MOUD Bootcamp

January 9, 2025

Daniel A. Nauts, MD, FASAM

Disclosure information

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- No disclosures

SPONSORS

- Montana Behavioral Health and Developmental Disabilities Division
- Montana Primary Care Association
- American Society of Addiction Medicine (ASAM)
- Northwest Society of Addiction Medicine

Your presenter

- Daniel A. Nauts, MD, FASAM
- Trainer/Montana Primary Care Association and American Society of Addiction Medicine
- Board certified Internal Medicine and Addiction Medicine
- Secretary Northwest Chapter American Society of Addiction Medicine
- Board member Drug Utilization Review, Mountain Pacific Quality Health
- Member Montana Medical Association Substance Use Disorder Committee
- Board member, 406 Recovery, non-profit telehealth

Objectives:

- Decrease barriers for MOUD
- List portals of entry, e.g., access points for care.
- Teach the relative effectiveness of options for MOUD.
- Implement low threshold care in your practice.
- Use evolving initiation/induction strategies in an increasingly complex environment
- Practice harm reduction or outcome centered care

Course Content

A Little Epidemiology

Neurobiology of SUD

Pharmacology of Medications for Opioid Use Disorder (MOUD)

Evidence Supporting MOUD

Making the Diagnosis

How to "Bupe" in the ED/Hospital/or Clinic

How to Have Patient Start at Home, e.g. Home Induction/Initiation

- Concepts of Maintenance Therapy
- Special Populations
- Management of Acute Pain
- Misc. Topics

Removal of the X-waiver

- December 29, 2023, President Biden signed the Consolidated Appropriations Act.
- Section 1262 rescinded the X-waiver required to prescribe buprenorphine products for the treatment of Opioid Use Disorder
- All associated requirements including recommendations for counseling and patient limits also eliminated.
- SAMHSA and DEA list the educational requirements that will be required to renew your DEA registration.

What does this mean?

- What gaps in expertise and knowledge exist among providers that could be alleviated with training?
- Has access to MOUD increased, remain unchanged, or decreased? To date, providers prescribing MOUD has only minimally increased.
- Can we get buy-in to low threshold care (aka harm reduction), outcome directed care and warm handoffs?
- Pharmacologic management is easy, but diminishing stigma is complex! What can you do?
- Other options for increasing access:
  - Telehealth
  - Collaborative practice agreements with pharmacists
  - EMS initiation post-overdose with Emergency Physician surpervision

Key relevant resources

- Shatterproof/ACEP Stigma Video, shatterproof.org
- Consensus Recommendations on the Treatment of Opioid Use Disorder in Emergency Departments, Annals of Emergency Medicine vol. 78, 3, Sept 2021.
- CA-Bridge Protocols/ bridgetotreatment.org
- CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022; MMWR/ November 4, 2022/ vol. 71, pg 54.
- VA/DoD Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain, May 2022.
- npsdiscovery@cfsre.org
- Andrew Herring, papers, high dose induction/initiation strategies, extensive clinical experience
- Miller, William, Rollnick, Stephen, **Motivational Interviewing,** 4th edition, 2023, Guilford Press.

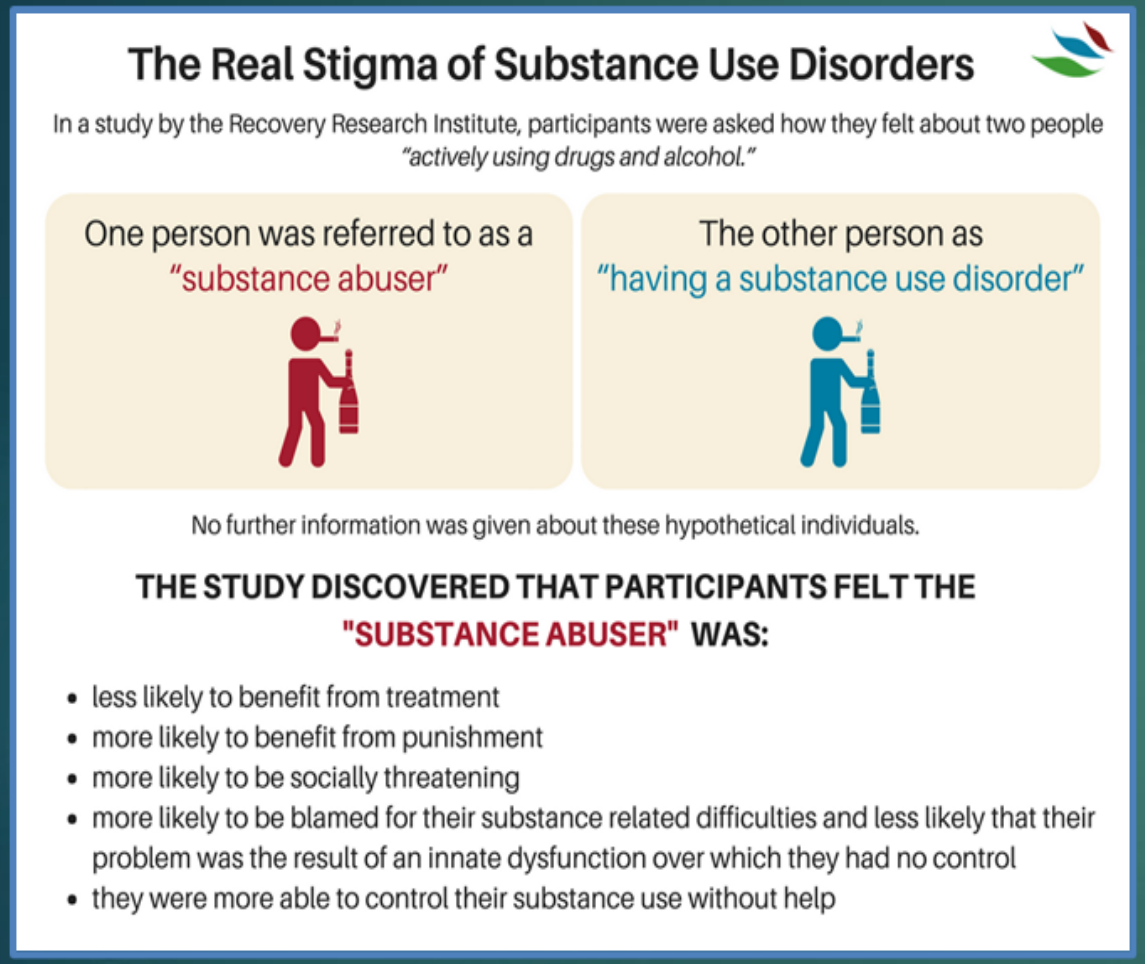
American Society of Addiction Medicine (ASAM) Definition of Addiction, Sept 15, 2019

- Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with substance use disorders use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.
- **Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases, such as diabetes.**

Recommendations: Avoiding Substance Use-Associated Discrimination

- CLINICIANS SHOULD EXAMINE THEIR ASSUMPTIONS AND DECISIONS FOR ANY PERSONAL BIASES THAT MAY AFFECT THEIR ABILITY TO PROVIDE EFFECTIVE CARE FOR INDIVIDUALS WHO USE SUBSTANCES. (A3)
- CLINICIANS AND OTHER STAFF INTERACTING WITH PATIENTS SHOULD USE NEUTRAL TERMS TO DESCRIBE ALL ASPECTS OF SUBSTANCE USE AND AVOID LANGUAGE THAT PERPETUATES STIGMA (SEE CHANGING THE LANGUAGE OF SUBSTANCE USE). (A2)

Stigma and Language: What We Say and How We Say It Matters



The Real Stigma of Substance Use Disorders

In a study by the Recovery Research Institute, participants were asked how they felt about two people *"actively using drugs and alcohol."*

One person was referred to as a "substance abuser"

The other person as "having a substance use disorder"

No further information was given about these hypothetical individuals.

THE STUDY DISCOVERED THAT PARTICIPANTS FELT THE "SUBSTANCE ABUSER" WAS:

- less likely to benefit from treatment
- more likely to benefit from punishment
- more likely to be socially threatening
- more likely to be blamed for their substance related difficulties and less likely that their problem was the result of an innate dysfunction over which they had no control
- they were more able to control their substance use without help

Three types of stigma

- **Public stigma:** negative attitudes and fears that isolate those with addiction
- **Structural stigma:** excluding those with addiction from opportunities and resources
- **Internalized stigma:** believing negative stereotypes about oneself

https://www.recoveryanswers.org/research-post/the-real-stigma-of-substance-use-disorders/
https://facesandvoicesofrecovery.org/wp-content/uploads/2019/06/Words-Matter-How-Language-Choice-Can-Reduce-Stigma.pdf
https://harmreduction.org/issues/harm-reduction-basics/undoing-stigma-facts/
https://www.asam.org/docs/default-source/default-document-library/nidamed_wordsmatter3_508.pdf?sfvrsn=5cf550c2_2

Addiction Terminology Do's and Don'ts

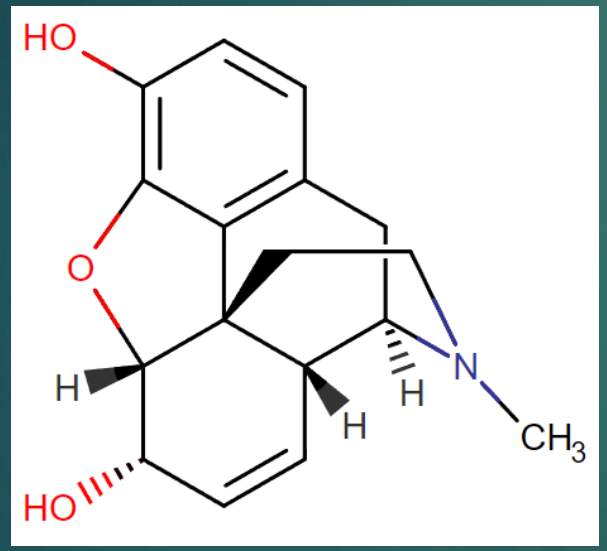
Grayken Center for Addiction
Boston Medical Center

Non-stigmatizing Language	*Stigmatizing Language*
Person with a substance use disorder	Substance abuser or drug abuser Alcoholic Addict User Abuser Drunk Junkie
Babies born with an opioid dependency	Addicted babies/born addicted
Substance use disorder or addiction Use, misuse Risky, unhealthy, or heavy use	Drug habit Abuse Problem
Person in recovery Abstinent Not drinking or taking drugs	Clean
Treatment or medication for addiction Medication for opioid use disorder/alcohol use disorder Positive, negative (toxicology screen results)	Substitution or replacement therapy Medication-assisted treatment Clean, dirty

OUD a Major Public Health Issue

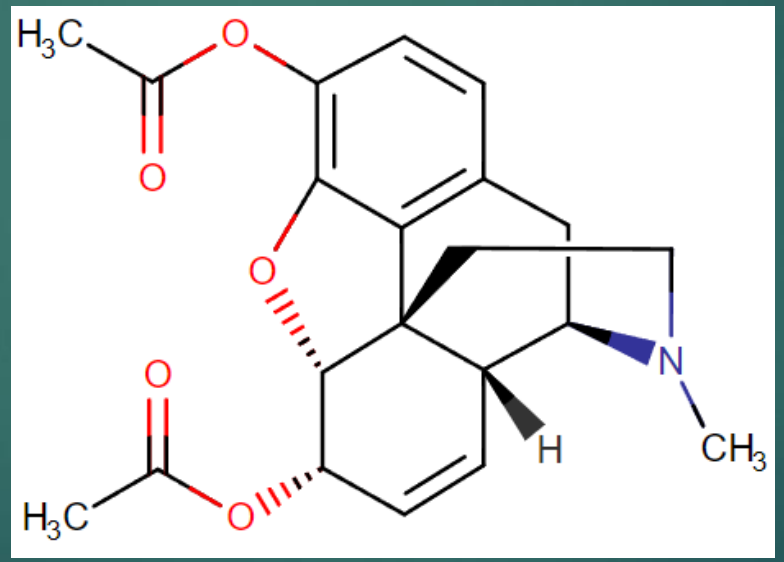
The Scope of The Opioid-Related Overdose Epidemic

Morphine

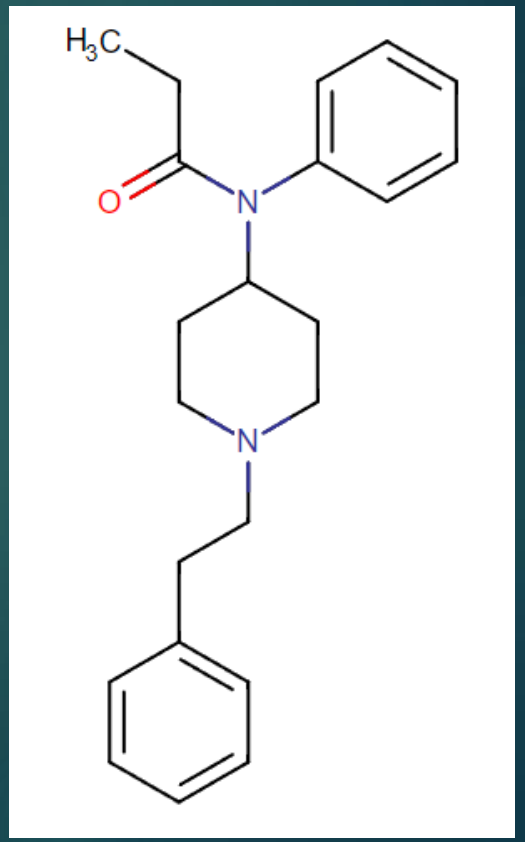


Heroin

Diacetylmorphine



Fentanyl



Lethal Opioid Doses

Opioid	Relative Potency
Morphine	x1
Heroin	x2
Fentanyl	x100
Carfentanil	x10,000 →

SOURCE: DOI: _____

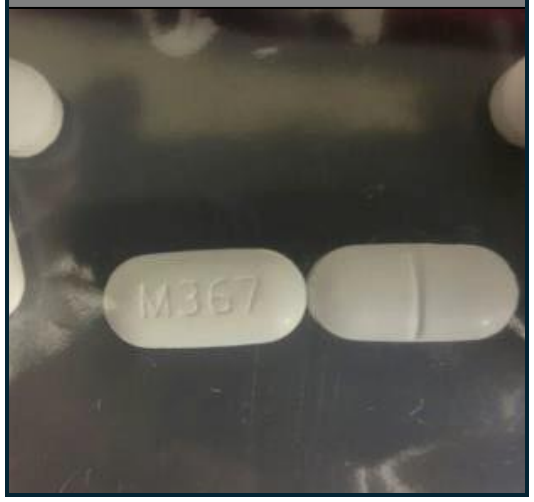
Fentanyl Disguised as Other Drugs is Linked to a Spike in U.S. Overdoses

Fentanyl-contaminated Xanax

DEA.gov

Fentanyl-contaminated Cocaine

Fentanyl-contaminated Hydrocodone



DEA.gov

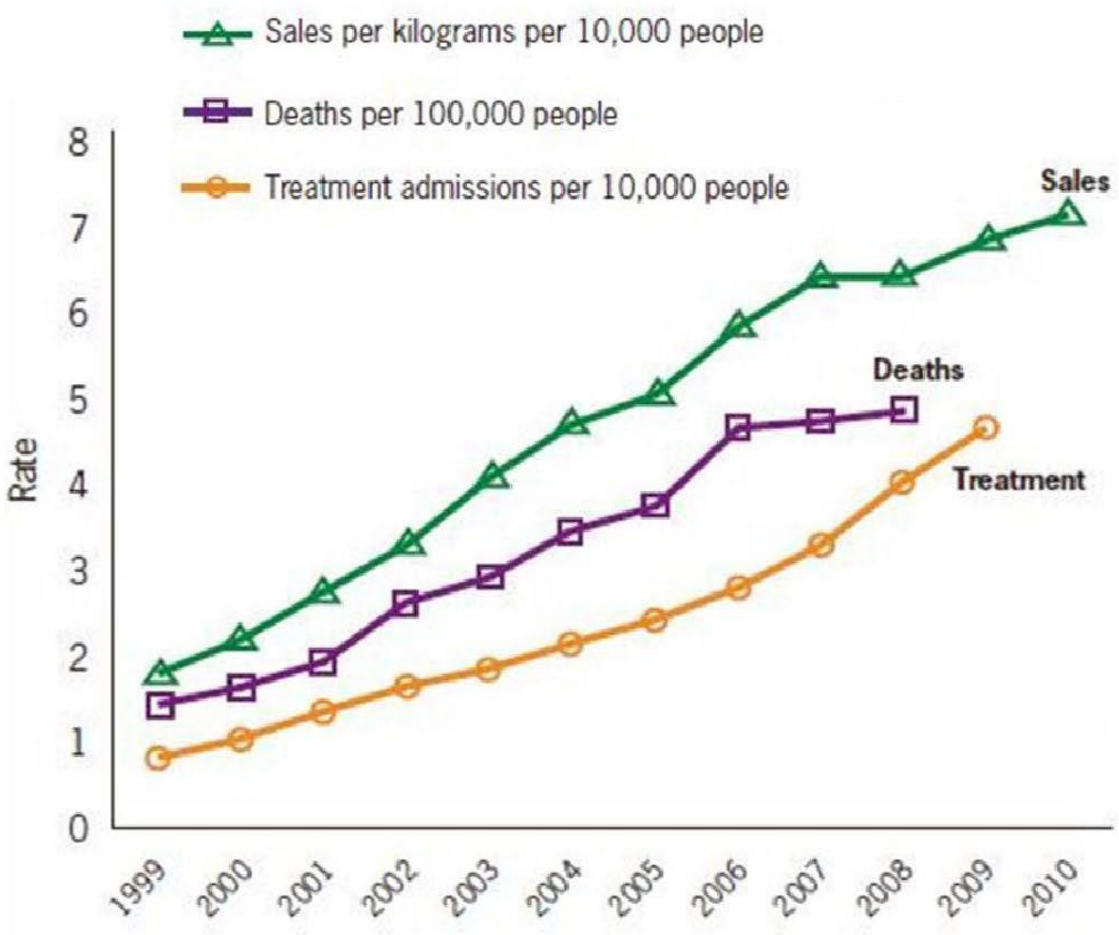
Increasingly Unsafe Drug Supply Adulterated With Xylazine

- Xylazine is a non-opioid sedative with analgesic and muscle relaxant properties.
  - FDA-approved as a veterinary tranquilizer
  - Acts as a central alpha 2 adrenergic receptor agonists
  - Referred to as “tranq”
- Increased prevalence of xylazine with presence in drug seizures in 48 out of 50 states
  - Complicates overdose reversal
  - Patients describe complicated withdrawal symptoms.
  - Increases risk for necrotizing skin wounds

SOURCE: DOI: 10.1111/j.1365-2885.1988.tb00189.x; 10.1016/j.drugalcdep.2022.109380; 10.1001/jamanetworkopen.2024.0572;

Current Epidemic Began With Escalating Use of Prescription Opioids

Rates of Opioid Overdose Deaths, Sales, and Treatment Admissions, United States, 1999 - 2010



SOURCES: NVSS, 1999-2008: ARCOS of the DEA, 1999-2010: Treatment Episode Data Set, 1999-2009.

