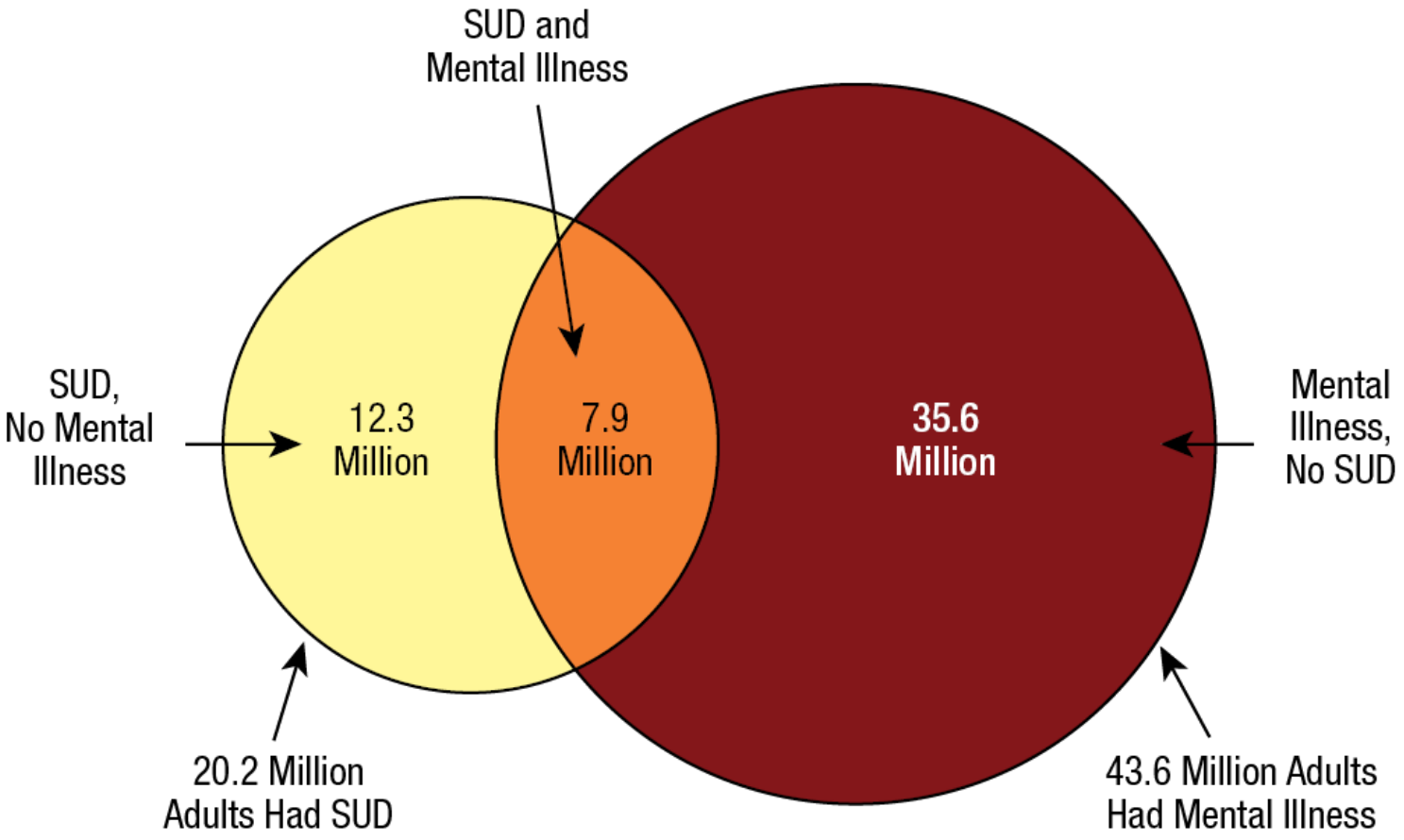
Module 9: Special Populations and Co-Occurring Disorders

Objectives

1. **Diagnose and discuss appropriate management of co-occurring substance use and other psychiatric disorders**
2. Discuss appropriate management of opioid use disorder in adolescents
3. Describe appropriate management of opioid use disorder during pregnancy
4. Discuss considerations affecting use of medications for addiction treatment in older patients
5. Identify potential interactions of antiretroviral medications with buprenorphine
6. Describe how liver and kidney impairments affect dosing of buprenorphine

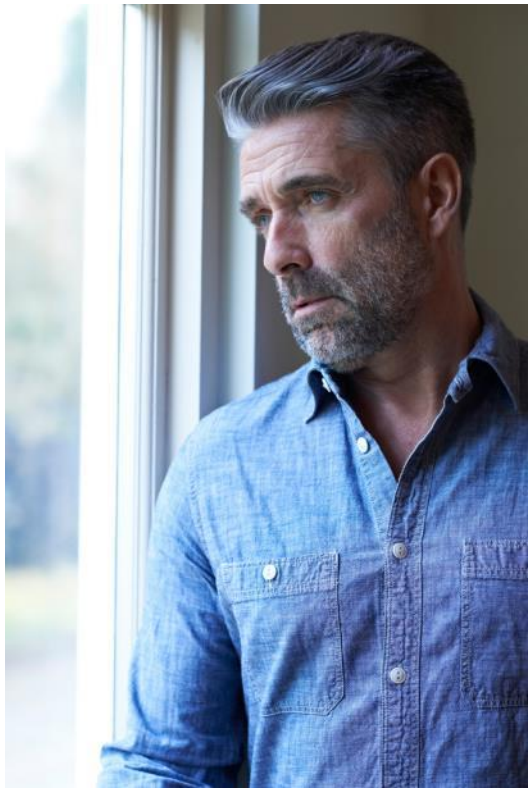
Co-occurring Psychiatric Disorders



SAMHSA, 2017

Depressive and Anxiety Symptoms

- Depressive and anxiety symptoms are common at treatment entry
- Symptoms may resolve within few days of stable treatment
- Symptoms that persist beyond acute intoxication and withdrawal can be worthwhile targets for treatment:
  - For example, with Selective Serotonin Reuptake Inhibitors
- Patients treated with MAT respond to medications for depression and anxiety at rates similar to those without opioid use disorders



Treatment of Co-Occurring Psychiatric Disorders

- Avoid use of benzodiazepines
  - Risk of misuse
  - Interactions with buprenorphine possible
  - First-Line Treatments for anxiety and depression
    - Selective Serotonin reuptake inhibitors
    - Psychotherapy (e.g.: cognitive behavioral therapy)
- Stimulants
  - Obtain collateral information from Prescription Drug Monitoring Program, Psychiatric and/or Primary Care Provider
  - If there is concern for Attention Deficit Hyperactivity Disorder (ADHD), consider Adult ADHD Self-Report Scale (ASRS) or refer patient to a Psychiatric or Primary Care Provider for assessment
  - Continue stimulants if they have been legitimately prescribed by Psychiatric or Primary Care Provider

Chang et al., 2005
Kampman et al., 2015

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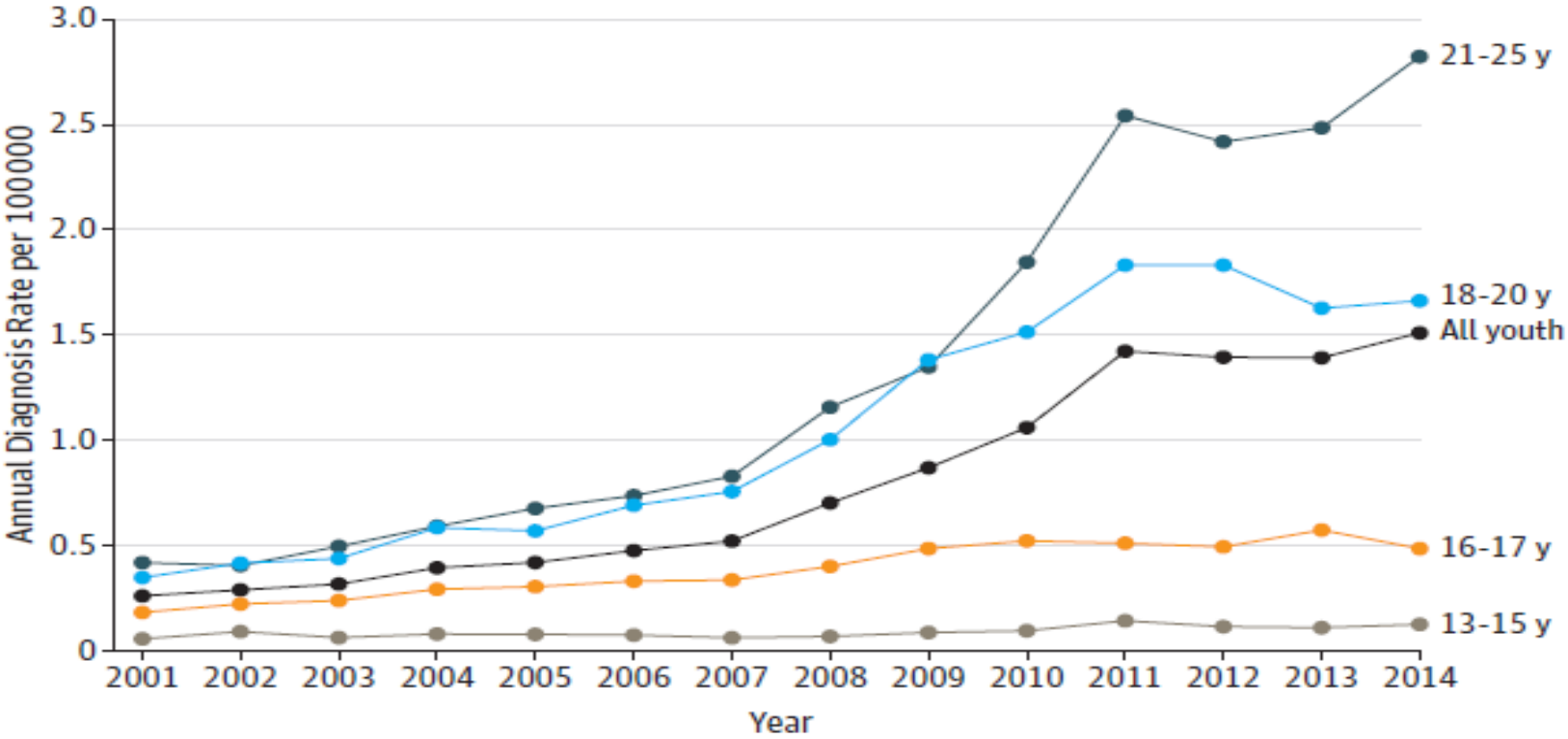
New Diagnoses of Opioid Use Disorder in Youth

Increasing incidence of OUD in Youth through 2014



Hadland et al., 2017

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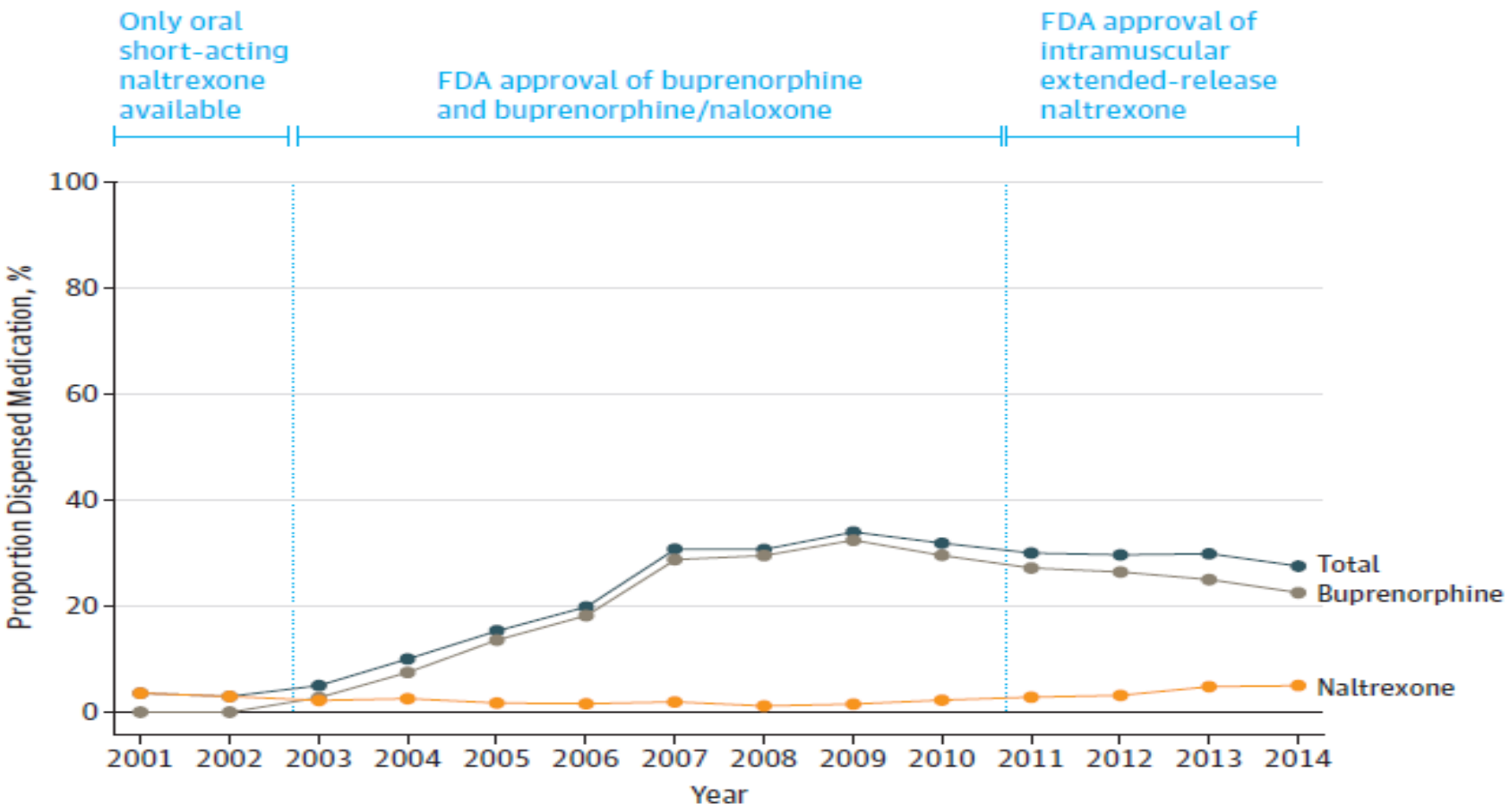
New Diagnoses of Opioid Use Disorder in Youth

- Prescription opioid misuse in youth has been declining since it peaked in 2008
- Youth heroin use has been increasing since 2012.
- The primary type of opioid misuse by adolescents seeking treatment for an opioid use disorder between 2010 and 2015 changed from predominantly prescription opioids to heroin.
- OUD in adolescents (as in adults) continues to be greatly undertreated.

Hadland et al., 2017
Martins S, et al. 2002.
Yule A, et al. 2018.
Mental Health Annual Report: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. 2015

Proportion of Youth Receiving Treatment within 6-months of Diagnosis



Hadland et al., 2017

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Adolescents

- Age:
  - DATA 2000 authorizes treatment of individuals age 16 and older
    - Buprenorphine is approved for individuals **at least** 16 years of age
    - Methadone is approved for individuals **at least** 18 years of age
  - 42 CFR § 8.12 – offers an exception for methadone in patients aged 16 and 17, who have a documented history of:
    - At least two prior unsuccessful withdrawal management attempts and have parental consent
  - Age of consent for medication varies from state to state:
    - Be familiar with the relevant state statutes
- Pregnancy:
  - Recommended to assess ALL female adolescent patients prior to starting buprenorphine to discuss treatment options

CFR 42, 2017
DATA, 2000

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Adolescents

- ***American Academy of Pediatrics***:
  - Recommends that pediatricians consider offering MOUD to their adolescent and young adult patients with severe opioid use disorders or discuss referrals to other providers for this service

- ***FDA Approved Medication Options:***
  - Buprenorphine (approved for patients>16yo)
    - Often considered to be the first choice
    - Significantly decreased use of opioids and cocaine
    - Much better treatment retention in comparison to no MAT
    - Decreased injecting
    - Decreased need for additional treatment while on medication
  - Methadone
  - Naltrexone ER (approved for patients>18yo)

If state law allows, if appropriate, may initiate buprenorphine Tx for OUD for adolescents in the ED.

- ***Psychosocial Treatment Options:***
  - Family Intervention Approaches
  - Vocational support
  - Behavioral interventions

AAP, 2016; Fishman et al., 2010; Kampman et al., 2015; Woody et al., 2008

PCSS Providers Clinical Support System

Objectives

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Opioid Use Disorder and Pregnancy

- Epidemiology:
  - ~21,000 pregnant women aged 15 to 44 misused opioid in the past month
  - Prevalence of opioid use among women who gave birth increased in the United States from:
    - 1.19 to 5.63 per 1,000 hospital births per year between 2000 and 2009

- American College of Obstetrics and Gynecology (ACOG) and ASAM:
  - Recommends screening for substance use as part of comprehensive obstetric care and should be done at first prenatal visit
- Key point for the ED: Do not delay treating opioid withdrawal in pregnant patients.