Prescription Opioid Crisis Focused on Needs of White Individuals With Opioid Addiction

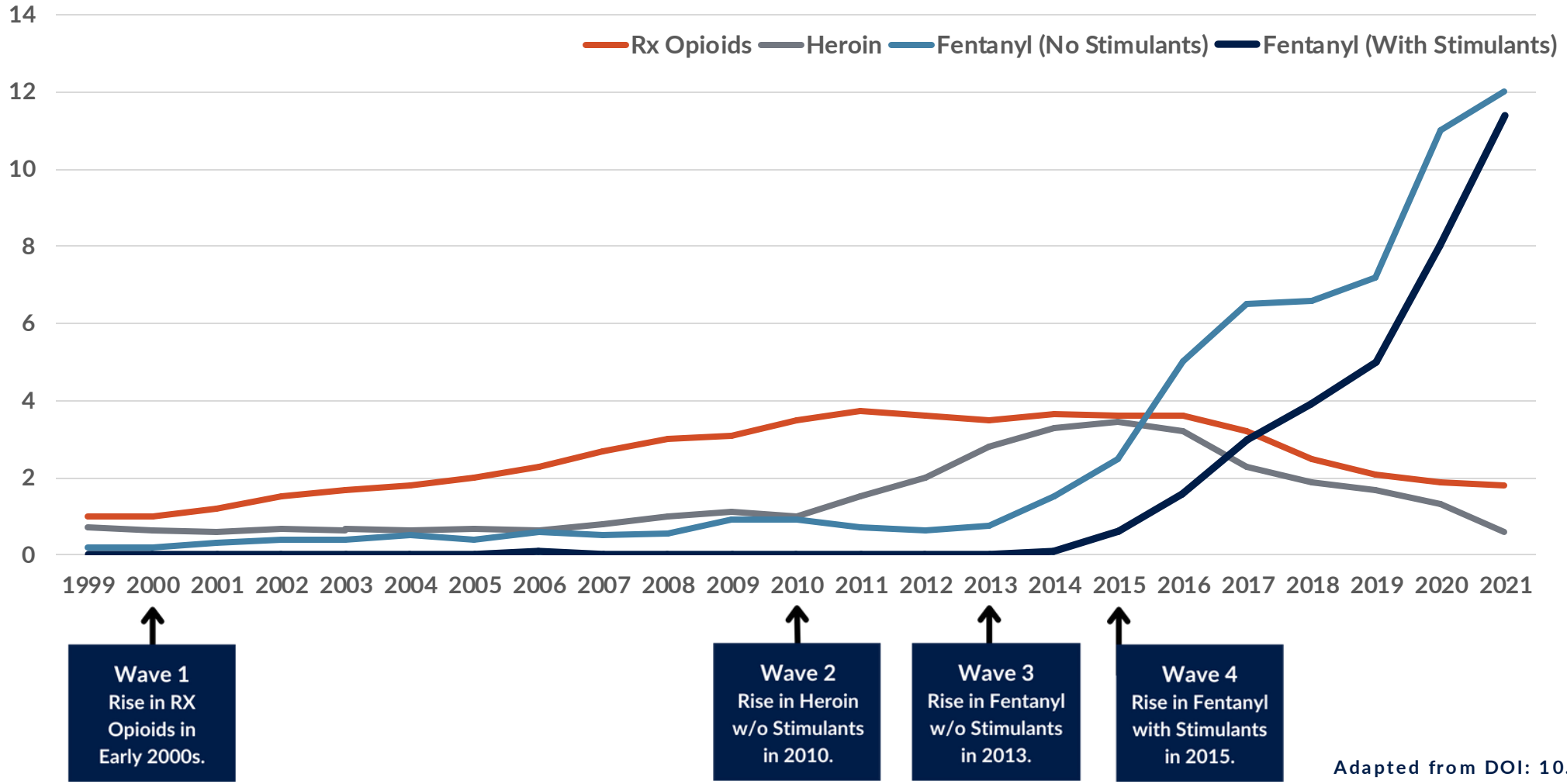
- It was driven by overprescribing of opioids to treat chronic pain.
- Early focus on the prescription opioid crisis centered on the needs of white individuals from rural and suburban areas.

From 1999-2021, almost 645,000 people died from an overdose involving any opioid, including prescription and illicit opioids.

In 2022, over 100,000 people died from an overdose. Over 75% of deaths involved an opioid.

– *Centers for Disease Control and Prevention*

The Overdose Crisis is an Epidemic with 4 Waves

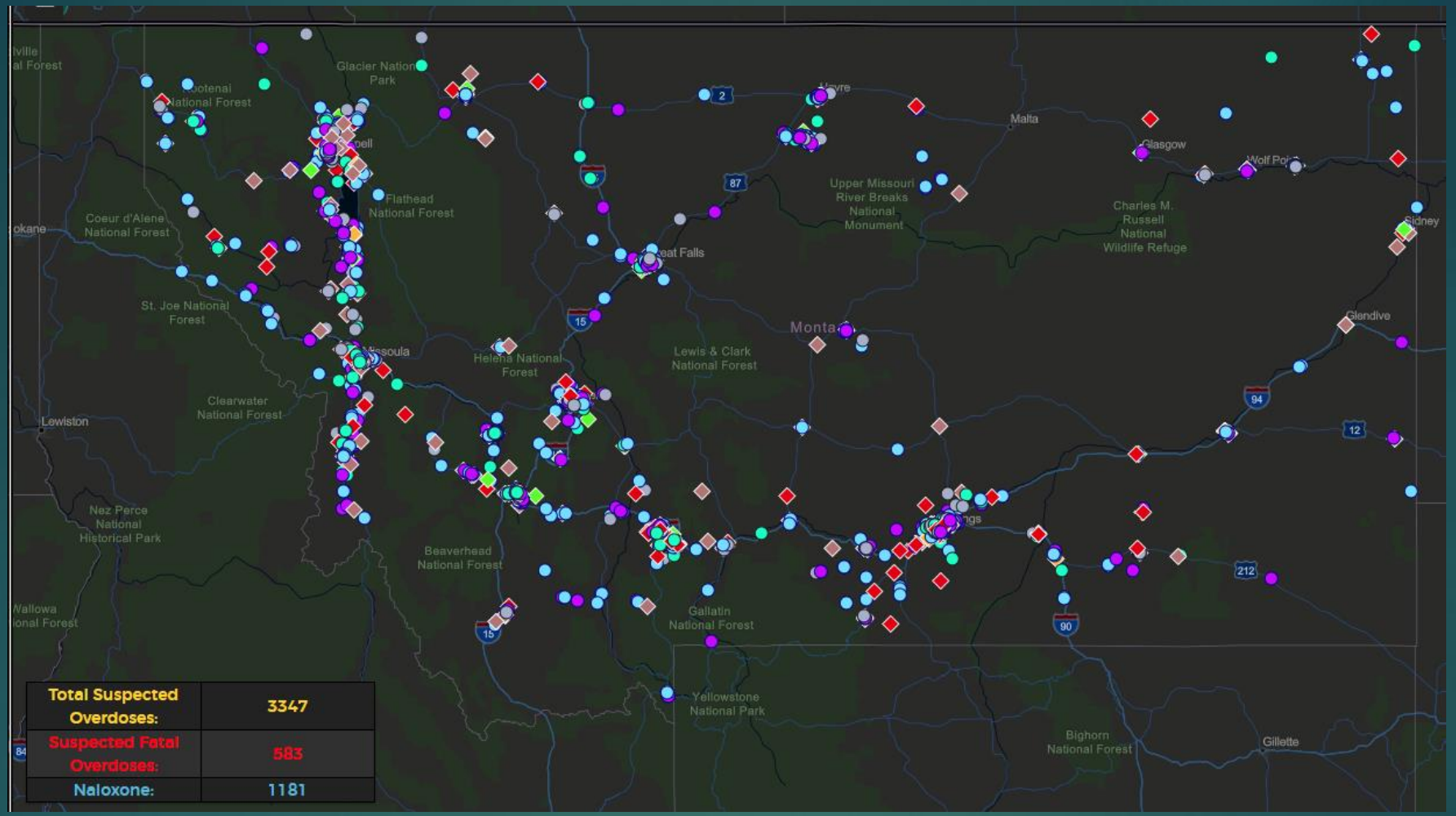


Adapted from DOI: 10.1111/add.16318

Opioid Use

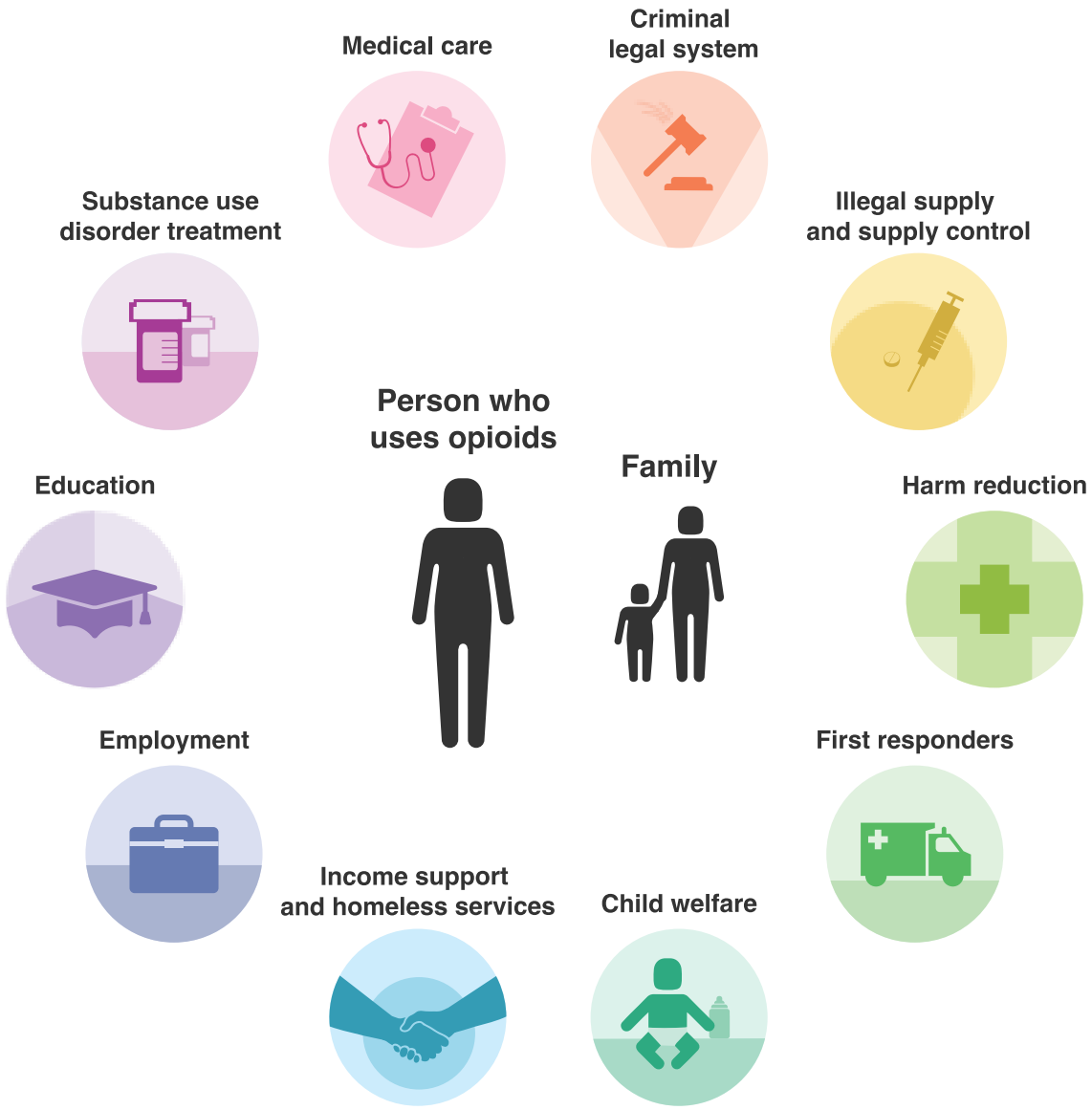
- Opioid addiction impacts individuals from every demographic and socioeconomic group.
- Overdoses are the leading cause of accidental death in the US, with opioids being the most common drug, particularly fentanyl.
- Overdose deaths contributed to declining overall life expectancy in the US.
- The social costs of OUD and fatal opioid overdoses was over 1 trillion dollars in 2017.
- Recent years characterized by increased deaths from polysubstance and rising racial disparities in fatal and nonfatal overdoses.

SOURCE: https://www.ncbi.nlm.nih.gov/books/NBK448203/

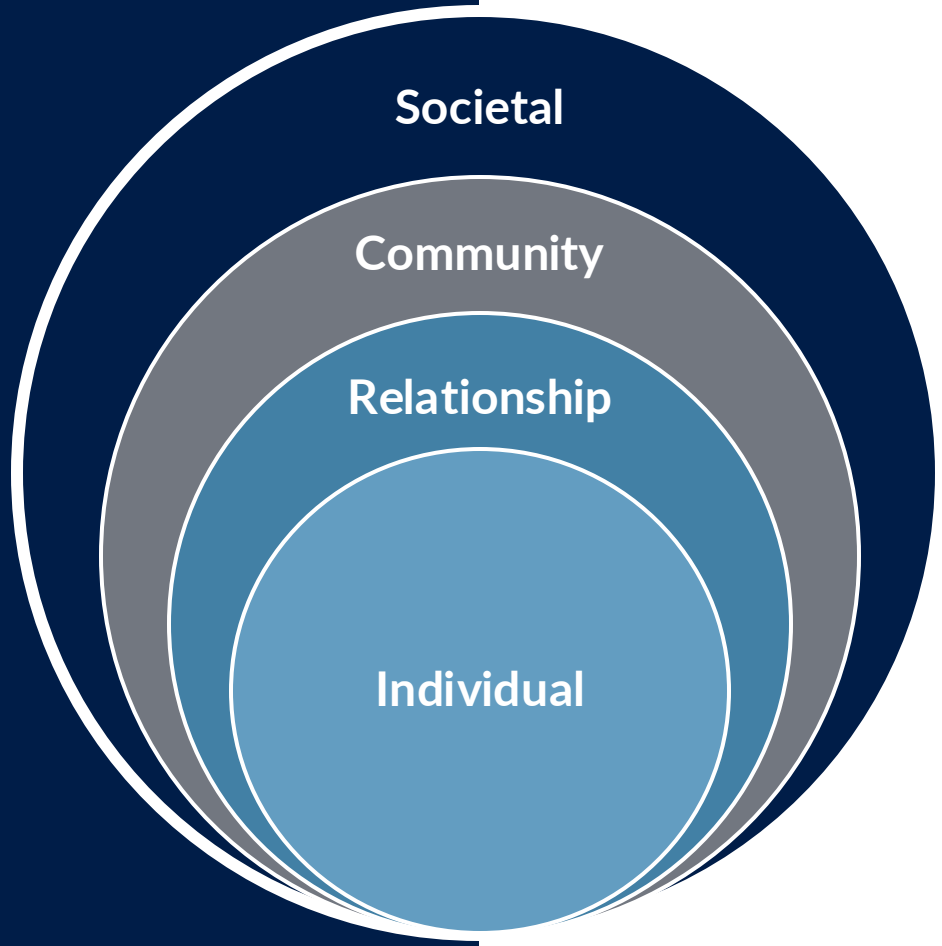


Montana January 1, 2020 – January 8, 2024

The Opioid Ecosystem



Social Determinants of Health (SDoH)



Socio-Ecological Model

- SDoH are conditions within a home, school, neighborhood, and community that affect a wide range of health, functioning and quality-of-life outcomes and risk.
- SDoH are “complex, integrated, and overlapping social structures, policies, and economic systems, including the social and physical environments, health services structure, and societal factors responsible for most inequities.”

- The World Health Organization

SOURCE: Healthy People 2030, 2021, HHS
Commission on Social Determinants of Health (CSDH), 2008, WHO

Trauma May Predispose Individuals to Develop an SUD and May Worsen Outcomes.