ACOG/ASAM 2017

Buprenorphine vs. Methadone in Pregnant Patients with OUD

- Consider Availability, Patient Preference
- Advantages:

Buprenorphine (Mono-Product)	Methadone
▪ Same efficacy as methadone ▪ Same rates of adverse events as methadone ▪ Lower risk of overdose ▪ Fewer drug interactions ▪ Less frequent NAS and milder abstinence symptoms in neonates ▪ Significantly decreased morphine dose required ▪ Significantly shorter hospital stay ▪ Significantly shorter duration of treatment	▪ More structure – better for patients in unstable situations ▪ Decreased risk of diversion ▪ More long-term data on outcomes So why methadone vs. buprenorphine? Methadone: More long-term data Higher rates of retention

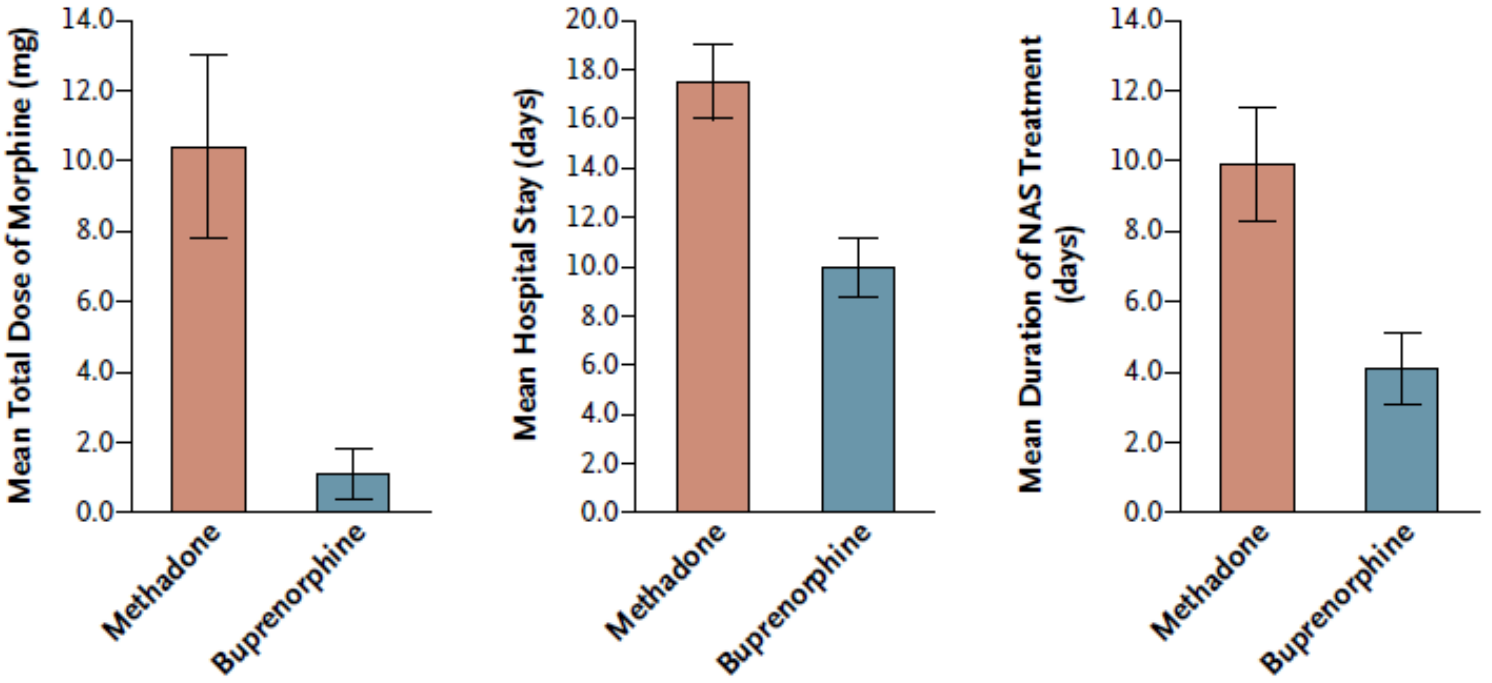
Fischer et al., 1998, 1999
Jones et al., 2010;
Kakko et al., 2008;
Kraft et al., 2017

Methadone Treatment

- Used to be first-line. Still commonly used for pregnant women with opioid use disorder
  - Use high enough dose to block cravings
  - Medication changes:
    - Second and third trimester:
      - Doses may need to be ***increased*** due to increased metabolism and circulating blood volume
        - Doses may need to be split
    - With advancing gestational age: Plasma levels of methadone progressively decrease and clearance increases
      - The half-life of methadone falls from an average of 22–24 hours in non-pregnant women to 8.1 hours in pregnant women
      - Along with increased dose, splitting the methadone dose into two 12-hour doses may produce more adequate opioid replacement in this period

Kampman et al., 2015

Maternal Opioid Treatment:
Human Experimental Research (MOTHER) Study



Comparison of Neonatal Opioid Withdrawal Syndrome: Maternal Methadone vs. Buprenorphine TX

Jones et al., 2010

PCSS Providers Clinical Support System

Use of Buprenorphine With or Without Naloxone in the Pregnant Patient

- During pregnancy: No significant dose increases needed though may require split dosing in 3rd trimester
- Postpartum: Gradually transition to original pre-pregnancy Buprenorphine dose and formulation
  - Note: Mother can breastfeed baby
- Buprenorphine/Naloxone:
  - The FDA labels naloxone as Pregnancy Category B (however the combination of buprenorphine-naloxone is Category C):
    - No known teratogenic effects in animals, however,
    - Controlled studies have not been conducted in humans
  - Increasing evidence that Buprenorphine/Naloxone may be safe in pregnancy
  - However, Buprenorphine *without* naloxone is still recommended for pregnant, opioid-dependent women, as the first option.
  - Misuse of Buprenorphine mono-product may be an indication for Bup/Nx in pregnancy.

Lund et al., 2013

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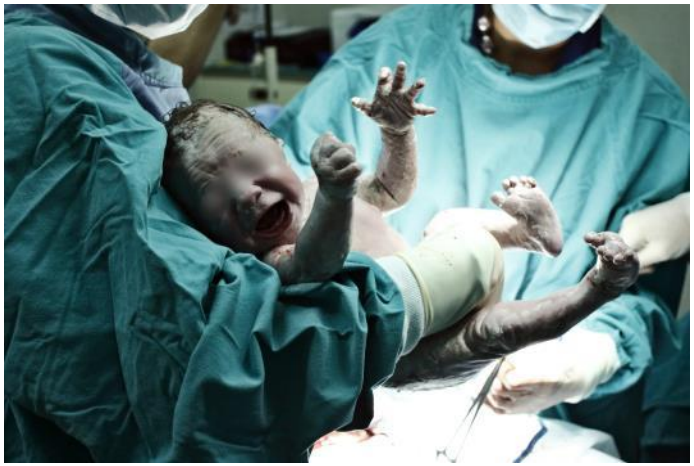
Neonatal Opioid Withdrawal Syndrome (NOWS)



- Epidemiology:
  - Increasing incidence of NOWS
  - Incidence of NOWS in newborns born to opioid-dependent women is between 70 and 95% and ~50% of infants will need medication treatment
- Symptoms:
  - Irritability, fever, diarrhea, hyperreflexia, seizure
  - Begins 24-72 hours of birth, with peak symptoms at 3-4 days, and continues for up to one week
- Complications:
  - Associated with untreated maternal OUD
  - Increased risk of placental abruption, preterm labor, maternal obstetric complications, and fetal death

Kakko et al., 2008
Patrick at al., 2015
Smith et al., 2017

NOWS Management

- Previously called “NAS”
- Medications:
  - Opioid therapy is preferred first-line intervention
    - Preferred Medications are:
      - Morphine
      - Methadone
  - Clonidine

- Non-Pharmacologic Approaches:
  - Rooming In results in a reduction in NOWS, length of stay, and cost

Holmes et al., 2016
Hudak et al., 2012

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Breast Feeding

- Not contraindicated for mothers on MAT
- Transferred amounts of methadone or buprenorphine are insufficient to prevent symptoms of NOWS
- Levels in human milk are low with calculated infant exposures of the maternal weight-adjusted dose being:
  - <3% for methadone and,
  - 2.4% for buprenorphine
- NOWS can occur after abrupt discontinuation of methadone

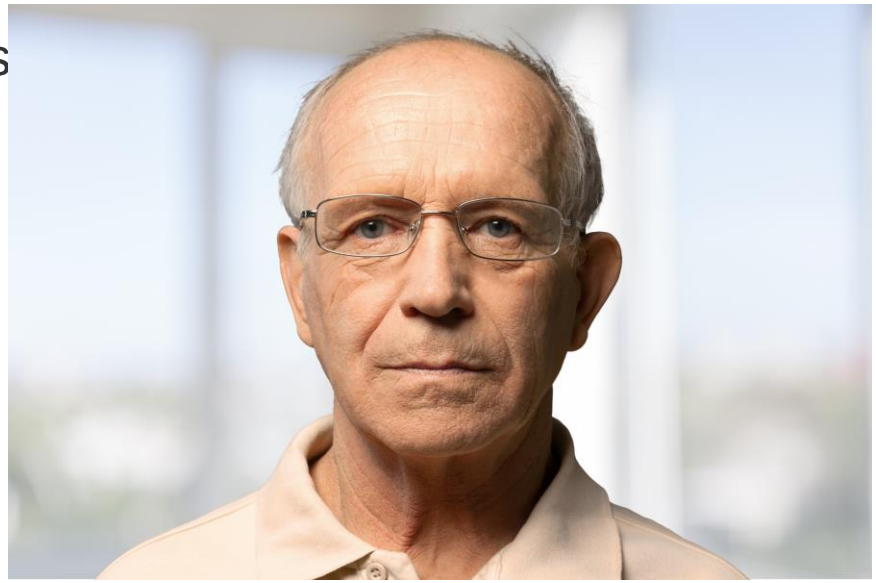
Sachs et al., 2013

Objectives

1. Diagnose and discuss appropriate management of co-occurring substance use and other psychiatric disorders
2. Discuss appropriate management of opioid use disorder in adolescents
3. Describe appropriate management of opioid use disorder during pregnancy
4. **Discuss considerations affecting use of medications for addiction treatment in older patients**
5. Identify potential interactions of antiretroviral medications with buprenorphine
6. Describe how liver and kidney impairments affect dosing of buprenorphine

Older Adults

- General population of older adults
  - Globally: 516 Million (2009) to 1.53 Billion (2050)
  - United States: 1 in 5 U.S. Residents will be age 65+ (by 2030)
- SUDs in older adults (2014):
  - 1 million individuals
    - 978,000 with an alcohol use disorder
      - 161,000 with an illicit drug use disorder
  - Expected to increase to 5.7 million individuals (by 2020)
- Dearth of high quality research on prescription drug misuse in older adults.
  - Past year prevalence of non-medical use of opioids is ~1.4%



Maree et al., 2016; Mattson et al., 2017; West et al., 2015; Wu et al., 2014

Older Adults and Opioid Use

- Unique features:
  - Physiologic changes:
    - Decreased metabolism of medications
    - Increased elimination time
  - Polypharmacy
  - Multiple co-morbidities (including cognitive declin
  - High prevalence of pain in older adults:
    - 25-50% of those living in community dwellings
    - 70% of those living in nursing homes
    - 80% of those living in long-term care
- Risks:
  - Self-poisoning has been reported as frequent mechanism of suicide

Chau et al., 2008;
West et al., 2015;
Wu et al., 2014

Older Adults – Treatment Considerations

- Evaluation:
  - Conduct thorough screening
  - Assist patients with cognitive impairments
  - Assess for suicidality
    - Self-poisoning has been reported as frequent mechanism of suicide in older adults.
- Medication Recommendations:
  - Buprenorphine:
    - First line: May be a good choice because of the increase susceptibility of the elderly to respiratory compromise.
    - Start low and go slow with dosing
    - Hepatic metabolism is slowed in older adults, so maintenance buprenorphine doses may be lower than those used in younger patients.
  - Methadone:
    - Potential for drug-drug interactions
    - QT Prolongation
    - Higher risk of overdose

Chau et al., 2008;
West et al., 2015;
Wu et al., 2014

Objectives

1. Diagnose and discuss appropriate management of co-occurring substance use and other psychiatric disorders
2. Discuss appropriate management of opioid use disorder in adolescents
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6. Describe how liver and kidney impairments affect dosing of buprenorphine

HIV – Positive Patients

- CYP 3A4 is the primary hepatic enzyme involved in metabolism of both methadone and buprenorphine
  - Many anti-retrovirals affect buprenorphine or Methadone levels and in some cases buprenorphine or Methadone levels affect anti-retrovirals levels
  - There are markedly fewer drug/drug interactions with buprenorphine and anti-retrovirals as compared to methadone and little or no interactions with naltrexone
  - Providers should consider referral to specialized HIV treatment programs and services – if available

CSAT, 2004
McCance-Katz et al., 2010
Moatti et al., 2000
Montoya et al., 1995

Objectives

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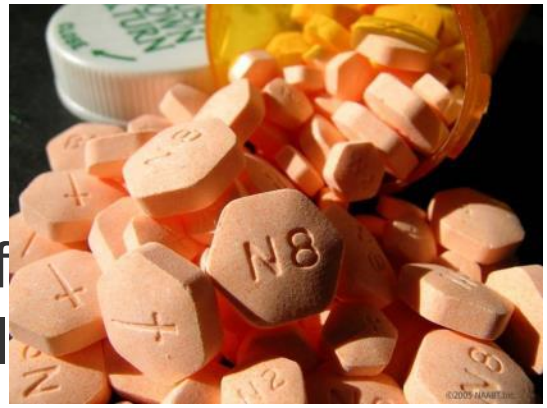
Patients with Renal Failure



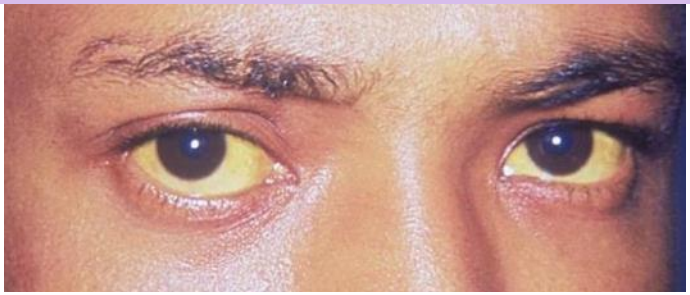
- Suitable to use **buprenorphine** in patients with renal failure
- No significant difference in kinetics of **buprenorphine** in patients with renal failure versus healthy controls
- No significant side effects in patients with renal failure
- **Buprenorphine and methadone** <u>can be prescribed to patients undergoing hemodialysis</u>

Patients with Compromised Hepatic Function

- Buprenorphine undergoes hepatic metabolism, primarily by the CYP450 3A4 system
  - Patients with compromised hepatic function could have reduced metabolism of buprenorphine, with resultant higher blood levels of the medication
  - No specific hepatotoxicity has been demonstrated for either methadone or buprenorphine
    - Case reports of buprenorphine induced liver and kidney failure in susceptible individuals, possibly through direct mitochondrial toxicity.*
  - Patients with impairments in hepatic function should be monitored closely

Berson , et al. 2001.
Zuin M,, et al. 2009.

Hepatitis and OBOT



- Hepatitis and impaired hepatic function:
  - Buprenorphine or Methadone are:
    - Contraindicated in patients with acute hepatitis
      - Not contraindicated in patients with mildly elevated liver enzymes.
      - Moderately elevated levels (>3times the upper limit of normal) should be monitored.
    - Active hepatitis: should be appropriately evaluated and treated
      - Etiology of moderate or markedly elevated liver function tests should be determined and treated.

Photo by: CDC/Dr. Thomas F. Sellers/Emory University

Summary

- Although Buprenorphine is approved for individuals over 16 years of age and Methadone is approved for individuals over 18 years of age providers can consider Naltrexone ER in combination with psychosocial treatment options for adolescents with OUD.
- Methadone has historically been considered first-line treatment of OUD in pregnant women. However, increasing evidence is demonstrating that Buprenorphine without naloxone is well-tolerated and efficacious with potential benefits for the newborn.

Summary

- Approximately 40% of adults with SUD had a co-occurring psychiatric disorder. Diagnosis and treatment of mental health issues can potentially have a positive impact on Opioid Use Disorder (OUD).
  - Buprenorphine is front-line treatment for older patients with OUD as there is a high potential for drug-drug interactions for older patients.
  - There are markedly fewer drug/drug interactions with Buprenorphine and antiretrovirals as compared to methadone.
  - Buprenorphine is suitable to use in patients with renal failure.
  - Unless the patient has acute hepatitis, pharmacotherapy with methadone or buprenorphine is not contraindicated on the basis of mildly elevated liver enzymes.