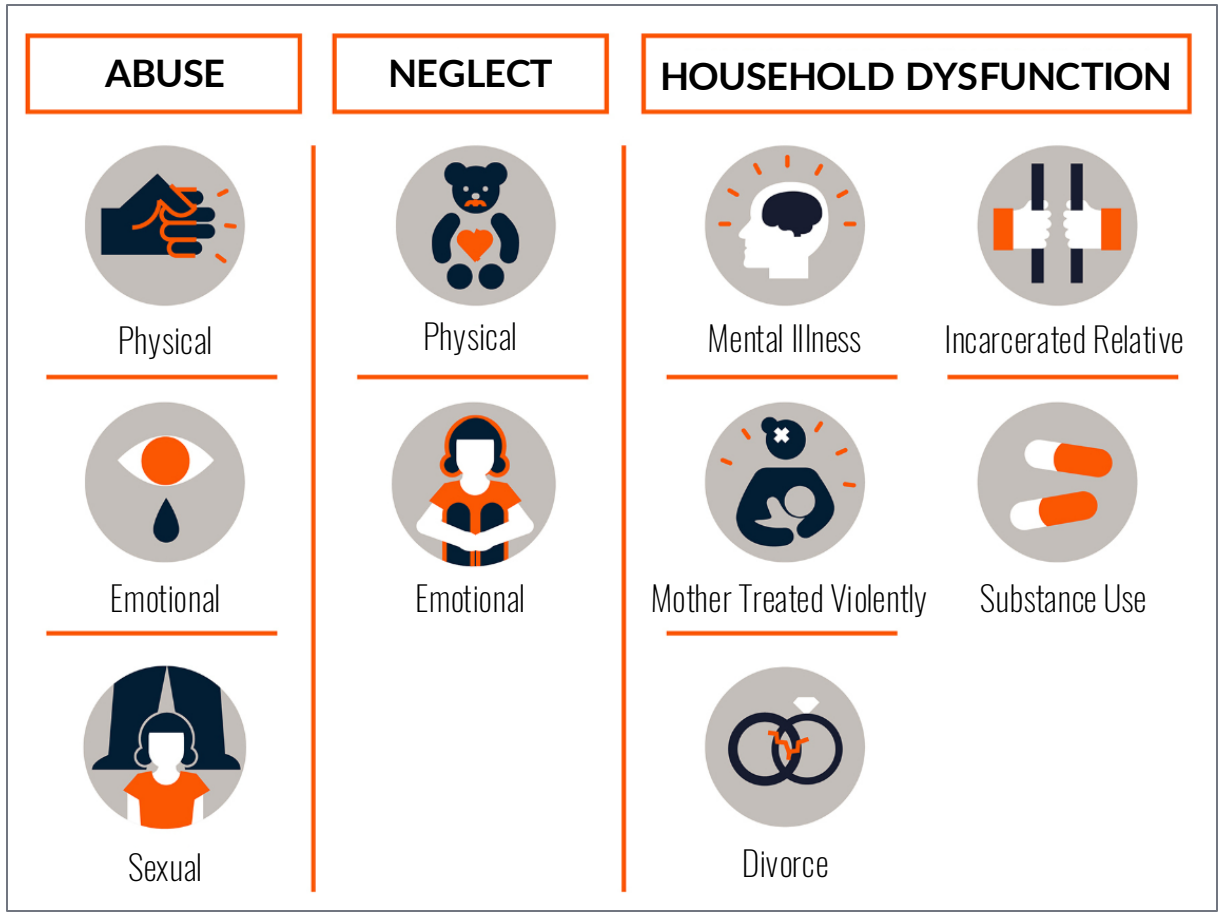


Image Adapted From The Robert Wood Johnson Foundation

- Adverse Childhood Experiences are strongly associated with SUD.
- Those with **4+** ACEs have a **4 to 12-fold** increased risk of SUD.
- *Trauma* and *PTSD* are associated with worse SUD treatment outcomes.

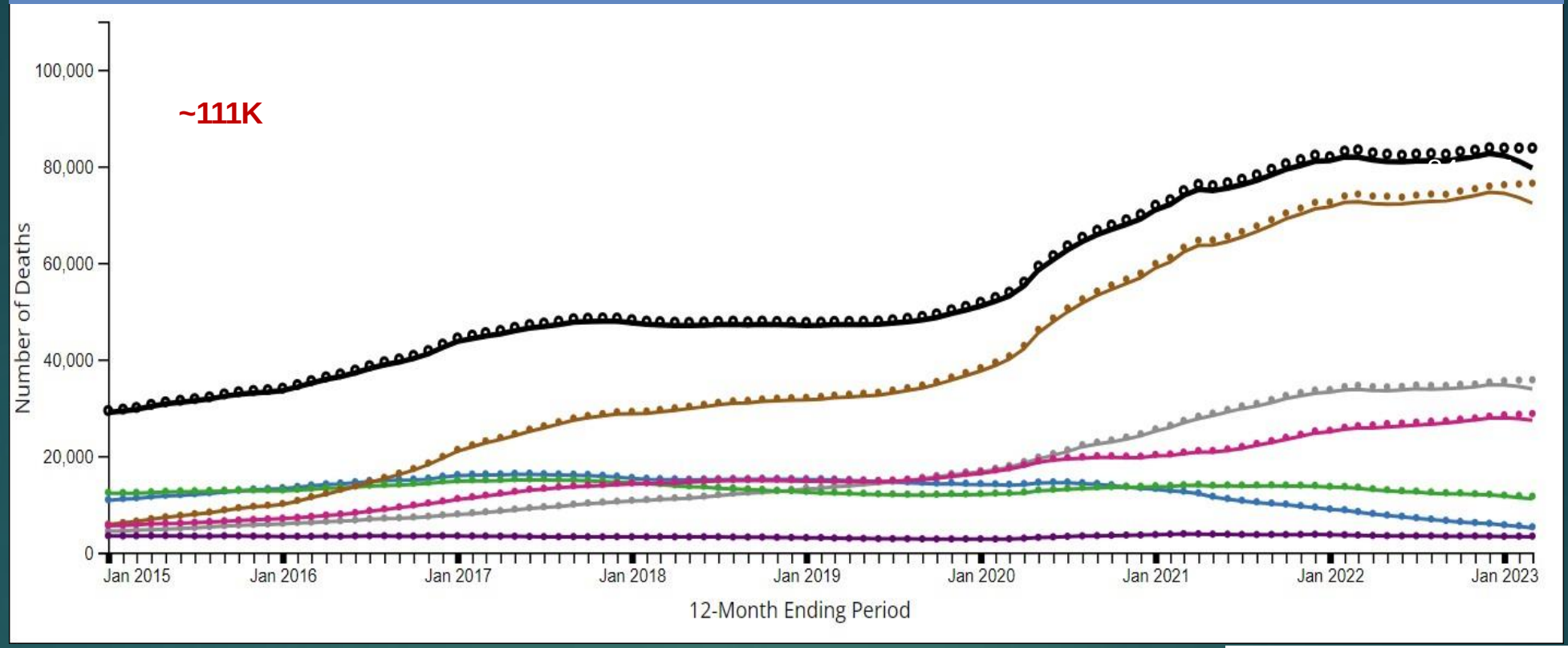
SOURCE: DOI: 10.1016/s0749-3797(98)00017-8.

Trauma-Informed Approaches to Care

- **Realize** the widespread impact of trauma.
- **Recognize** the signs and symptoms of trauma in patients, families, staff.
- **Respond** by fully integrating knowledge about trauma into clinic policies, procedures, and practices.
- **Resist** re-traumatization.

SOURCE: SAMHSA Tip 57

Number of Drug Overdose Death by Drug Class



12 months ending April 2023

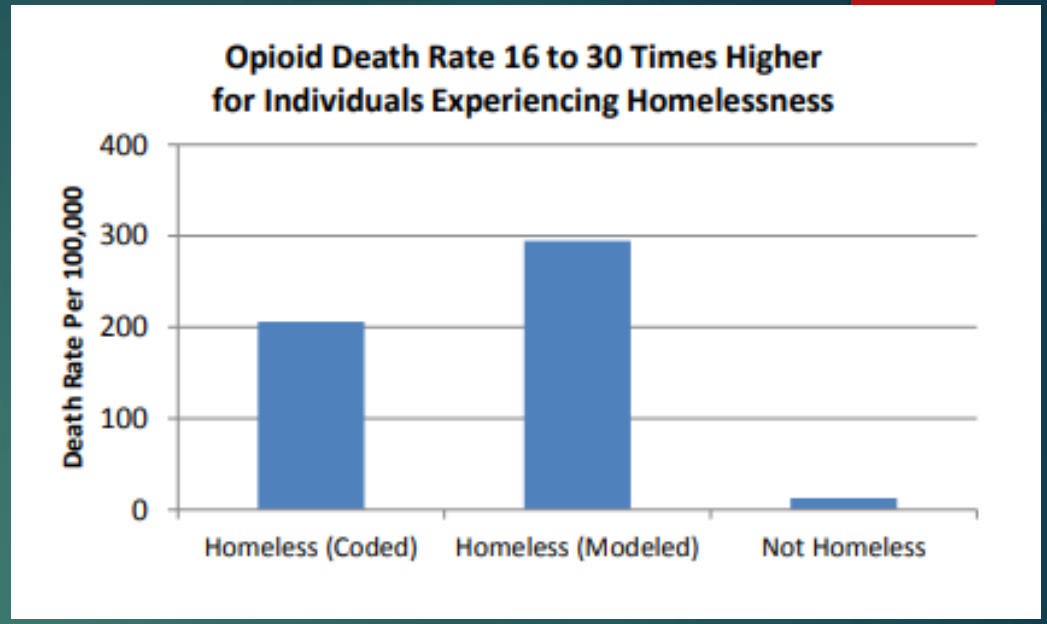
Adolescents and young adults

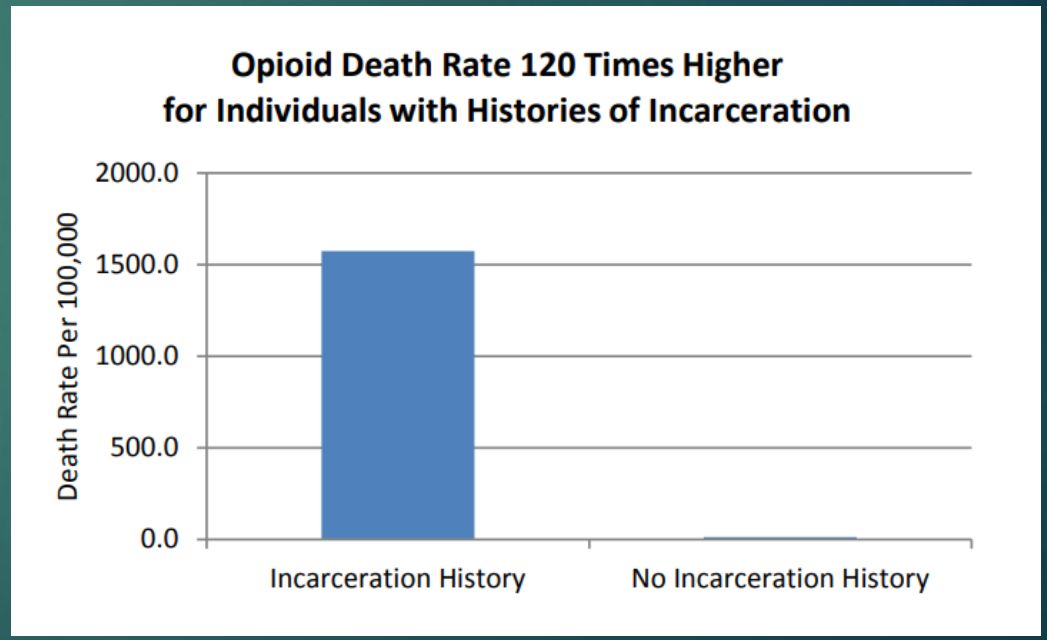
- 2/3 individuals in OUD treatment first use before 25
- 1/3 use before 18
- 2021 Monitoring the Future, 10% high school students used prescription opioids nonmedically.
- OD deaths 14-18 doubled 2019-2021
- Counterfeit drugs driving problem
- Fentanyl responsible for 75% of all deaths in teens
- Most deaths opioids, plus benzos, and methamphetamine or cocaine.

Hadland, Scott, MD, MPH, MS, 2022 American Academy of Pediatrics National Conf, Anaheim, CA

Overdose *Does* Discriminate

- Those at greatest risk of death often most marginalized
- People experiencing incarceration, homelessness, serious mental illness have markedly higher rates of overdose death
- Treatment models not designed with these populations in mind





MA DPH. https://www.mass.gov/files/documents/2017/08/31/legislative-report-chapter-55-aug-2017.pdf

Receipt of opioid use disorder treatments prior to fatal overdoses and comparison to no treatment in Connecticut,2016-2017

HEIMER, ET AL, DRUG AND ALCOHOL DEPENDENCE 254 (2024) 111040

Medication vs. Non-medication Treatment

- Relative risk is reduced following exposure to MOUD treatment, even if treatment was not continued.
- Exposure to non-MOUD treatment provided no protection against fatal opioid poisoning.
- To reduce overdose deaths access to agonist-based treatment needs to expand.
- This is unlikely to succeed if access to non-MOUD treatment is made more available through misappropriation of opioid settlement dollars to non-evidence based intensive outpatient and residential treatment.
  - Heimer, R., et al, Drug and Alcohol Dependence 254 (2024) 111040

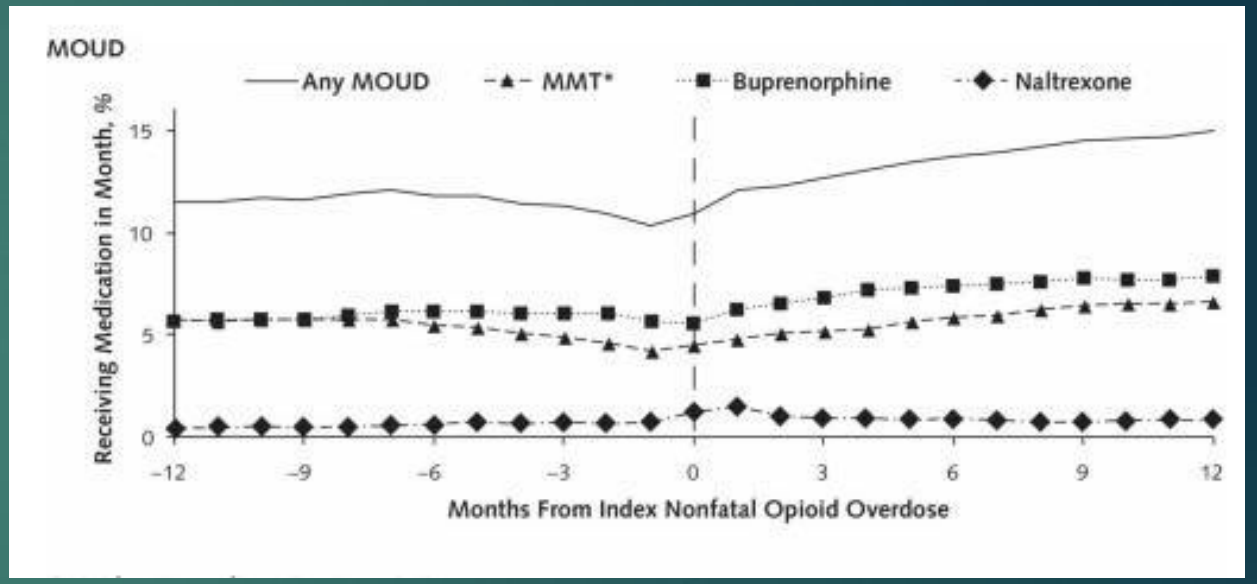
MOUD and Opioid Mortality 17,568 OD Survivors

- **Decrease in opioid related mortality**
  - ***59% methadone***
  - ***38% buprenorphine***
  - ***Both meds associated with a decrease in all cause mortality***
- ***No association found between Naltrexone and mortality!***
- **Marc Larochelle, Annals of Internal Med, Aug 2018**

Among Those at Highest Risk of Death, Treatment Retention Low

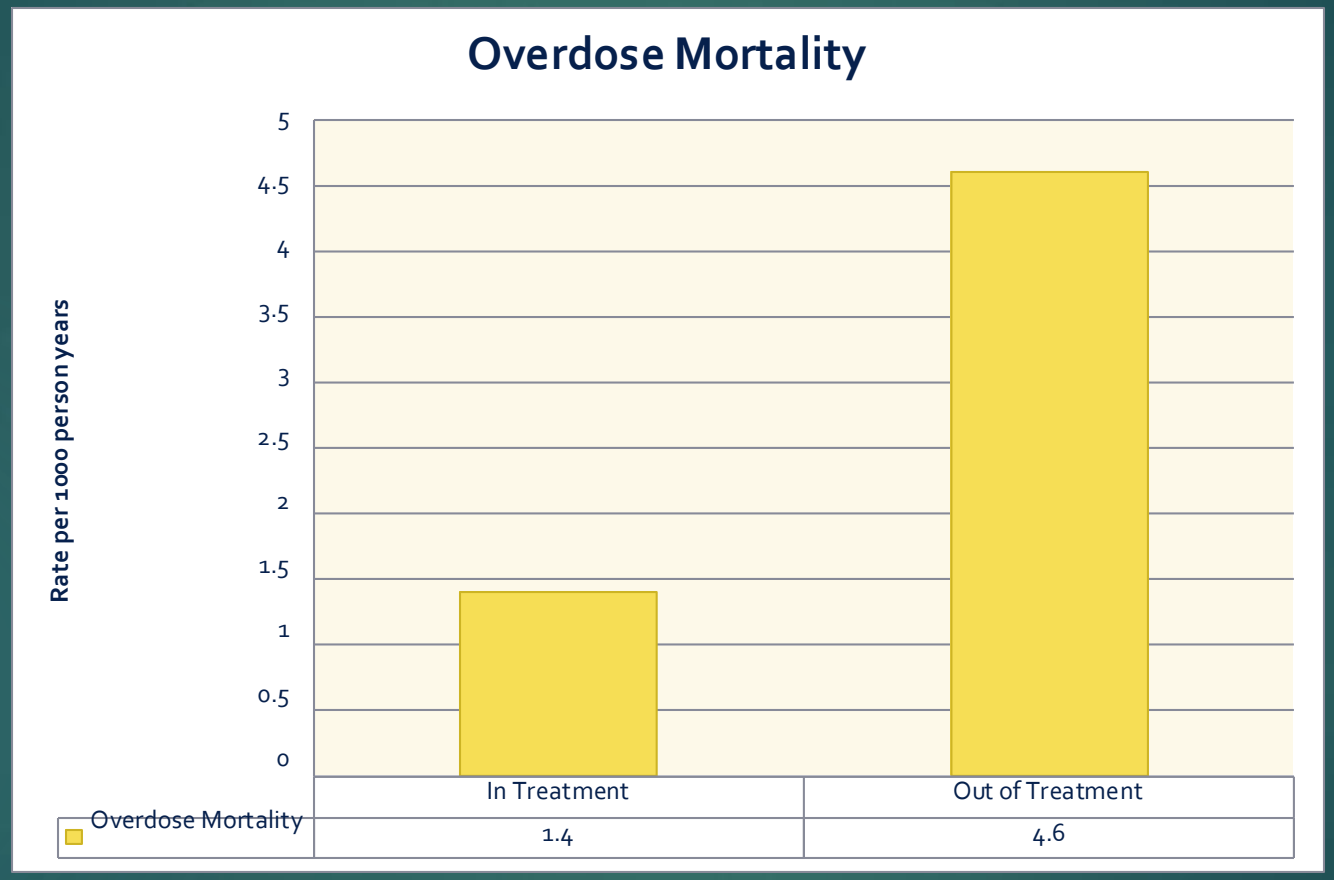
- In 12 months after nonfatal overdose, 11% of participants received MMT for median of 5 months, 17% bupe for median of 4 months, and 6% NTX for median of 1 month

- Despite short duration of treatment, there was a reduction in all-cause mortality with MMT (AHR 0.47) and bupe (AHR 0.63). For NTX, there was no mortality benefit (AHR 1.44)



Larochelle MR. Ann Intern Med. 2018 Aug 7;169(3):137-145.