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Appendix: Interaction of Anti-Retroviral Agents with Methadone and Buprenorphine

Anti-Retroviral Agent	Effects	Comment
Abacavir (ABC)	Methadone clearance increased by 22%	Patients should be monitored for methadone withdrawal symptoms; dose increase unlikely, but may be required in a small number of patients
Zidovudine (AZT)	AZT Concentration increased by 29-43% by Methadone	Monitor for AZT adverse effects, in particular bone marrow suppression (especially anaemia).
Efavirenz (EFV)	Decreased methadone Cmax (45%) and AUC (52%), withdrawal reported Decreased Buprenorphine concentration	• Methadone: Symptoms of withdrawal may develop after 3-7 days, requiring significant increases in the methadone dose • Buprenorphine: Observe; may need dose increase
Nevirapine (NVP)	Decreased Methadone levels, withdrawal reported	Methadone Withdrawal symptoms frequent; Usually between 4 and 8 days after starting nevirapine; in case series of chronic methadone recipients initiating nevirapine, 50-100% increases in the daily methadone doses were required to treat opiate withdrawal

WHO, 2009

- CYP 3A4 is the primary hepatic enzyme involved in metabolism of both Methadone and Buprenorphine

Appendix: Interaction of Anti-Retroviral Agents with Methadone and Buprenorphine

Atazanavir(AN)	Buprenorphine: Increased effects	Observe; buprenorphine dose reduction may be necessary
Indinavir (IDV)	Buprenorphine: Potential for increased Effects	Observe; buprenorphine dose reduction may be necessary
Lopinavir/ ritonavir (LPV/r)	Methadone levels: Decreased significantly	Methadone withdrawal possible; monitor and titrate to methadone response as necessary
Ritonavir (RN)	Methadone: Decreases concentrations even at boosting dosage Buprenorphine: Potential for increased Effects	• May require higher methadone dose, even if only booster doses of ritonavir used; observe closely for signs of methadone withdrawal • Buprenorphine: Observe. Dose reduction may be necessary
Saquinavir (SQV)	Buprenorphine: Potential for increased Effects	Buprenorphine: Observe. Dose reduction may be necessary
Tipranavir (TPV)	Buprenorphine: Potential for increased Effects	Buprenorphine: Observe. Dose reduction may be necessary

- CYP 3A4 is the primary hepatic enzyme involved in metabolism of both Methadone and Buprenorphine

WHO, 2009

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Motivational Interviewing & Evidence-Based Counseling

Objectives

1. How to Enhance Motivation in the ED: Key Components of Motivational Interviewing
2. Describe the fundamentals of Screening, Brief Intervention, and Referral to Treatment (SBIRT)
3. Outline the key components of behavior
4. Describe various evidence-based counseling approaches for opioid use disorders

Bird's Eye View

- Providers, staff, and patient advocates can enhance a patient's willingness to start treatment using evidence-based based techniques
  - Physicians, including ED physicians or consultants (Addiction, Psychiatry, etc.)
    - PAs, APRNs
    - Social Workers
    - Health Promotion Advocates
    - Peer Navigators

- Most effective techniques in ED to enhance motivation to enter treatment are based on Motivational Interviewing

"Motivational interviewing is a collaborative conversation style for strengthening a persons on motivation and commitment to change."

Miller & Rollnick

Motivational Interviewing (MI)

- Developed by William Miller and Stephen Rollnick in the 1980's
  - Clinical tool conceptualized for individuals "less ready" for change
- Over 25,000 articles citing MI
- 200 Randomized Controlled Trials

- Effectiveness of MI varies widely across counselors, studies, and sites within studies
- Fidelity of delivery affects outcomes
- Can be done in ED to enhance willingness to enter treatment

MI Definitions and Skills

- Brief Definition
  - Collaborative conversation style for strengthening a person's own motivation and commitment to change in a spirit of acceptance and compassion
  - Person-centered counseling style for addressing the common problem of ambivalence about change

- Core Interviewing Skills
  - Open Questions
  - Affirming
  - Reflecting:
    - Simple
    - Complex
  - Summarizing

Miller and Rollnick, 2013

Practical Aspects of MI

- Be open minded
- Listen > ask > give advice
- Do not ask more than 3 consecutive questions
- Avoid wordiness
- Avoid interrupting
- Cooperate, do not force knowledge
- Use patient as consultant
- Be open, be direct

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Enhancing Motivation using the Brief Negation Interview

Step 1. Raise the Subject/Establish Rapport

- Introduce yourself
- Raise the subject of opioid use and ask permission to discuss OUD
- Assess patients subjective level of physical discomfort (i.e., withdrawal)

Step 2. Provide Feedback

- Review patients drug use and patterns
- Ask the patient about and discuss drug use and its negative consequences
- Make a connection (if possible) between drug use and visit or medical issues
- Provide feedback on OUD diagnosis and treatment options (e.g., medication (BUP, methadone, naltrexone), behavioral outpatient programs, 12-step, and/or harm reduction strategies.

Step 3. Enhance Motivation

- Assess readiness to change – with regard to starting preferred treatment
  - "On a scale of 1-10, how ready are you to start Buprenorphine right now?
- Enhance Motivation
  - Ask a series of open-ended questions designed to evoke "Change Talk" (or motivational statements) about their target behavior.
  - Reflect or reiterate the patient's motivational statements regarding entering treatment.

Step 4. Negotiate & Advise

- Negotiate goal regarding the target behavior (e.g. starting BUP)
- Give advice
- Complete a referral/treatment or goal agreement, and secure and provide the actual referral for treatment

D'Onofrio, 2005

BNI "CHEAT SHEET"

STEP 1	Establish Rapport	Do you mind if we talk about _____?
STEP 2	Provide Feedback	a. What connection might you see between (drug use behavior) & (negative consequence, e.g., overdose)? b. Reflect & Ask open questions. c. Provide info on Rx & harm reduction strategies.
STEP 3	Enhance Motivation Readiness Ruler	Pick 1 alternate, positive behavior (i.e., reduce or refer) a. 1-10 Question b. Why not a lower # (If 1: What would it take to turn that 1 into simply a 2?) c. Reflect & Synthesize
STEP 4	Negotiate a Plan	What's your next step, if any? Reinforce, suggest, recommend follow-up. Focus on reduce/refer

Pantalone, 2018

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Responses

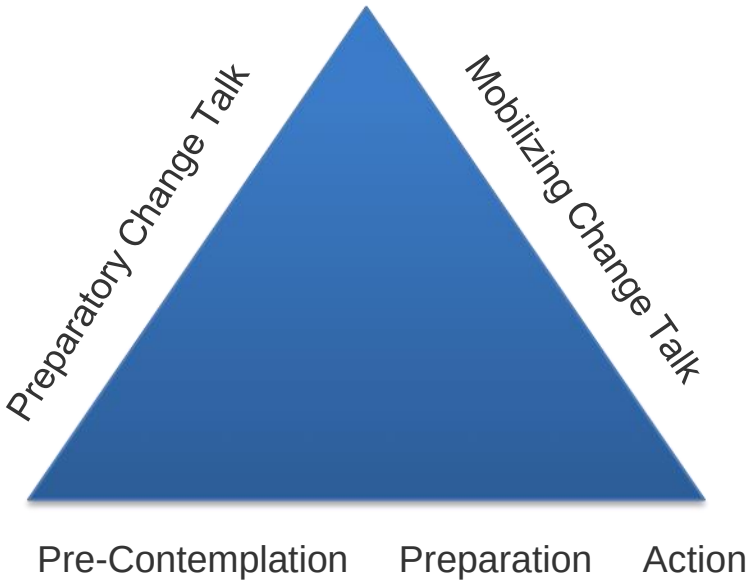
MI-Consistent	MI-Inconsistent
Asking Permission	Giving advice or information without permission
Affirming and Supporting	Confronting the person by disagreeing, arguing, correcting, shaming, blaming, criticizing, labeling, ridiculing, or questioning the person's honesty
Emphasizing freedom of choice, autonomy and control	Directing the person by giving orders, commands, or otherwise challenging the person's autonomy

Facilitating Change:
Change Talk

	Questions	Type of Change Talk
Desire	What would you *like* to be different?	Preparatory
Ability	What do you think you *could* do?	Preparatory
Reasons	What would be some good *reasons* to make this change?	Preparatory
Need	How *important* is it for you to do this?	Preparatory
Commitment	So what do you think you *will* do?	Mobilizing
Activation	What are you *willing* to do?	Mobilizing
Taking Steps	What steps have you already taken?	Mobilizing

Ambivalence

- Ambivalence is a normal step on the road to change
- Should be explored not confronted
- Can involve simultaneously conflicting motivations
- Contemplating change involves self-talk, thinking about the pros and cons of available alternatives



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MI: The Long Game

You may not see the results of MI during a single encounter:

- Don’t discount the importance of “planting a seed”
- Don’t underestimate the value of building a therapeutic relationship (which may be particularly important if patients feel stigmatized or have had prior poor ED experiences related to OUD)
- Someone else down the road may see the fruits of your labor

Objectives

1. How to Enhance Motivation in the ED: Key Components of Motivational Interviewing
2. **Describe the fundamentals of Screening, Brief Intervention, and Referral to Treatment (SBIRT)**
3. Outline the key components of behavior
4. Describe various evidence based counseling approaches for opioid use disorders

Screening, Brief Intervention, Referral and Treatment (SBIRT)