Deaths Increase When Treatment Stopped/Unavailable



N=15 831 people treated with buprenorphine over 1.1-4.5 years (Sordo BMJ. 2017 Apr 26;357:j1550.)

Sordo et al. *BMJ* 2017;357:j1550

Opioid Use Disorder

1. Tolerance[2]
2. Withdrawal[2]

Loss of Control

3. Larger amounts and/or longer periods
4. Inability to cut down on or control use
5. Increased time spent obtaining, using, or recovering
6. Craving/compulsion

Use Despite Negative Consequences

7. Role failure: work, home, school
8. Social, interpersonal problems
9. Reducing social, work, recreational activity
10. Physical hazards
11. Physical or psychological harm

APA. (2013). *DSM* (5th ed.)

[1] Mild (2-3), moderate (4-5, severe (≥6)
[2] Not valid if opioid taken as prescribed

DSM5 interview

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

DSM5 interview

- **8. Have you ever gotten high before doing something that requires coordination or concentration like driving, boating, hunting, climbing a ladder, or operating heavy machinery?**
- **9. Have you continued to use even though you knew that the opioid caused overdoses, infections, and emotional problems such as depression, anxiety, agitation, and irritability?**
- **10. Have you found you need to use much more drug to get the same effect that you did when you first started using it?**
- **11. When you reduced or stopped using, did you have withdrawal symptoms or felt "dope sick" when you cut down or stopped using?**
- **Mild=2-3, moderate=4-5, severe=6 or more. 1 point for each yes.**

Neurobiology of Addiction

- Polymorphisms of drug receptors appear to be associated with phenotypic expression of vulnerability once opioids consumed
- Adverse Childhood Events (ACEs)
- Events surrounding first exposure are often outside the patient's control
  - Family
  - Local environment/potential recovery environment
  - Iatrogenic (the prescription opioid epidemic—Purdue Pharma and others with influence of CMS and JCAHO
- Concomitant Psychiatric Disease
  - A minority of patients with SUD have severe psychiatric illness as well, but anxiety, mood disorders, and trauma disorders common as well as personality disorders

Saxon, 2005

WHY DO PEOPLE USE DRUGS?

TO FEEL GOOD

To stimulate pleasant feelings, sensations, euphoria, and to share them

TO FEEL BETTER

To lessen anxiety, worries, fears, depression, hopelessness, and withdrawal; to relieve pain, both physical and emotional

SOURCE: DOI: 10.3389/fpsyt.2019.00592

Addiction is a Biopsychosocial Disease

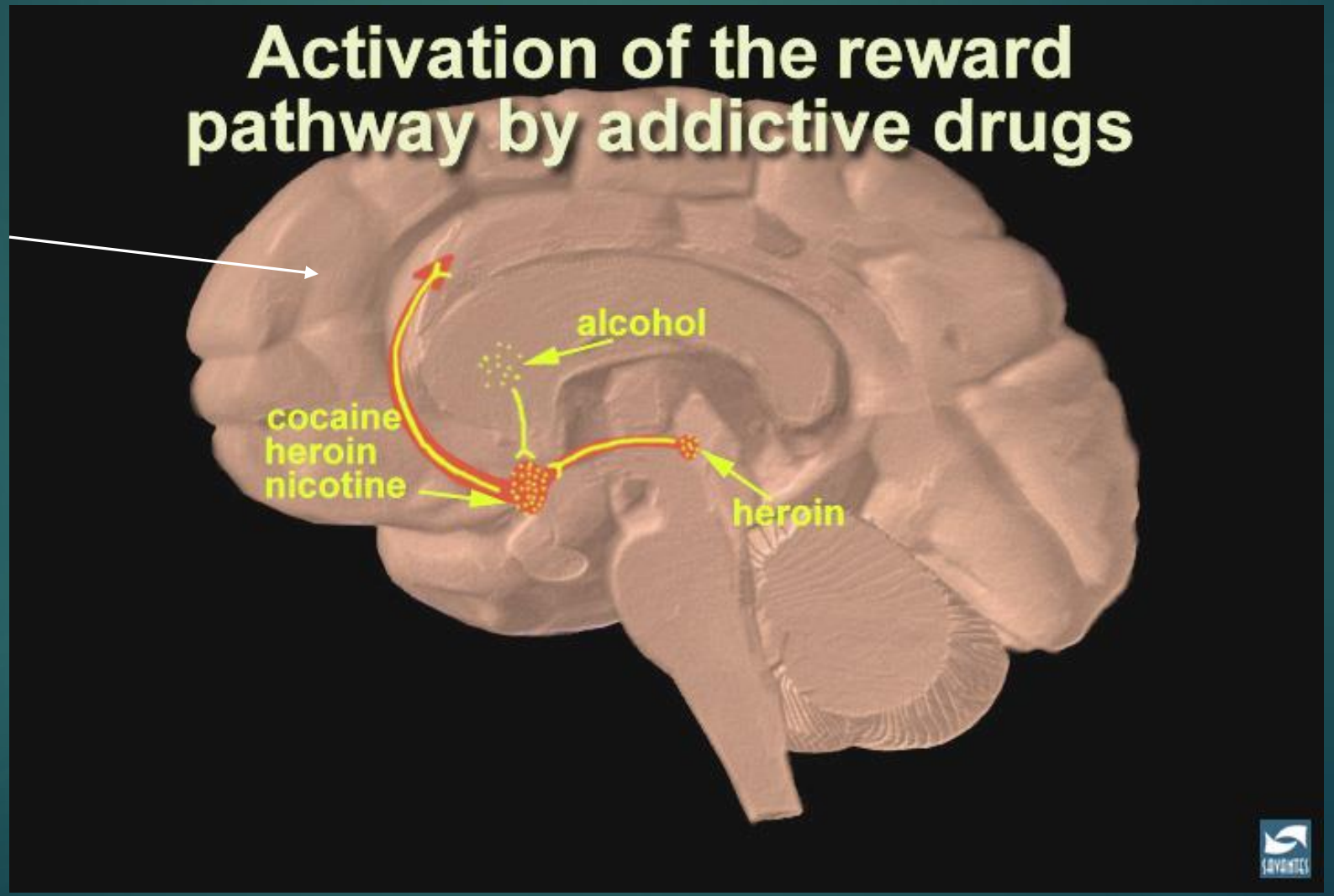
Biological

Psychological

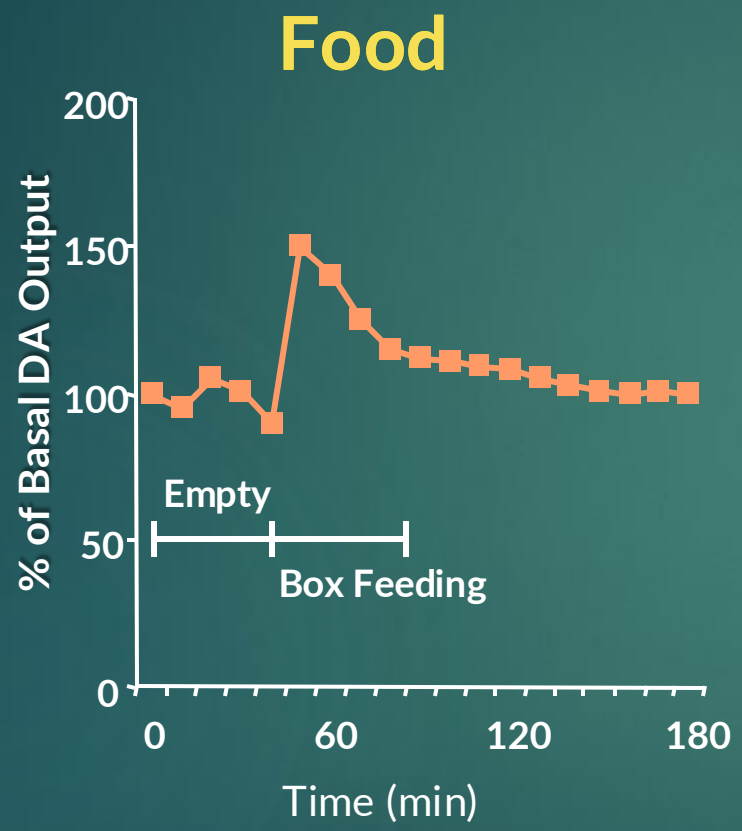
Social

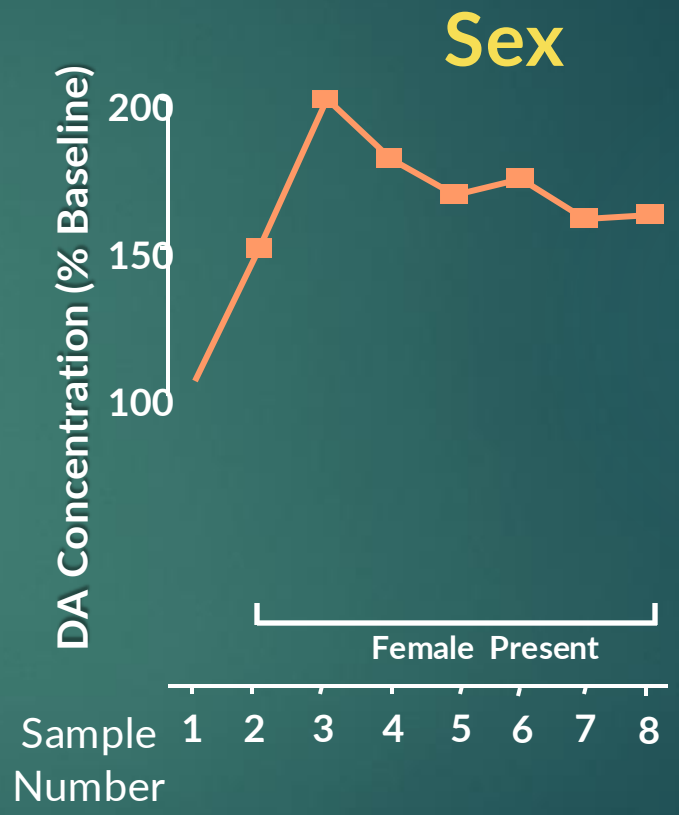
All addictive drugs act directly or indirectly via dopaminergic pathways…

Dopamine



Natural Rewards and Dopamine Levels



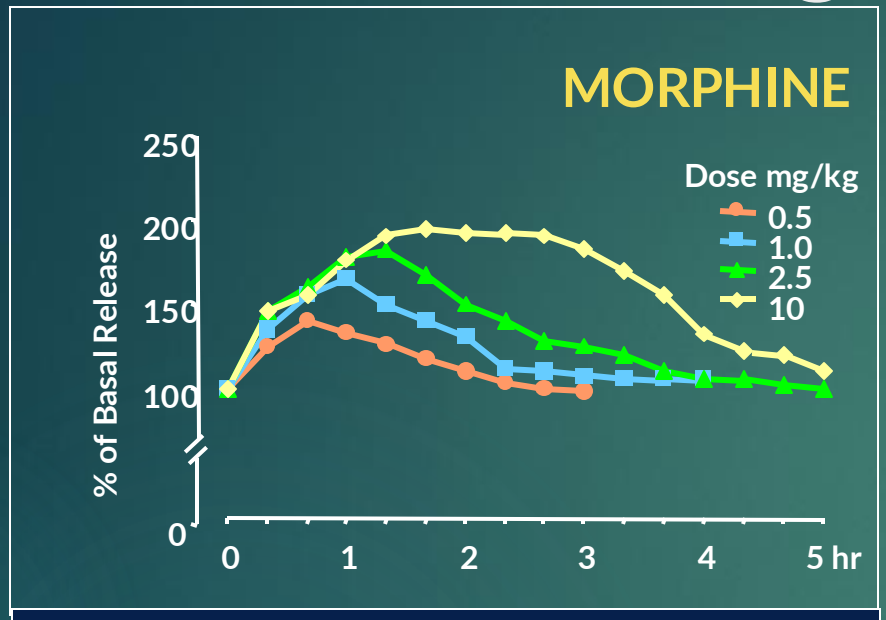


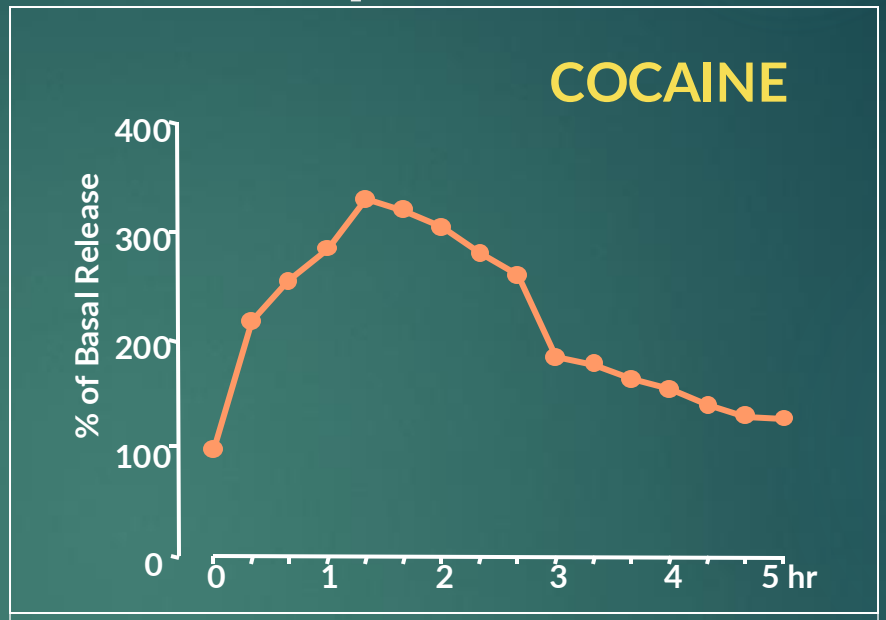
Slide courtesy of Petros Levounis, MD

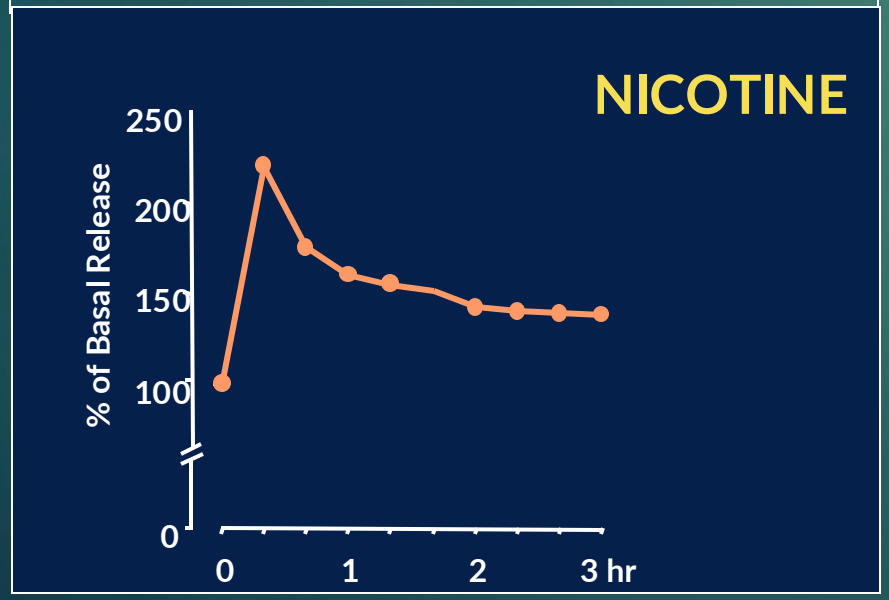
Adapted from: Di Chiara et al, *Neuroscience*, 1999