- The United States Preventive Services Task Force (USPSTF) has recommended that all adults in primary care be screened to identify unhealthy alcohol use, and that those with unhealthy use receive a brief counseling intervention
  - Brief Intervention (BI):
    - Based on a Harm-Reduction Model – emphasizes reduction in use rather than abstinence
    - Time-limited, Client-centered counseling session designed to reduce substance use
    - NOT linked to "readiness to change" – can be used in pre-contemplative patients
    - Generally delivered by health care professional
    - Average duration 5-20 minutes

Babor et al., 2017
Whitlock et al., 2004
Zgierska and Fleming, 2014

SBIRT

5-A's	Description
Ask	Screening and Assessment of risk level ▪ Can include screening questionnaire, lab or physical findings
Advise	Direct advice from the Clinician about the patient's substance use ▪ Review results in an objective manner ▪ Convey concerns with a strong, clear and personalized language
Assess	Evaluate patient's willingness to change the unhealthy behavior after hearing the Clinician's advice. If patient is not willing to change substance use then: ▪ Clinician should restate concerns ▪ Convey support and a willingness to help when the patient is ready ▪ Encourage patient to reflect about perceived benefits of continued use vs. decreasing or stopping use ▪ Explore barriers to change
Assist	Help agreeable patient develop a treatment plan in accord with their goals ▪ Use behavior change techniques e.g. Motivational Interviewing ▪ Start with small, achievable steps ▪ Articulate a concrete and specific plan
Arrange	Follow-up visits, specialty referrals and educational materials

Agerwala and McCance-Katz, 2012
Zgierska and Fleming, 2014

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Objectives

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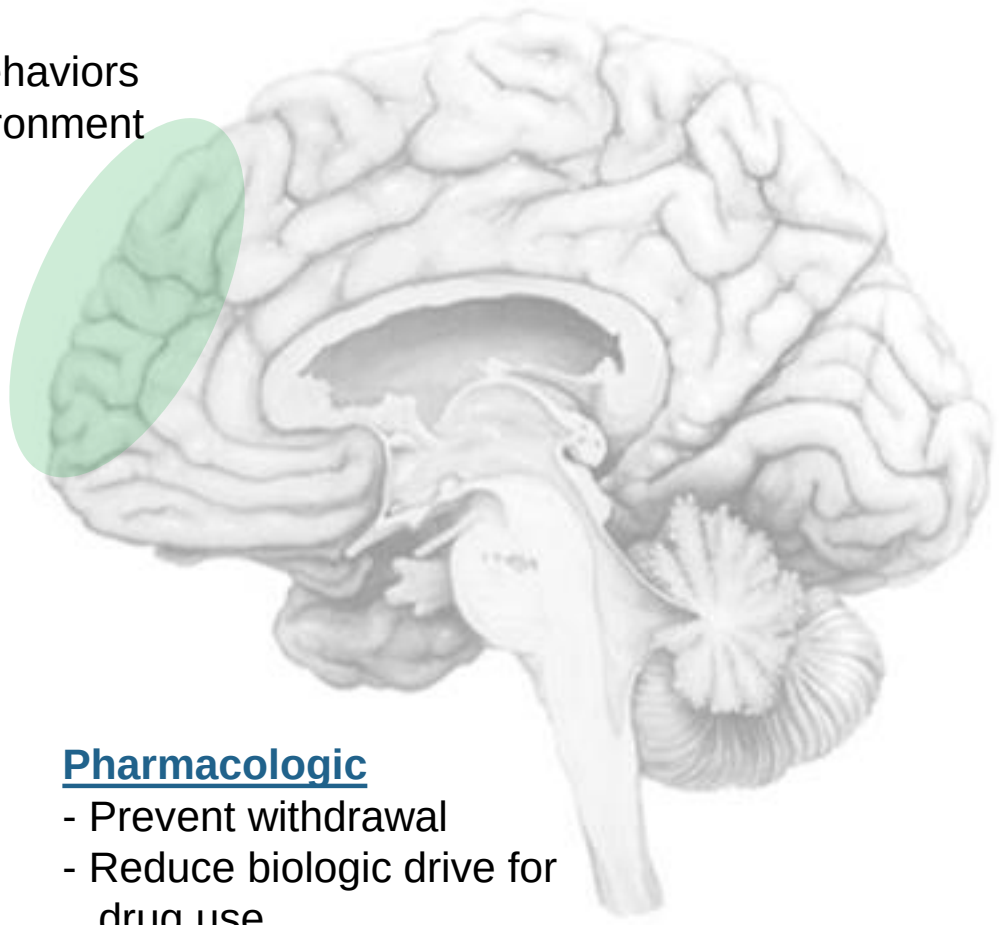
2. Describe the fundamentals of Screening, Brief Intervention, and Referral to Treatment (SBIRT)
3. **Outline the key components of behavior**
4. Describe various evidence based counseling approaches for opioid use disorders

Treatment Strategies

Behavioral

- Learn new behaviors
- Manage environment



Pharmacologic

- Prevent withdrawal
- Reduce biologic drive for drug use

ABC's of Behavior

Antecedents
- What happened *before*?

Cues
Triggers
Stressors

Behavior
- What did you *do*?

What could be done instead?

Consequences
- What came *after*?

Our brains listen most to immediate consequences.

Ramnero & Torneke 2011

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Objectives

1. How to Enhance Motivation in the ED: Key Components of Motivational Interviewing
2. Describe the fundamentals of Screening, Brief Intervention, and Referral to Treatment (SBIRT)
3. Outline the key components of behavior
4. **Describe various evidence-based counseling approaches for opioid use disorders**

Various Modes of Evidence Based Counseling Approaches

- Cognitive-Behavioral Therapy
- Medication Management
- Mutual Support Groups
  - (e.g. AA, NA, Smart Recovery)

Medical Management

Most sessions 15-25 minutes, weekly to monthly:

- Monitor self-reported use, lab markers, consequences
- Monitor adherence, response, adverse effects
- Educate about SUD consequences, treatments
- Encourage abstinence
- Encourage use of community supports and healthy lifestyle changes

VA DoD Guidelines, 2015

Mutual Support Groups

Can be a helpful adjunct to medical management of OUD:

- **Narcotics Anonymous**
  - Founded in 1947 based on a 12-step model of sobriety with a fundamental evoking of God or a Higher Power
  - Many chapters may be resistant to the benefit of medications for OUD Treatment **If referring patients: ****<u>Find a medication-friendly meeting in your area</u>!****
- **Self Management and Recovery Training (SMART) Recovery**

Cognitive Behavioral Therapy

- Evidence-based on social learning theories and principles of operant conditioning
- Key Features:
  - An emphasis on functional analysis of drug use, i.e., understanding drug use within the context of its antecedents, behaviors and consequences
  - Skills training, that help the individual recognize:
    - States/ situations of vulnerability to drug use;
    - Strategies to avoid high-risk situations whenever possible
    - Utilize skills to cope effectively with those situations if they are unavoidable

Carrol, 1998, 2005
McHugh et al., 2010

Providers Clinical Support System

Summary

- Motivational Interviewing is a collaborative, goal-oriented style of communication with particular attention to the language of change that can be used by any trained provider or patient advocate.

- It is designed to strengthen personal motivation for and commitment to a specific goal, such as starting treatment for OUD, by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion.

- Do not let your inability to refer to counseling be a barrier to starting buprenorphine! While some may benefit from additional counseling, most do well with medication and counseling associated with medical management of buprenorphine.

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Special Legal & Regulatory Considerations

Learning objectives

Provide the Emergency Physician with a knowledge of:

- Buprenorphine prescribing rules: the “72 hour rule” and the DEA license "X-waiver"
- Confidentiality Regulations - 42 CFR Part 2
- DEA Compliance – Prescribing and Dispensing/Administering
- Key Clinical Documentation and record keeping
  - Particularly helpful if considering using the X-waiver license to work in a clinic

Key Questions

Qs: What is the “DATA 2000 DEA X-waiver”?

Are There Rules about Using Buprenorphine in the ED?

What is the “72 Hour Rule”?

DATA 2000/ X-Waiver

- "DATA 2000"? "X-waiver"? What does this refer to?
- "Drug Addiction Treatment Act of 2000"
  - (went into effect in 2002)
- Provided a "waiver" to treat opioid addiction outside of a traditional opioid treatment program (e.g. a "methadone clinic") – to **PRESCRIBE buprenorphine**.
  - There is no special license/certification required to work as a provider in a methadone clinic.
- Applies to "schedule III, IV and V medications with FDA approval to treat addiction…"

(pssst… Buprenorphine is the only one!)