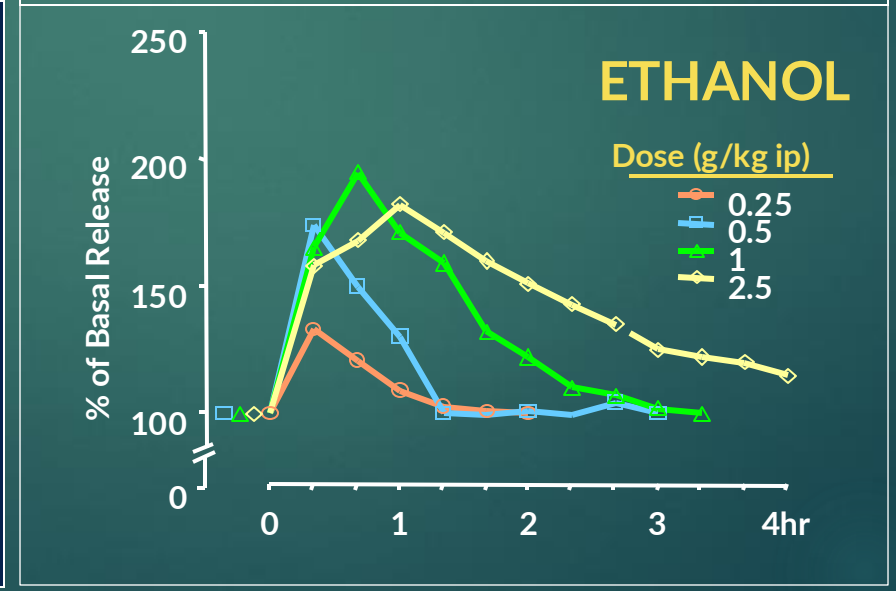
Adapted from: Fiorino and Phillips, *J Neuroscience*, 1997

Effects of Drugs on Dopamine Levels





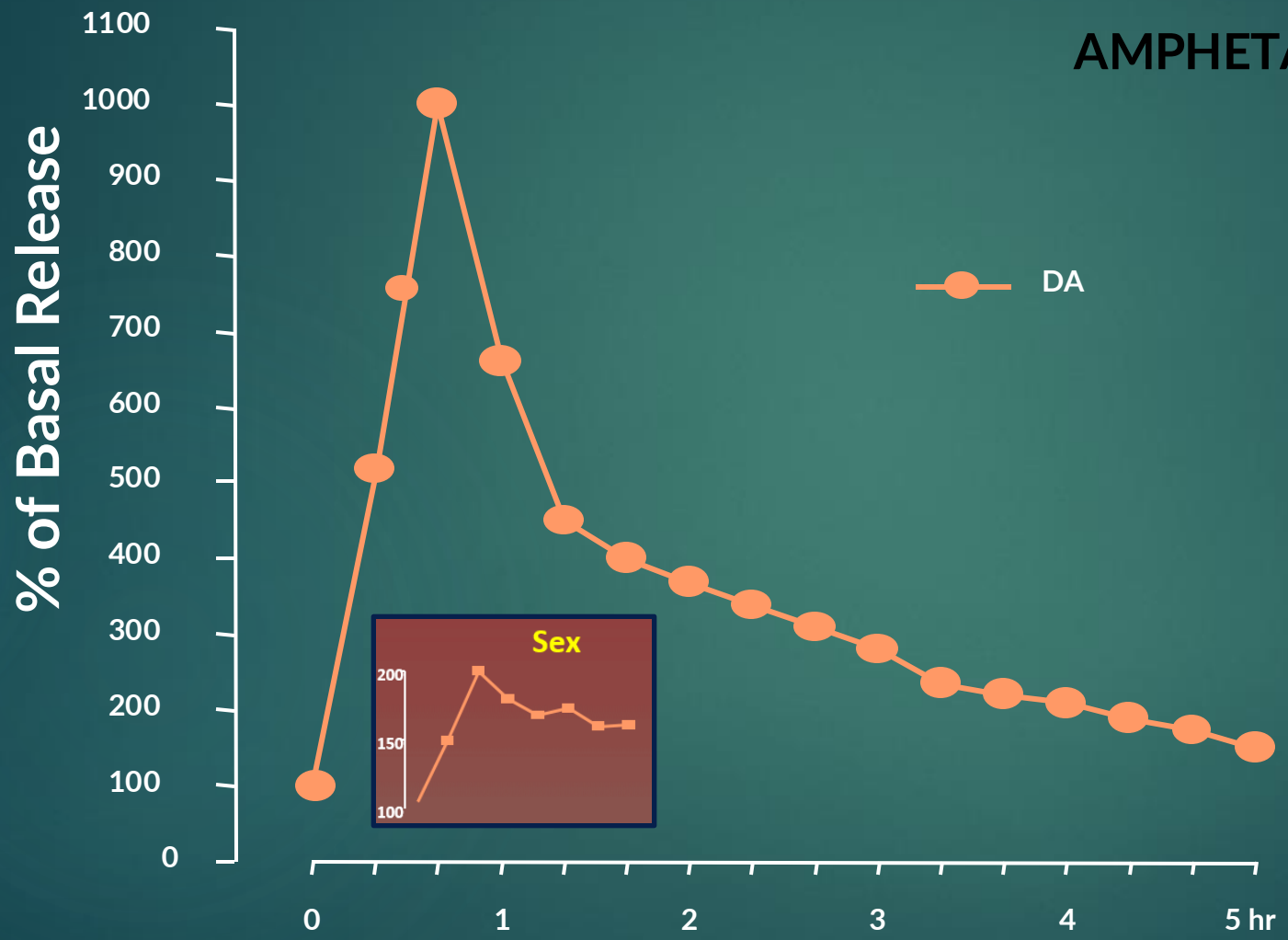




Slide courtesy of Petros Levounis, MD

Adapted from: Di Chiara and Imperato, *Proceedings of the National Academy of Sciences USA*, 1988; courtesy of Nora D Volkow, MD

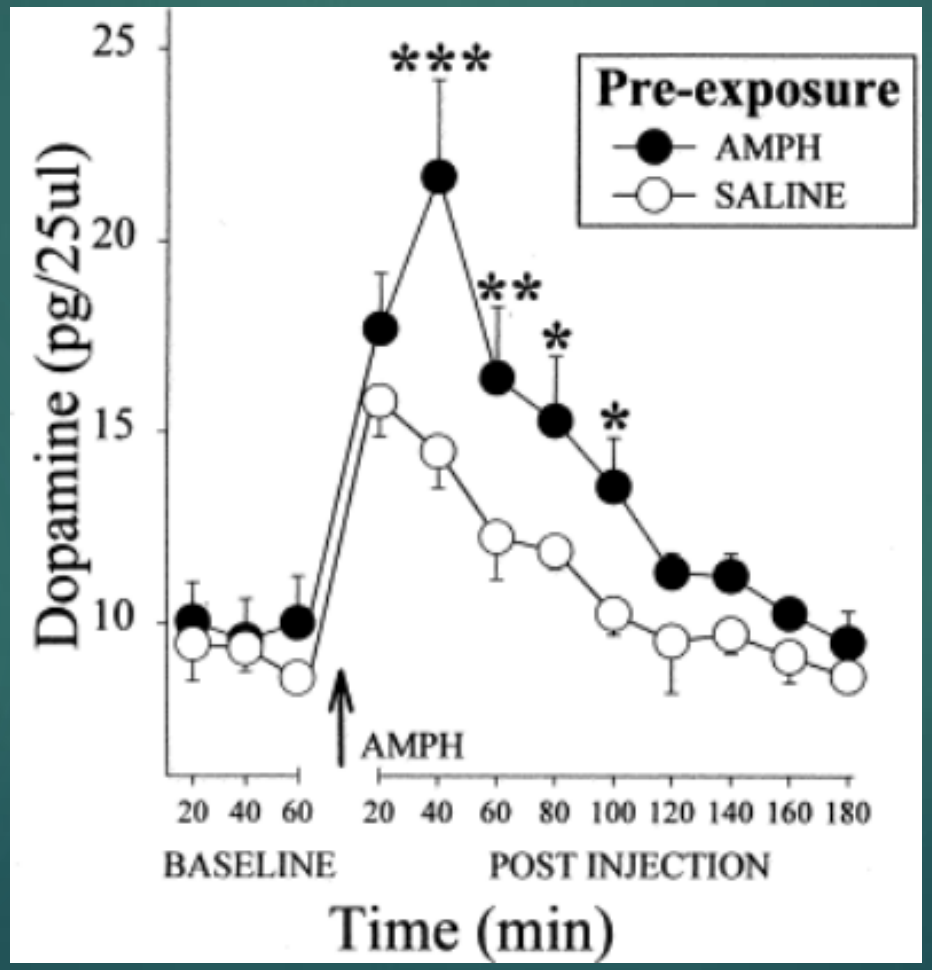
Effects of Amphetamines on Dopamine Levels



Slide courtesy of Petros Levounis, MD

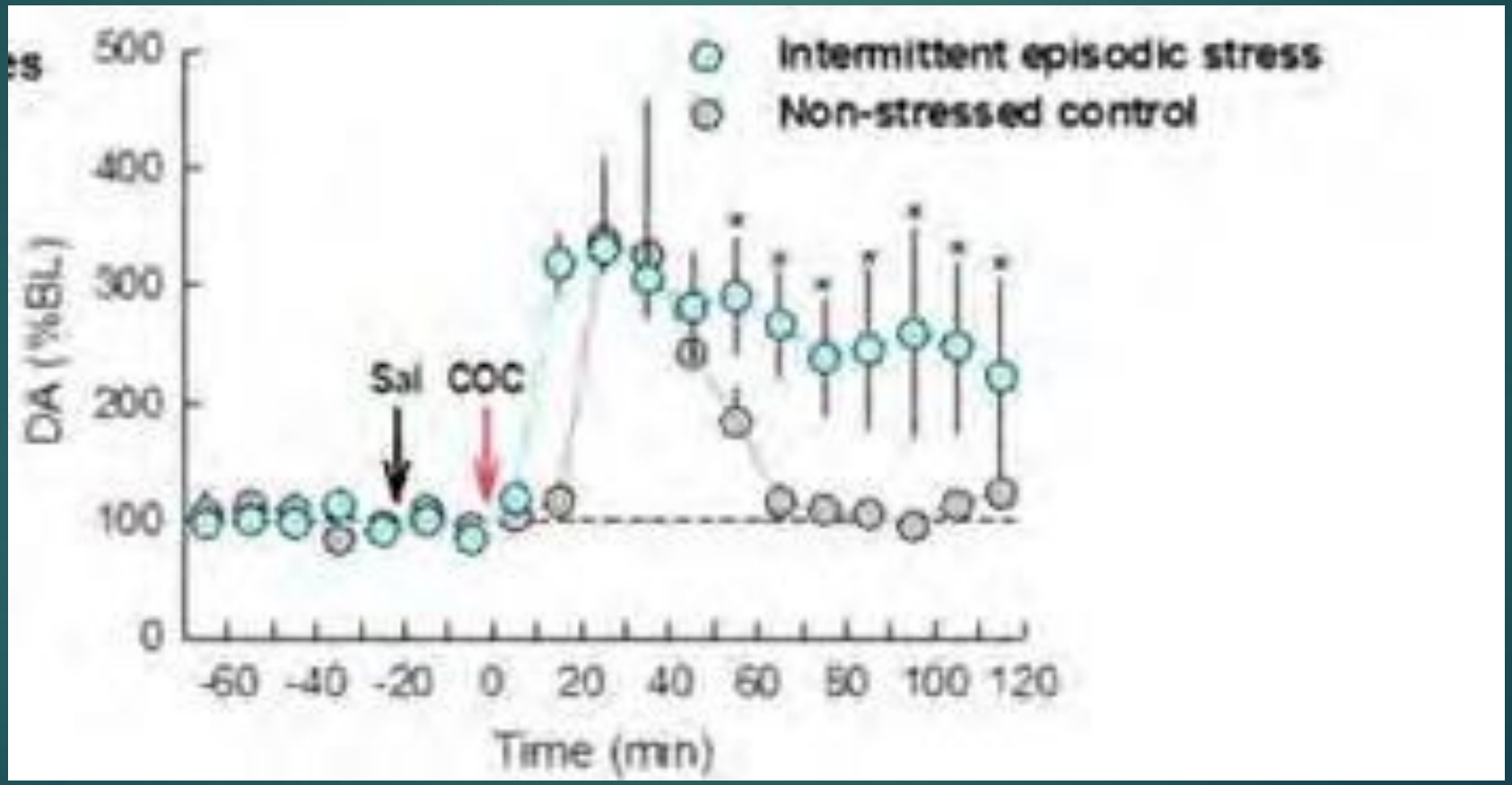
Adapted from: Di Chiara and Imperato, *Proceedings of the National Academy of Sciences USA*, 1988; courtesy of Nora D Volkow, MD.

REPEATED DRUG USE SENSITIZES THE DOPAMINE RESPONSE



Slide credit: Lorraine et al. 2000, ASAM DATA 2000 Treatment of Opioid Use Disorder course, 2021