DATA 2000/ X-Waiver

- Requirements to get an “X-waiver”:
  - Active state medical license
    - As of 2017, PAs & APRNs eligible
  - Valid individual DEA license
  - Eight-hour course for MD/DOs & 24 hours for PA/APRNs
  - Organizations that can provide the course are codified in the law
  - Patient limits apply to patients treated “at any one time”
    - A rolling limit of current prescriptions
    - 30 patients in the first year (will apply to most EPs)
    - May increase to 100 pts in year two
    - May increase to 275 in year three

DATA 2000/ X-Waiver

- Again, the "X-waiver" permits the provider to PRESCRIBE buprenorphine:
- "for the treatment of opioid use disorder, including *maintenance*, *detoxification …* and *relapse prevention*"
- Assuming, that "the practitioner has the *capacity* to provide directly, by referral, [or in other manner] appropriate counseling and other appropriate ancillary services."
  - As an ED provider, referring a patient to an addiction treatment program is sufficient.
  - An ED provider is not required to ensure that a patient follows up with such a program (and there is no "warm hand-off requirement").

“Three Day Rule” – the highlights

- Again, **per the DEA, ANY** licensed provider (MD, DO, PA, APRN) may **administer** a daily dose of buprenorphine to an ED patient for up to 3 days in a row.
  - A DEA X-waiver license is **NOT** required
  - Every ED is a “DEA Registered Facility” – so no special license or permit is required of the hospital
- Does not have to be the same provider all 3 days
- The “dose” (in milligrams of buprenorphine) is NOT specified
  - During a single ED visit, there is no limit on the milligrams of buprenorphine which can be administered (“loading” is possible) – see additional ACEP publications: loading with up to 24-32mg, in select patients.

“Three Day Rule” – the highlights

- The route of administration is NOT specified
  - Thus, depot injections of long acting subcutaneous or intramuscular formulations of buprenorphine have not been specifically excluded.
- Patients CANNOT be dispensed a 3-day supply
  - It has to be administered to the patient in the ED, so they ha to come back for subsequent doses
- However, An “X-waiver” is required to *prescribe* any buprenorphine for the treatment of OUD.
  - *Prescribing* even a single dose (to be filled at a pharmacy) for the purpose of treating OUD –- requires an X-waiver.
  - The clinician must also have an X-waiver to order any dose(s) of buprenorphine to be dispensed from the ED to take home.

“Three Day Rule” – Referral to Clinic?

- *Is it **necessary** to be able to refer a patient to an opioid addiction treatment clinic, to administer buprenorphine in the ED for withdrawal or ongoing treatment?*
- Officially, it is required …
- However, the DEA is primarily concerned about **DIVERSION** of prescribed, or dispensed, buprenorphine.
- The DEA is far, far less concerned about medications ordered and administered in hospitals.

No limit for admitted patients!

- If admitting the patient to the hospital, NO limit on days of administration:
  - NO “limitations on a physician or other authorized hospital staff to maintain or detoxify a person with buprenorphine as an incidental adjunct to medical or surgical conditions other than opioid dependency.”
  - “A patient with an opioid dependency who is admitted to a hospital for a primary medical problem … [e.g. acute MI] … may be administered opioid agonist medications such as methadone and buprenorphine to prevent opioid withdrawal that would complicate the primary medical problem.”
  - A DATA 2000 X-waiver is NOT required
  - Does NOT apply if the ***primary*** diagnosis for hospital admission is ”opioid withdrawal or opioid use disorder”

http://www.samhsa.gov/medication-assisted-treatment/legislation-regulations-guidelines/special-circumstances-providing-buprenorphine

Back to the DATA 2000/ X-Waiver

- So, if an ED provider isn't required to have an X-waiver to be able to administer buprenorphine in the ED …
  - **Why should an emergency physician get an X-waiver?**
- ED providers should get "X-waivers" to:
  - Learn more about Opioid Use Disorder, AND …
  - When EPs prescribe buprenorphine from the ED:
    - Patients don't need to return to the ED daily ("three day rule") to get a dose of buprenorphine, waiting to get into a clinic.
    - Patients who receive buprenorphine are less likely to return to the same ED within 30 days for a drug-related visit
    - Patients are twice as likely at 30 days to be in treatment!!

Berg 2007
D'Onofrio 2015

More Questions

Qs: Are there special privacy rules for treating addiction?

What is “42 CFR Part 2”?

Why can’t I tell from the PDMP that a patient is in methadone treatment?

Federal Health Privacy Laws

- **HIPAA**: Health Insurance Portability and Accountability Act of 1996
  - Minimum safeguards to protect privacy of protected health information (PHI)
- *"Confidentiality of Alcohol and Drug Abuse Patient Records, Title 42 Code of Federal Regulations (CFR) Part 2"* **-- "42 CFR Part 2"**
  - Promulgated in 1975, updated in 1987, further revisions anticipated
  - Governs confidentiality of alcohol and drug treatment and prevention information
  - Extra protections because of the potential for SUD information to be used against an individual
    - Loss of employment, housing, child custody
    - Discrimination (health professionals, insurers)
    - Criminal justice consequences

Federal Health Privacy Laws

- **Think of 42 CFR Part 2 as "HIPAA Plus"**
  - Potential use of substance use disorder information against an individual.
  - Protects confidentiality of the identity, diagnosis, prognosis, or treatment of any patient records maintained in connection with the performance of any federally assisted program or activity relating to substance abuse education, prevention, training, treatment, rehabilitation, or research.
  - Ensure that a patient receiving treatment for a substance use disorder in a Part 2 program is not made more vulnerable than an individual with a substance use disorder who does not seek treatment (e.g. from criminal prosecution)

Who is covered by 42 CFR Part 2?

- Applies to federally assisted drug/alcohol treatment and prevention “programs”

- ”Program” not clearly defined but is interpreted as the following:
  1. Standalone individual or entity whose...
  2. Specific unit within a general medical facility whose...
  3. Individual within a general medical facility whose...

  ... primary function and identify is to provide drug/alcohol diagnosis, treatment, or referral for treatment

Who is covered by 42 CFR Part 2?

An individual or entity that holds itself out as providing and provides OUD diagnosis, treatment, or referral for treatment

– i.e., The primary role is to provide these OUD services

42 CRF Part 2 **does NOT apply** to general medical facilities

- e.g., **Hospital**, **Emergency Department**, Primary Care

42 CRF Part 2 **DOES apply** to alcohol/drug programs within them

- e.g., Inpatient detox unit or outpatient OUD clinic within a medical center
- e.g., Addiction specialist working in a primary care practice

Code of Federal Regulations
(CFR) 42 C.F.R. Part 2

- 42 C.F.R. Part 2:
  - **Must obtain signed patient consent** before disclosing information to any third party
    - Including records of prescriptions to pharmacy
  - Disclosure includes any communication (oral, written, or electronic) identifying someone as having an alcohol/drug problem or being a patient in an alcohol/drug program (past or current)
- Additional information at:
  - https://www.samhsa.gov/about-us/who-we-are/laws-regulations/confidentiality-regulations-faqs
- An Example Consent Form can be found in TIP-40:

  https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf

CFR, 2017
CSAT, 2004

Some Exceptions to Disclosure Rules

- Internal communications (within the program)
- Qualified service organization agreement
- Crimes on premises or against personnel
- **Medical emergencies**
- Mandated reports
- IRB approved research
- Audit and evaluation
- Court orders

**Confer with your legal department if uncertain

Consequences of Violating 42 CFR Part 2

- Criminal penalty
- Loss of substance use disorder treatment program license or certification
- Patients may take legal action

Why should emergency physicians care about 42 CFR?

- More difficult to get records from an Opioid Addiction Treatment Clinic/Facility for patients in the ED/hospital:
  - Clinic Staff are trained to vigorously protect patients' privacy.
  - Addiction clinics always expect a signed Release of Information (ROI) form.
    - If a patient can't give consent (e.g. the patient is intubated), an addiction clinic will expect documentation of the emergent medical condition and the reason the patient can't give consent.

      -Will expect in writing before giving any verbal information.
  - Most addiction clinics aren't open after hours but are expected to have an "after hours" phone number for emergencies.
- Addiction Clinics also expect an ROI from the patient before requesting ED records.
  - Consider getting a signed ROI of the ED record (before the patient leaves the ED), part of your standard "warm hand-off" process.

Why isn't Methadone treatment listed on PDMP reports?

- If a patient receives treatment in a methadone program (also known as an "OTP" – for "Opioid Treatment Program"), that information is NOT reported to state prescription data monitoring programs (PDMPs).
  - Protected by 42 CFR Part 2.
  - No medication is "prescribed"
    - No prescription – no report to the state board of pharmacy.
  - Methadone programs only "administer" and "dispense" methadone (and in some programs, buprenorphine as well).
    - Methadone clinics report daily to the "State Opioid Treatment Authority" (the "SOTA") in each state.
  - Some patients are aware of this, and may still seek prescriptions of opioids for either personal use, or to divert.
- EXCEPTION: Methadone is ***prescribed*** for pain (rarely a good idea), methadone will show up on the PDMP.

Qs: Any special documentation requirements?

Any special documentation tips?

ED Documentation Tips:

- If prescribing buprenorphine, **put the diagnosis of "moderate" or "severe opioid use disorder**" on the chart:
  - This diagnosis is usually easily supported by a well-documented ED chart, particularly if patients present with:
    - Opioid Overdose
    - Opioid withdrawal
    - Heroin use
    - History of smoking, snorting, or injecting opioids.
    - An abscess or other infectious complication from injecting opioids.
  - Should be documented when prescribing buprenorphine for the treatment of opioid use disorder
  - If done in the ED this can expedite referral process for many outpatient treatment providers!
    - See next page of DSM-V criteria for OUD – most patients in the ED with OUD complications easily meet the criteria.

DSM-5 Criteria for SUDs

Loss of control
- more than intended
  - amount used
  - time spent
- unable to cut down
- giving up activities
- craving

Physiology
- tolerance
- withdrawal

formerly "dependence"

Consequences
- unfulfilled obligations
  - work
  - school
  - home
- interpersonal problems
- dangerous situations
- medical problems

formerly "abuse"

- 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

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APA, 2013

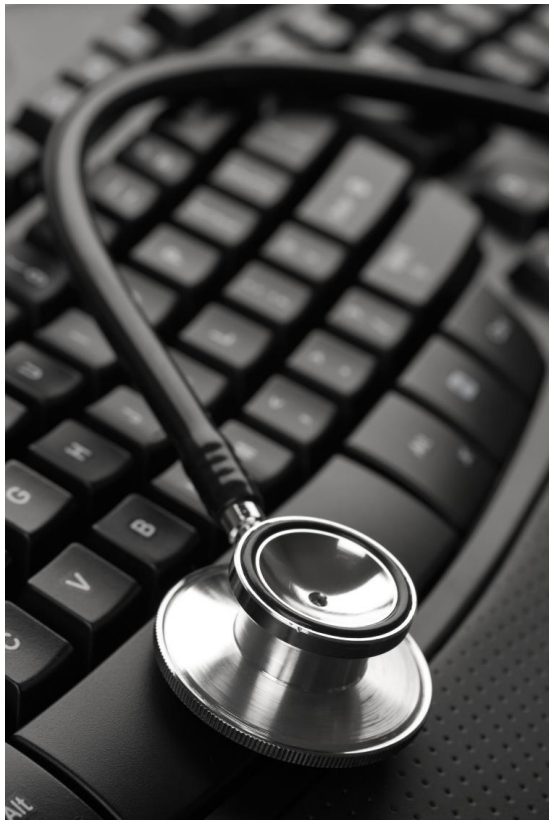
ED Documentation Tips:

- Documentation of patient education:
  - How to properly take buprenorphine (always and only sublingual).
  - Safe storage.
  - Build into the discharge instructions.
- Plan for referral:
  - Know your local treatment options and build the “smart phrase” into the EMR discharge instructions.
  - Partner with administration to develop a hand-off process (use ED social workers, care coordinators, etc.)

Medical Record Keeping

Storage of Records:

- Must keep available according to state and federal requirements
- Can be kept at a central location (but must notify DEA)
- Must be kept in a double-locked, secure place when not in use
- Note: Electronic Medical Records meet these criteria



Qs: Anything to know about DEA Compliance?

Prescribing and Dispensing/Administering?

Office/ED-Based Buprenorphine Storage and Dispensation

- Buprenorphine dispensing/administration is a legal practice under DATA 2000
- Must provide medication security and storage
- Must maintain the following records for 2 years (longer in some states):
  - Inventories of buprenorphine received and amounts dispensed
  - Reports of theft or loss
  - Destruction of controlled drugs
  - Records of dispensing

These records should be covered by your hospital pharmacy and electronic medical record in the ED/hospital-based setting

-- But this is another reason that many clinics only perform buprenorphine initiation by prescription (as opposed to witnessed “in-office induction”)

DATA, 2000

Drug Enforcement Agency (DEA)

- Authorized by the Controlled Substances Act (21 U.S.C. 822 (f) 880 and 21 CFR 1316.03:
  - Conduct periodic inspections to ensure prescribers and programs comply with:
    - Patient limits that they are waivered to treat (30/100/275)
      - Rarely an issue for EM Providers.
    - Record Keeping and Security,
    - Other requirement of the Controlled Substances Act
      - All should be easy for EM providers with an EMR.
  - These inspections are low-key and not intended to be punitive
    - Easiest if the hospital EMR can produce a report of an individual doc's buprenorphine prescribing.

Buprenorphine Prescription Requirements: 21 CFR

- Basic rules for writing prescription for buprenorphine from the ED:
  - Full identifying information for the patient, including his/her name and address
  - Medication name, strength, dosage form, and quantity
  - Directions for use
  - Dated and signed on the day they are issued
  - All of the above should be simple with any EMR.
- DEA number and DATA 2000 identification number (which begins with the prefix X) – must be on the script!!
  - **Review with your EMR administrator** – may not be easy to automate.
- A hospital ED can only provide a "take home" pack of bup/nx if the ordering ED provider has an X-waiver.
  - **Another reason for ED docs to get X-waivers!**

FSMB, 2004, 2013

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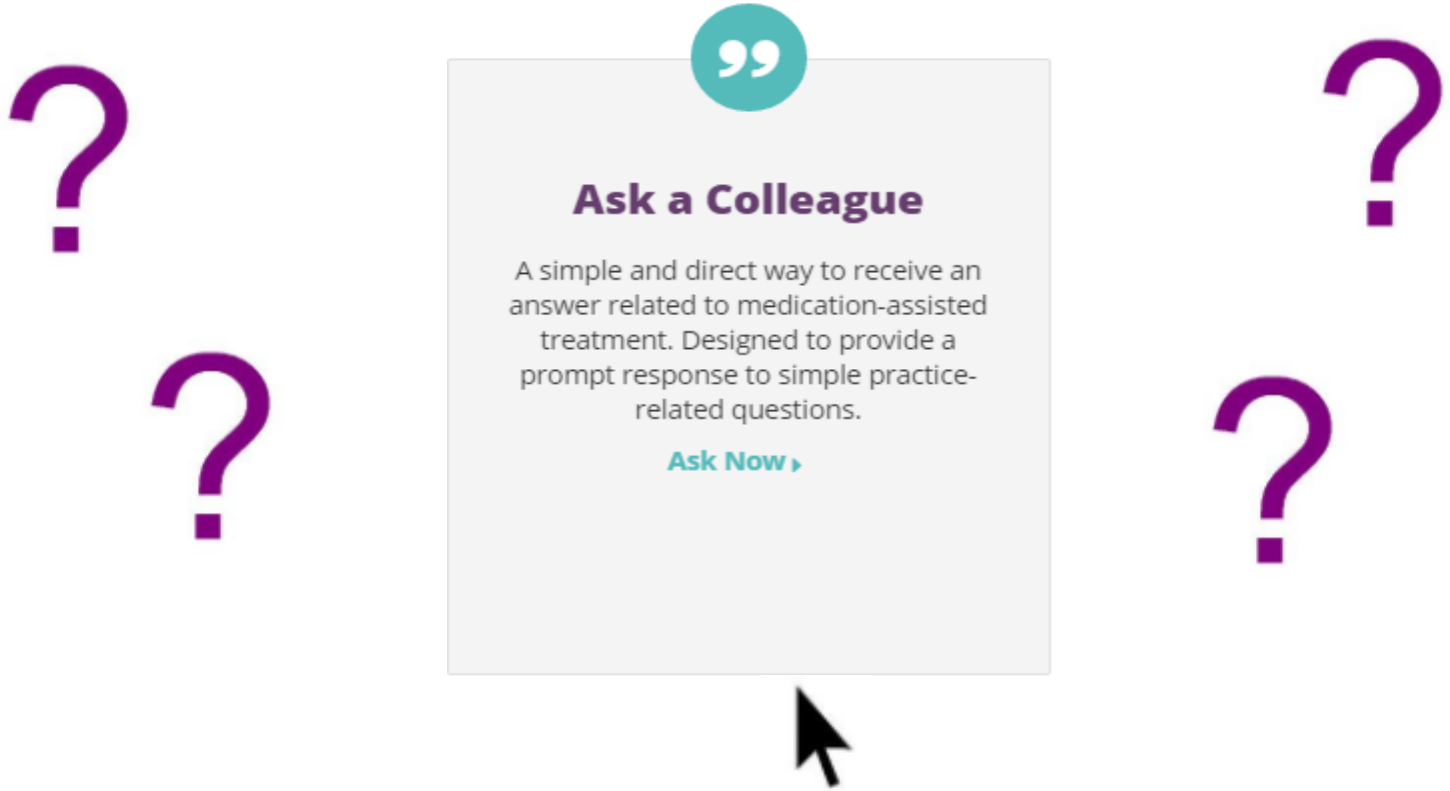
PCSS Discussion Forum

Have a clinical question?



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