STRESS ALSO SENSITIZES THE DOPAMINE RESPONSE

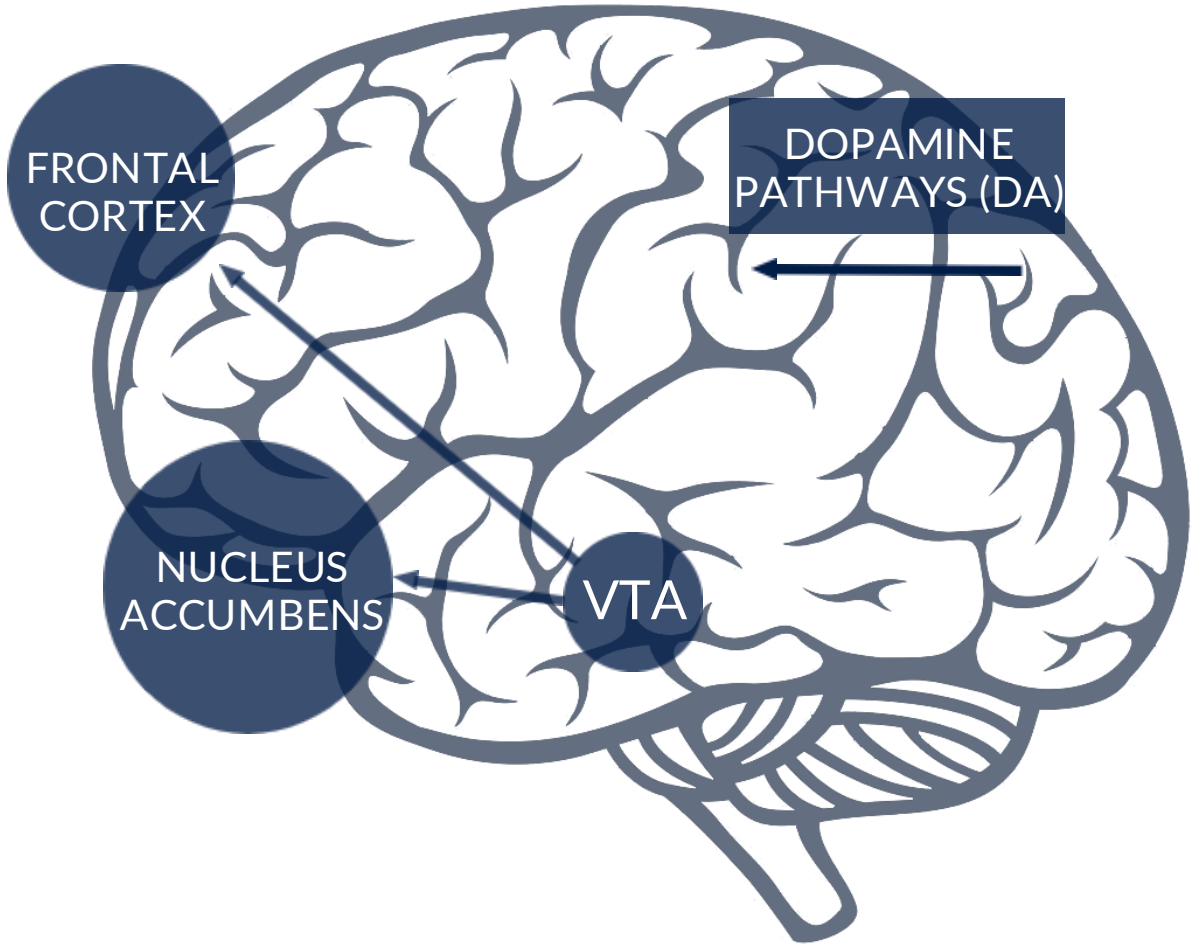


Slide credit: ASAM DATA 2000 Treatment of Opioid Use Disorder course, 2021

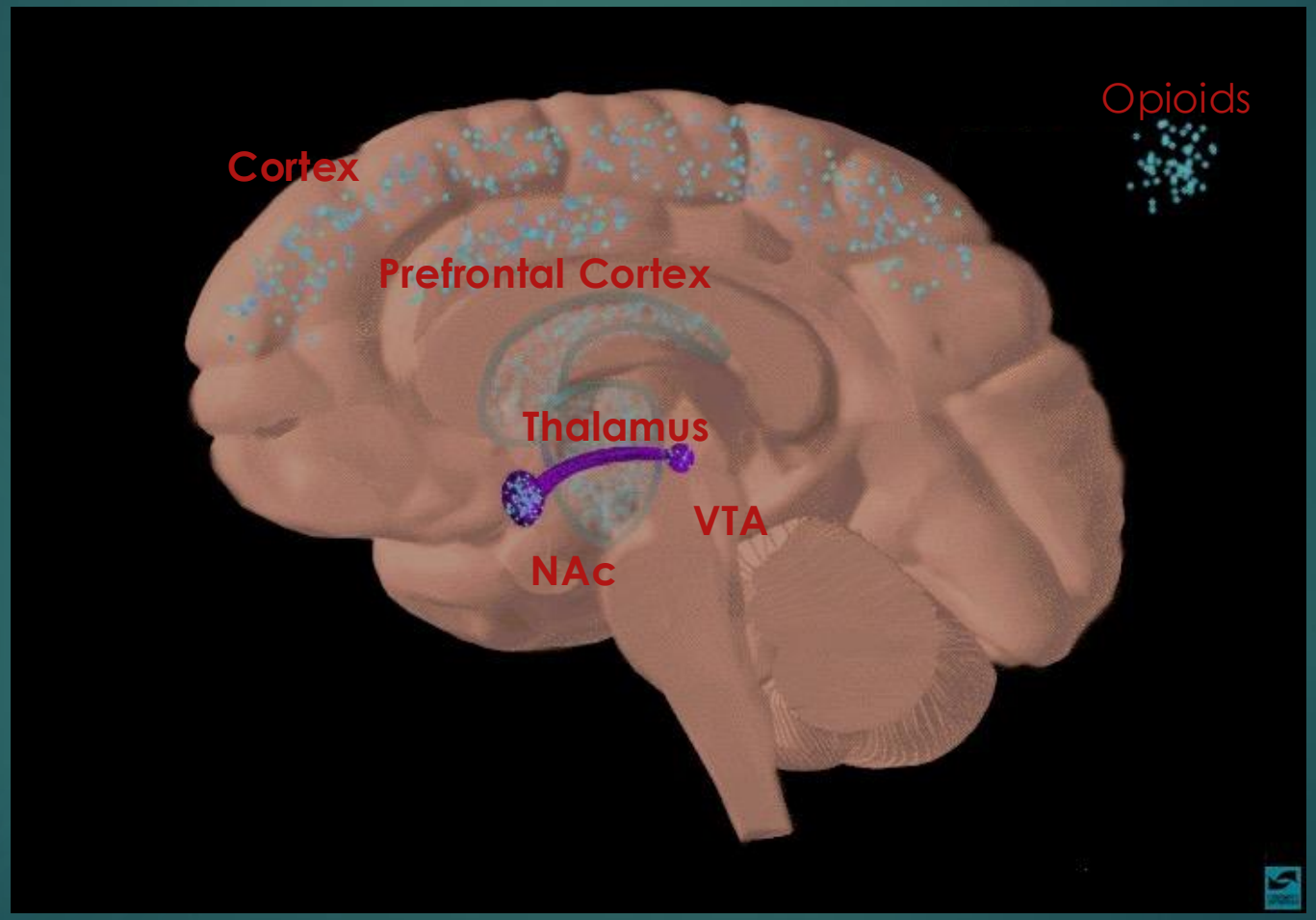
Shimamoto 2011

Reward Pathways

Mesolimbic Dopaminergic Circuitry (Limbic System)

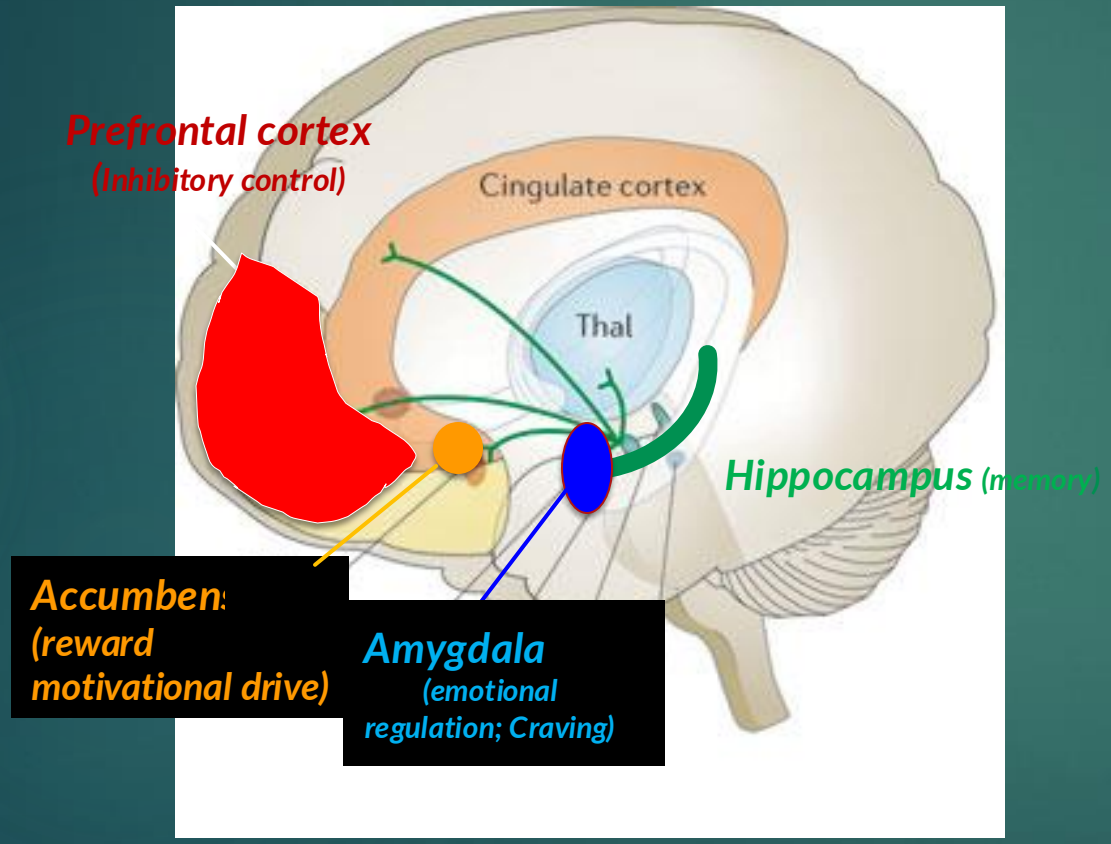


Opioid Binding



NIDA, 2017

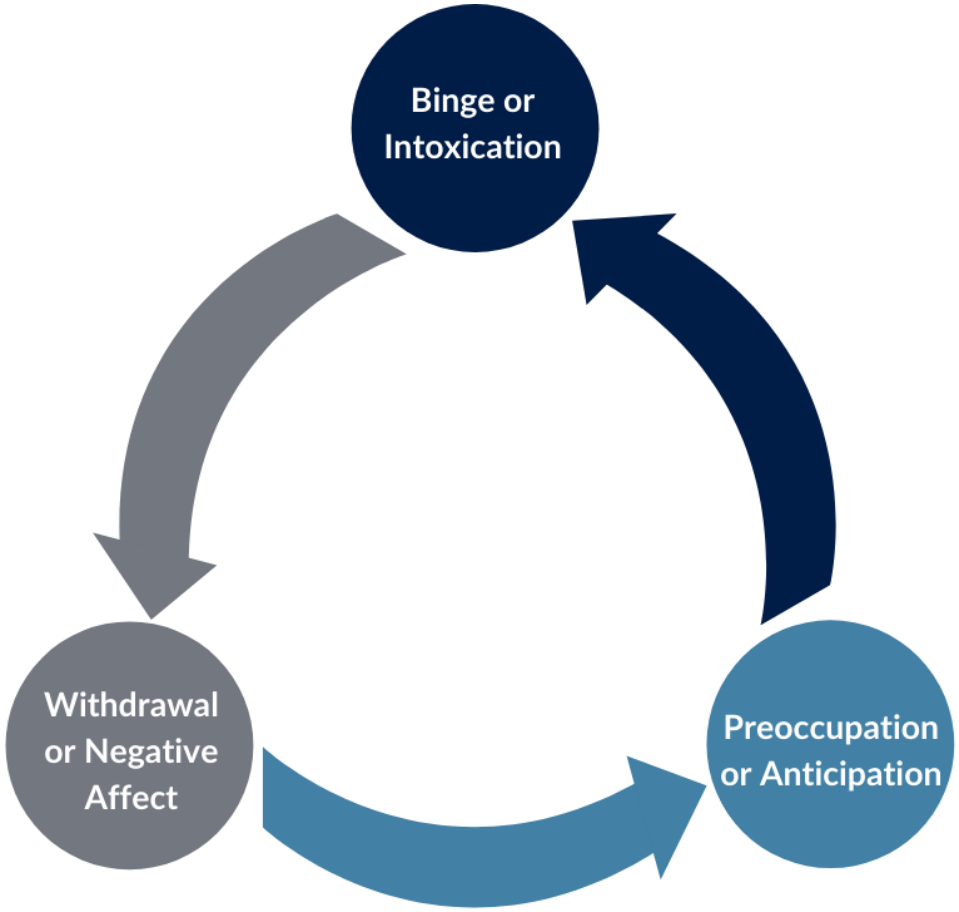
The Neurobiological Challenge of Addiction



↓ *Inhibitory control*
↑ *Increase reward drive*
↑ *Craving*
↑ *Drug memories*

Source: Yasmin Hurd, PhD

Three Stages of the Addiction Cycle



- **Stage 1:** Binge or Intoxication
- **Stage 2:** Negative Affect or Withdrawal
- **Stage 3:** Preoccupation or Anticipation (Craving)

SOURCE: DOI: 10.1001/jamapsychiatry.2018.3126

Acute Opioid Withdrawal

	Symptoms / Signs
Mild	Anxiety, drug craving
	Yawning, sweating, runny nose, tearing eyes, restlessness, insomnia
	Dilated pupils, gooseflesh, muscle twitching, muscle & joint aches
	Nausea, extreme restlessness, elevated BP, heart rate > 100, fever
Severe	Vomiting, diarrhea, abdominal cramps, curled-up body position

Clinical Opiate Withdrawal Scale (COWS)

01 **Resting Pulse Rate**
SCORE: 0-4

02 **Sweating**
SCORE: 0-4

03 **Restlessness**
SCORE: 0-5

04 **Pupil Size**
SCORE: 0-5

05 **Bone or Joint Aches**
SCORE: 0-4

06 **Runny Nose or Tearing**
SCORE: 0-4

07 **Gastro-Intestinal Upset**
SCORE: 0-4

08 **Tremor**
SCORE: 0-4

09 **Yawning**
SCORE: 0-4

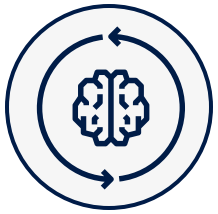
10 **Anxiety or Irritability**
SCORE: 0-4

11 **Gooseflesh Skin**
SCORE: 0-5

SCORE

- 5-12 mild
- 13-24 moderate
- 25-36 moderately severe
- >36 severe

Determinants of Withdrawal Risk



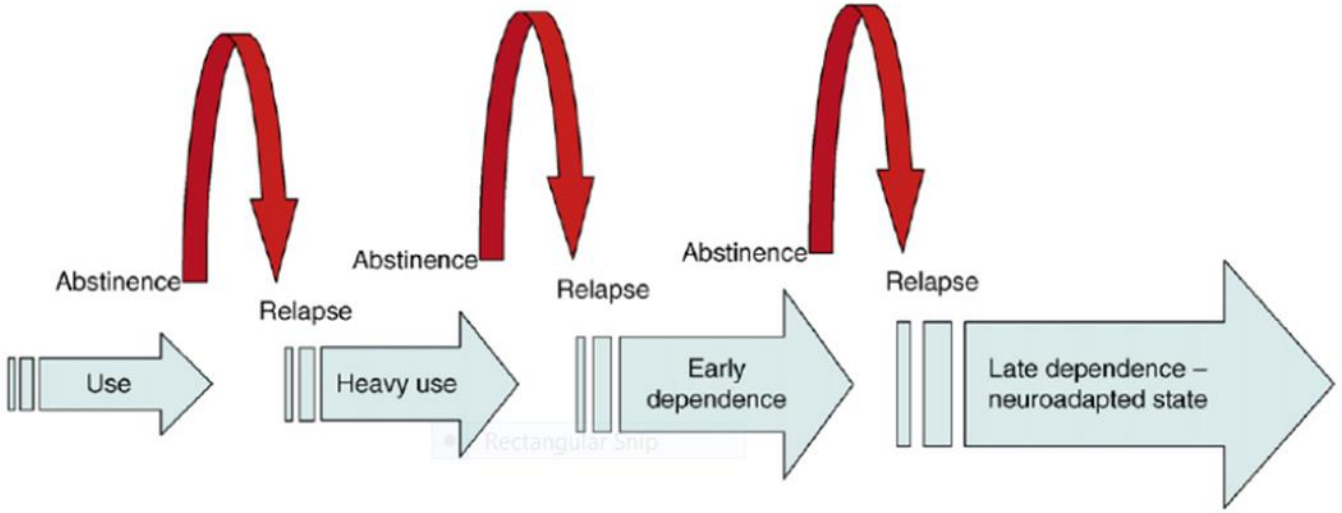
Exposure to steady state level of medication:

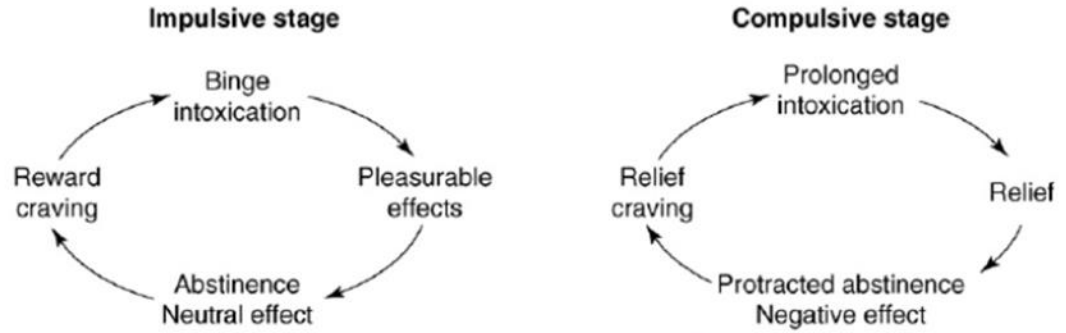
- Neuro-adaptation to opioids

Higher intensity withdrawal from:

- Higher steady state levels
- Longer term exposure
- Faster rate of medication clearance
- Short vs. long half-life agents

Transition from Positive to Negatively Reinforced Drug Use





Positive Reinforcement → **Negative Reinforcement**

From: Koob GF, Alcohol Clin Exp Res, 2003, 27:232-243.

Tolerance, Physical Dependence, and OUD

Chronic Opioid Exposure

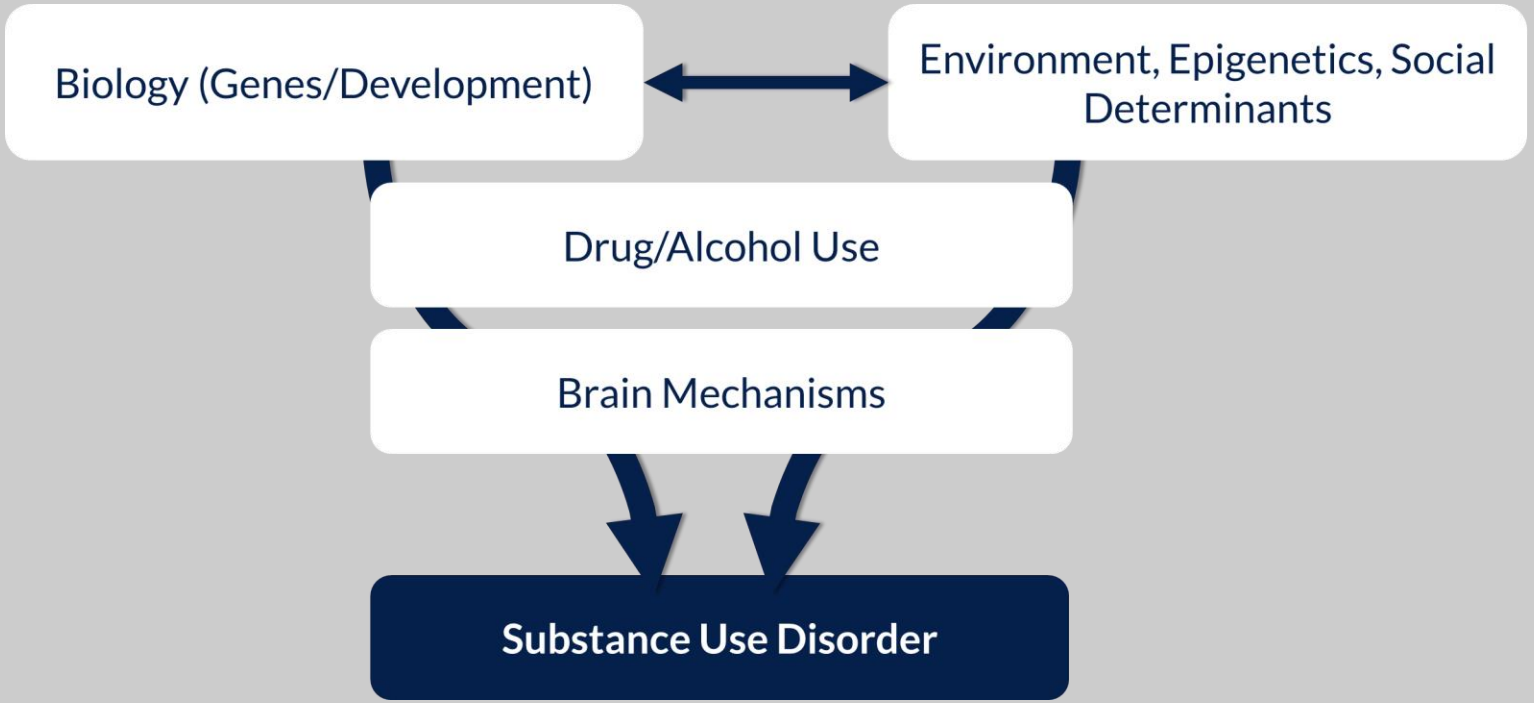
Tolerance

Increased dosage needed to produce specific effect, develops rapidly for CNS and respiratory depression.

Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure and DO NOT equal addiction or opioid use disorder.

Physical Dependence

Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction.



Development Of Substance Use Disorders Involves Multiple Factors

Opiates and Opioids

Opiates:

Natural compounds present in opium poppies: e.g., morphine, codeine, thebaine

VS.

Opioids:

Manufactured as:

- **Semi-synthetic opioids**: derived from an opiate, e.g., heroin, oxycodone, hydromorphone, buprenorphine
- **Synthetic opioids**: completely synthesized to function similarly to natural opiates, e.g., methadone, fentanyl, nitazenes

Endogenous Opioids and Their Receptors

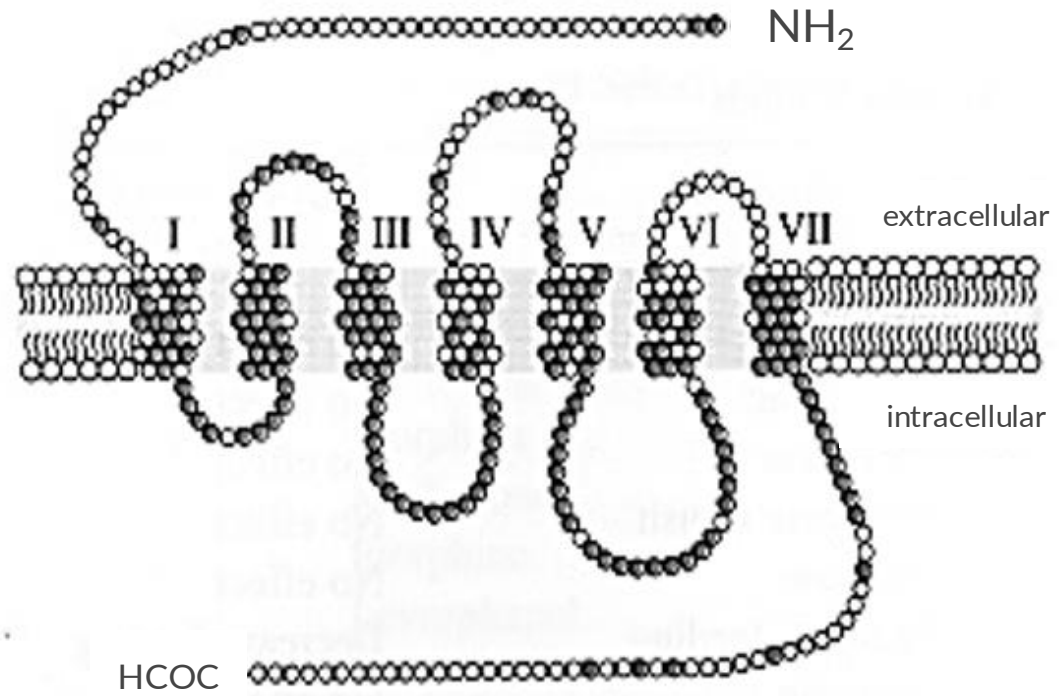
Endogenous Ligand	Opioid Receptor Types
Beta Endorphins	**Mu**
Enkephalins	Delta
Dynorphins	**Kappa**
Nociceptin /OrphaninF / Q	ORL-1

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

BEWARE OF KRATOM--ASK

Mu-Opioid Receptor

- *G-protein coupled* receptor
- *Subtypes and > 100* polymorphisms to the mu-opioid receptor gene
- *High affinity* for beta-endorphin and enkephalins
- *High affinity* for morphine
- *Low affinity* for dynorphins
- *Acute changes in neuronal excitability* via "disinhibition" of presynaptic release of GABA



Buprenorphine Kappa-opioid Receptor Antagonist

Stimulation of kappa-opioid receptor with dynorphin-like peptides

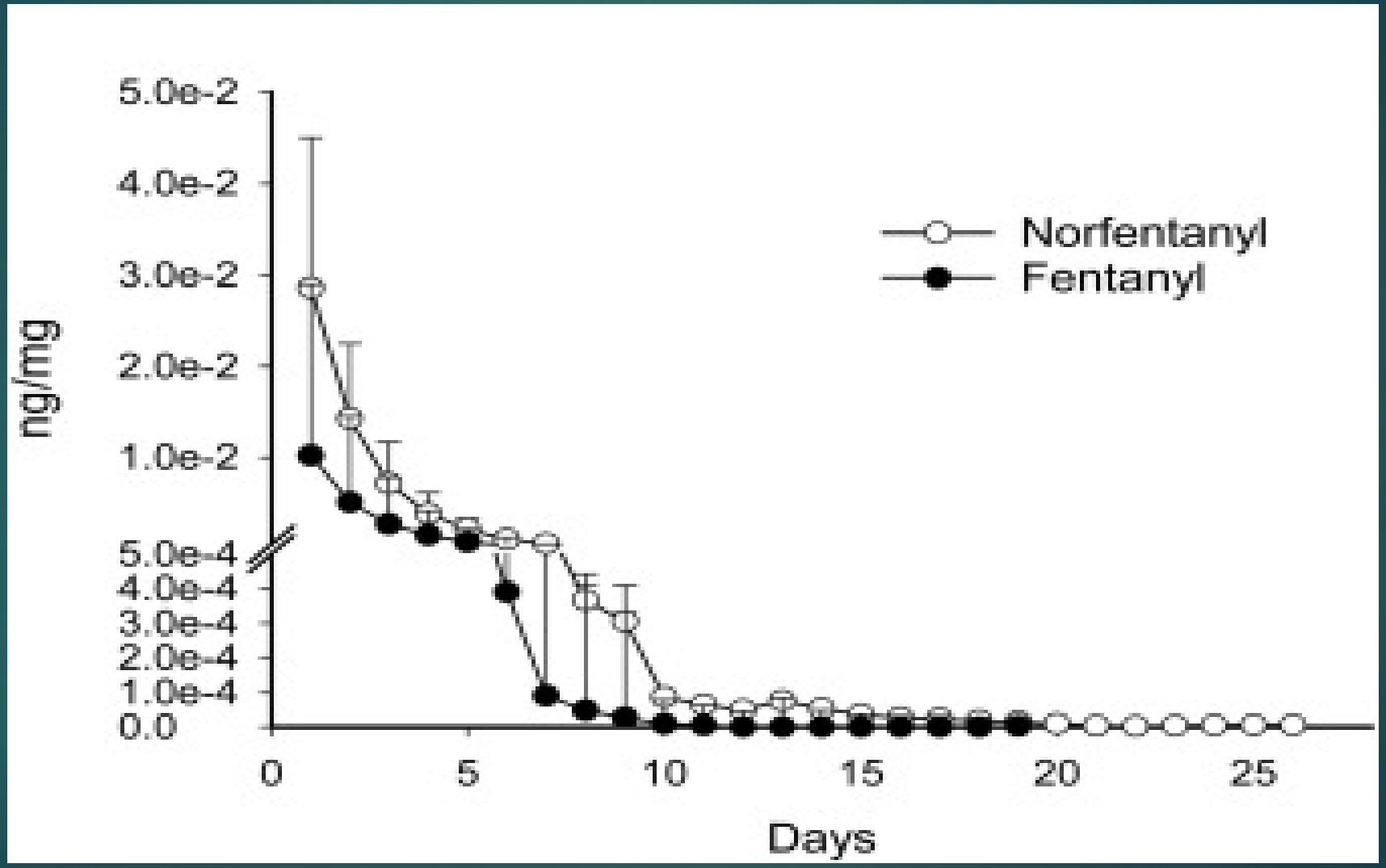
- Inhibits dopamine release in the striatum (nucleus accumbens and caudate putamen), inducing negative mood state in humans and animals

Buprenorphine is an antagonist at the kappa receptor

- Antidepressant-like effects
- Anxiolytic effects
- Prevent stress-induced negative emotional states

Image sources: NIDA, SF Public Health

Fentanyl and Norfentanyl Elimination



Huhn, AS, et al. Protracted renal clearance of fentanyl in person with opioid use disorder. Drug and Alcohol Dependence. 2020; 214: 1-4

History of xylazine

- Xylazine is a non-opioid used as a sedative, anesthetic, muscle relaxant, and analgesic for animals. It is a strong synthetic alpha-2 adrenergic agonist, synthesized in 1962 in Germany by Bayer as an anti-hypertensive, analgesic, hypnotic, and anesthetic. *It was not approved for human use due to severe CNS depressant effects.*
- A veterinary medication used for procedural sedation in both small and large animals (approved for veterinary use in the US by the FDA)
  - Not a controlled substance; not scheduled in the US as it is not intended for human use
  - When used in combination with opioids, enables use of lower doses of opioids and enhances both sedation and anesthesia
- Initially emerged sporadically in the literature as a substance of use in the 1980s and 1990s, emerged as a substance of widespread misuse in Puerto Rico in the early 2000s and was known as 'anestesia de caballo'

Thanks to Joseph D'Orazio

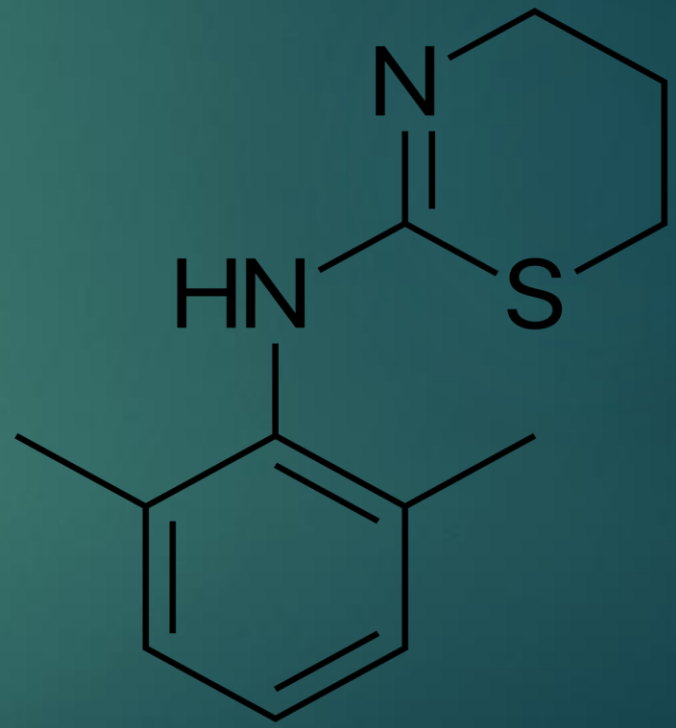
Epidemiology: Xylazine

- Xylazine in the drug supply is following a multi-year progression of appearing increasingly in the unregulated drug supply
- Over the last decade, the number of novel psychoactive substances (NPS) has increased, and they have increasingly replaced the historical heroin supply in parts of the US and Canada
  - heroin->heroin + fentanyl->heroin + fentanyl + carfentanil + etizolam->heroin + etizolam + isotonitazene/nitazenes, etc. + flualprazolam + xylazine + brorphine + O-DMST + U-47700
  - ***What does all this mean?***

Xylazine: Structure, Pharmacology, and Clinical Effects

- Alpha-2 adrenergic agonist that *stimulates central alpha-2 receptors:*
  - Decreases sympathetic nervous system outflow -> sedation (decreases the release of NE and dopamine)
  - **CNS DEPRESSION: *No effect on respiratory rate, blunted response to airway occlusion (hypoxia) similar to other sedatives (benzodiazepines, barbiturates), synergistic effect with opioids***
- Similar effects to *imidazoline* compounds, such as clonidine, dexmedetomidine, oxymetazoline, tetrahydrazoline, tizanidine, and lofexidine
  - **Major clinical effect is profound sedation**
  - **But *NO* imidazoline receptor activity, so *NO* hypotension/bradycardia**
  - Increase in vagal tone is reported in the veterinary literature
  - Acts on alpha-2 receptors in pancreatic beta cells, inhibiting insulin release->hyperglycemia
  - One of xylazine's metabolites, 2,6-xylidine, has been classified as potentially genotoxic and carcinogenic in humans based on animal studies
- Pharmacokinetics:
  - Typical anesthesia dose ranges (0.2-1 mg/kg IM or IV)
  - Time to effect is 1-2 minutes (depending on administration route); lipophilic, diffuses widely, good bioavailability
  - Average duration of substance effect up to 4 hours, but can last longer
  - Routes of Administration: IV, IM, SC, PO, inhalation, insufflation, ocular

Xylazine Structure



Similar chemical structure to phenothiazines, TCAs, and clonidine
Thanks to Joseph D'Orazio, MD

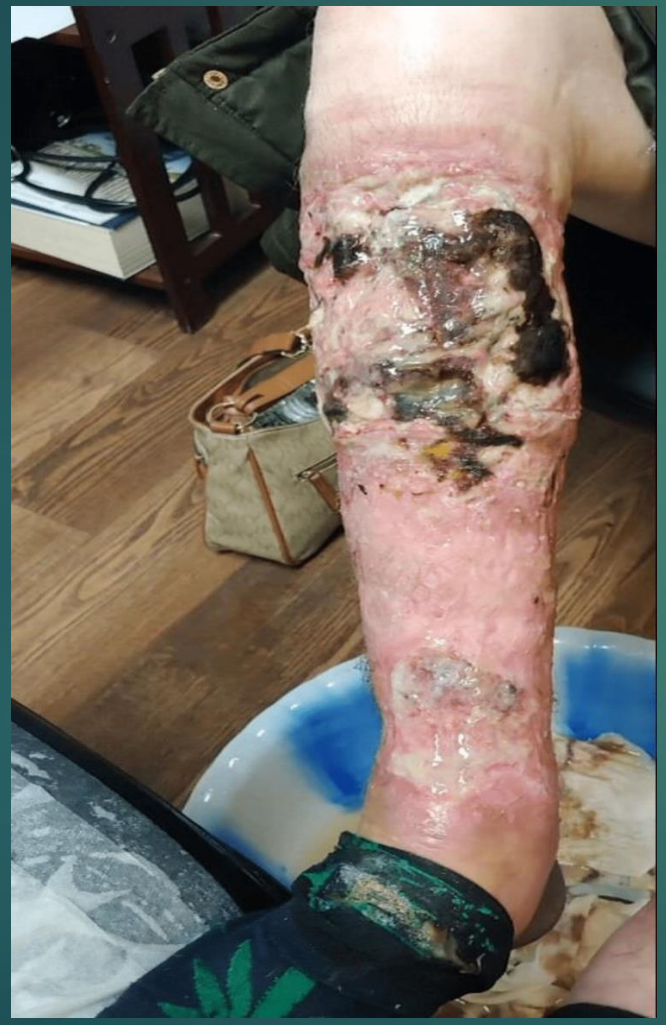
Forensic Sci Int. 2014 Jul;240:1-8

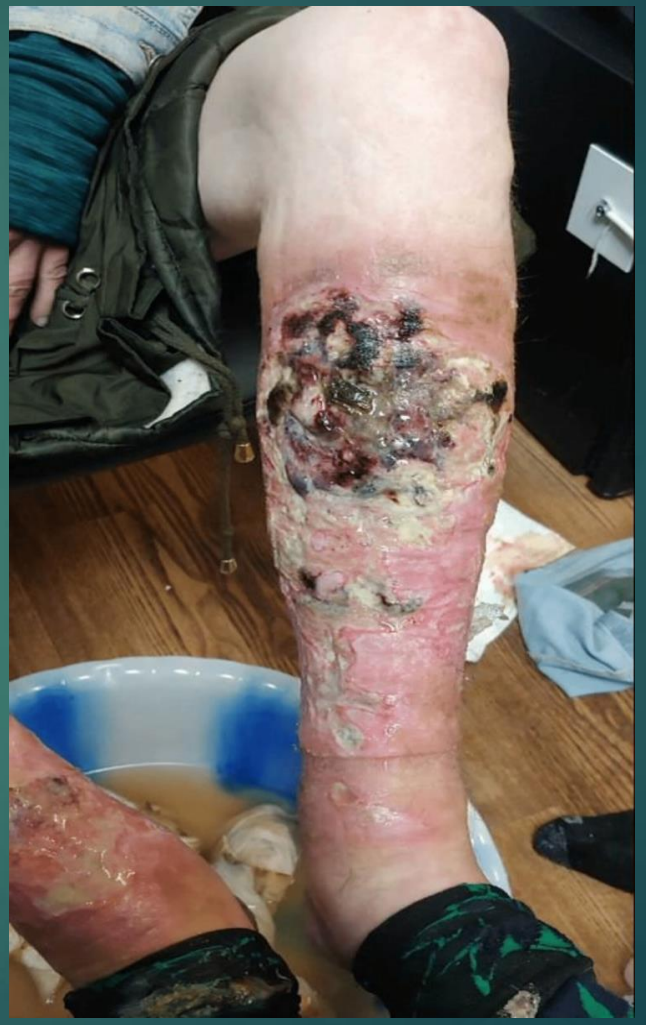
BCCDC Harm Reduction Services, 1/24/22

ToxTalks, Blue Ridge Poison Center, 2/2022

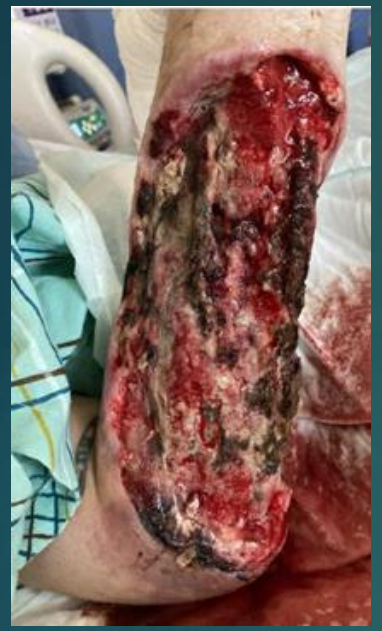
Warning, the following wounds may be difficult for some if non-medical!

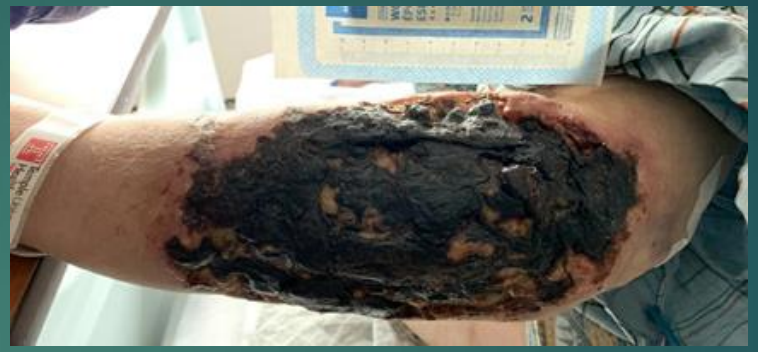
Differential?

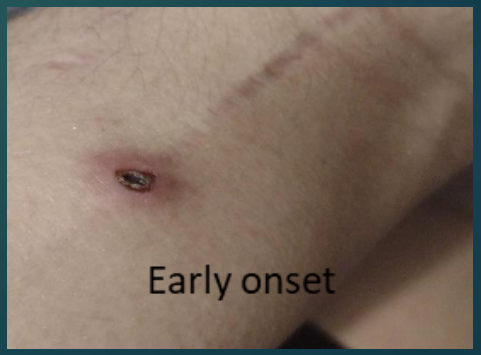


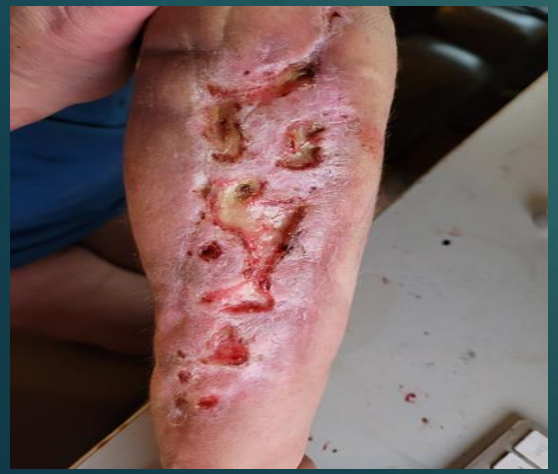


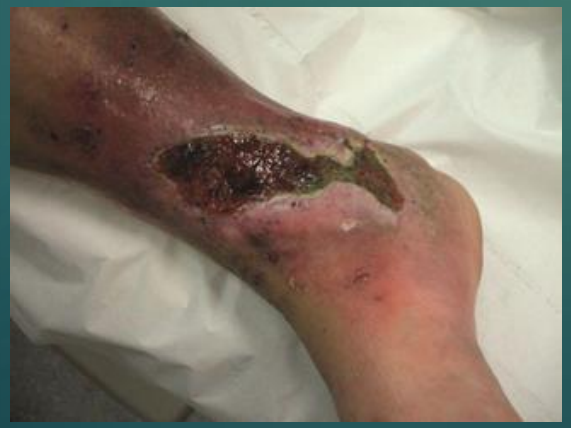
Xylazine and Skin Ulcers/Wounds





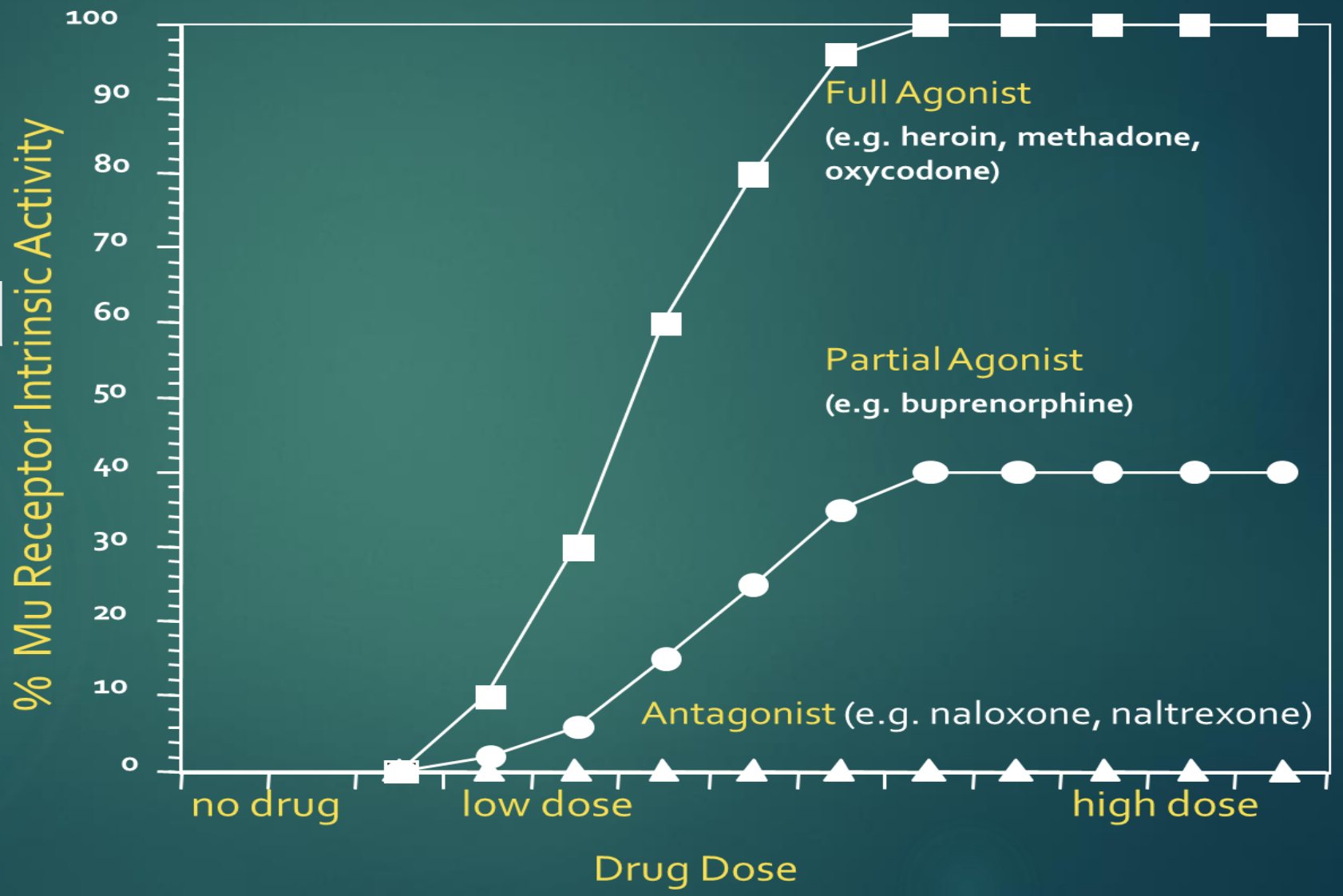




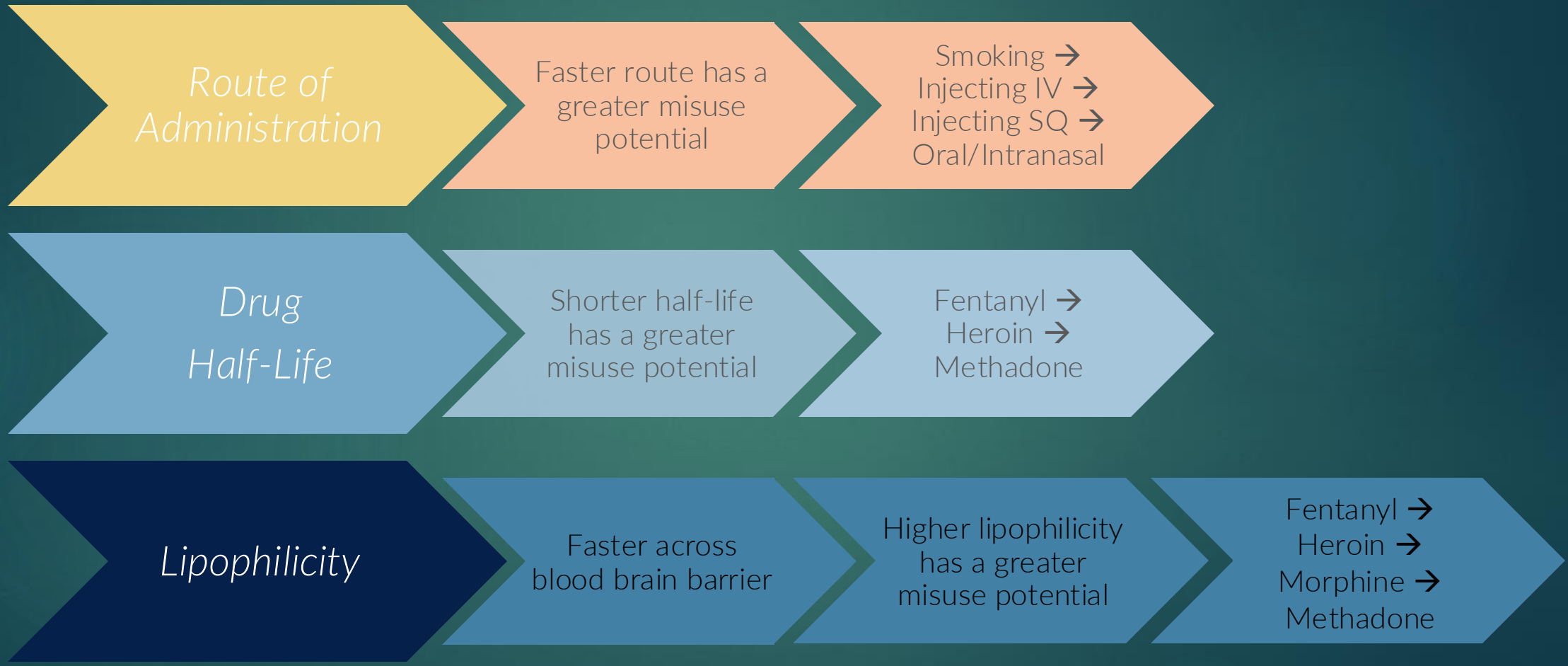


NHRC Xylazine Office Hours, 4/2022

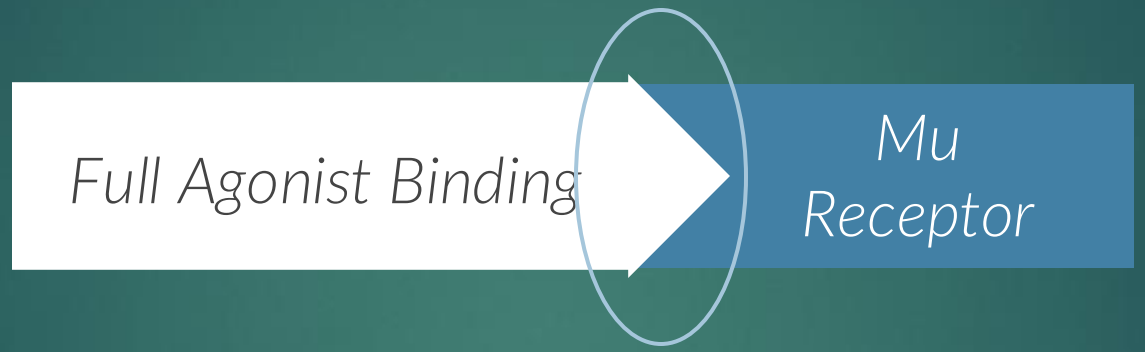
Opioid Agonists and Antagonists



Opioid Characteristics that Increase Euphoria



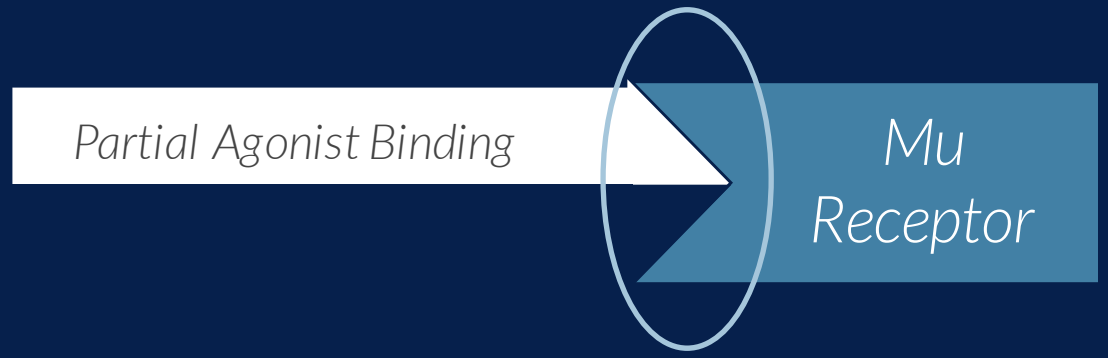
Full Opioid Agonist



A full agonist

- activates the Mu receptor.
- is reinforcing/rewarding.
- is the riskiest opioid type (i.e., sedation and respiratory depression).
- includes fentanyl, heroin, methadone, & others.

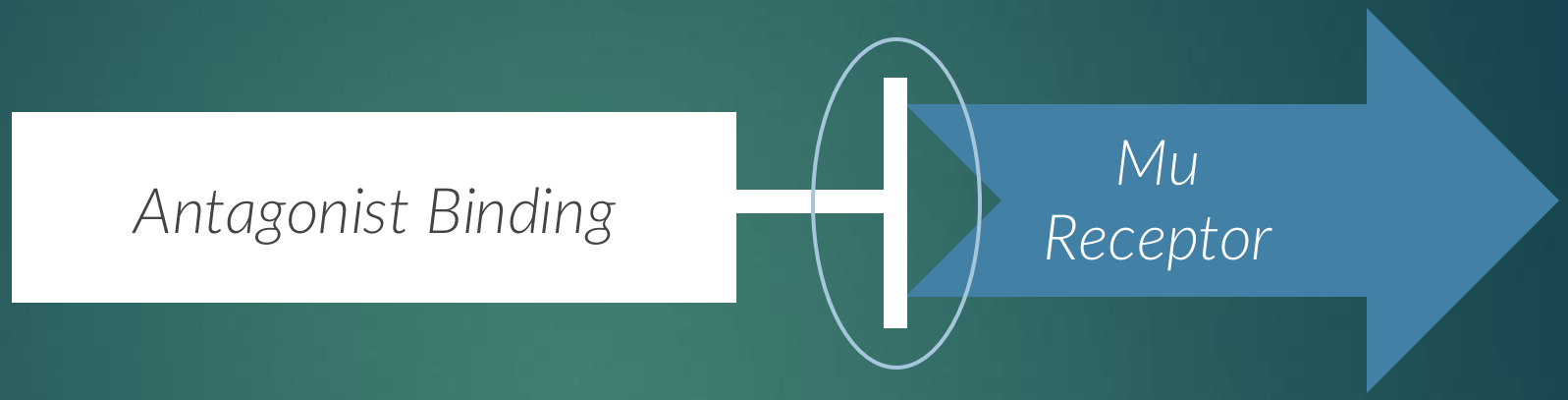
Partial Opioid Agonist



A partial agonist

- activates the Mu receptor with ceiling effect.
- is relatively less reinforcing/rewarding.
- is a less risky opioid type (i.e., sedation and respiratory depression).
- includes buprenorphine.

Opioid Antagonist



An antagonist

- occupies without activating.
- is not reinforcing/rewarding.
- blocks or displaces opioid agonists.
- includes naloxone and naltrexone.

Receptor Affinity

Buprenorphine's Affinity

- ***Affinity*** is the strength with which a drug physically binds to a receptor.
- ***Buprenorphine's affinity*** is very high; it will displace full agonists.
- ***Receptor binding strength,*** high or low, is NOT the same as receptor activation (agonist or antagonist).

High Affinity binding

Mu Opioid Receptor Range of Ki Value	
Buprenorphine	0.21 to 1.5
Fentanyl	0.7 to 1.9
Methadone	0.72 to 5.6
Naloxone	1 to 3 (antagonist effects)
Morphine	1.02 to 4
Codeine	65 to 135

PDSP Ki Database https://pdsp.unc.edu/databases/pdsp.php

Wang D, Sun X, Sadee W. Different effects of opioid antagonists on μ, δ-, and κ-opioid receptors with and without agonist pretreatment. *J Pharmacol Exp Ther.* 2007;321(2):544-52.

Receptor Dissociation

DISSOCIATION is the speed (slow or fast) of dis-engagement of drug from the receptor

Buprenorphine's dissociation is slow

Buprenorphine stays on the receptor a long time and blocks full agonist from binding

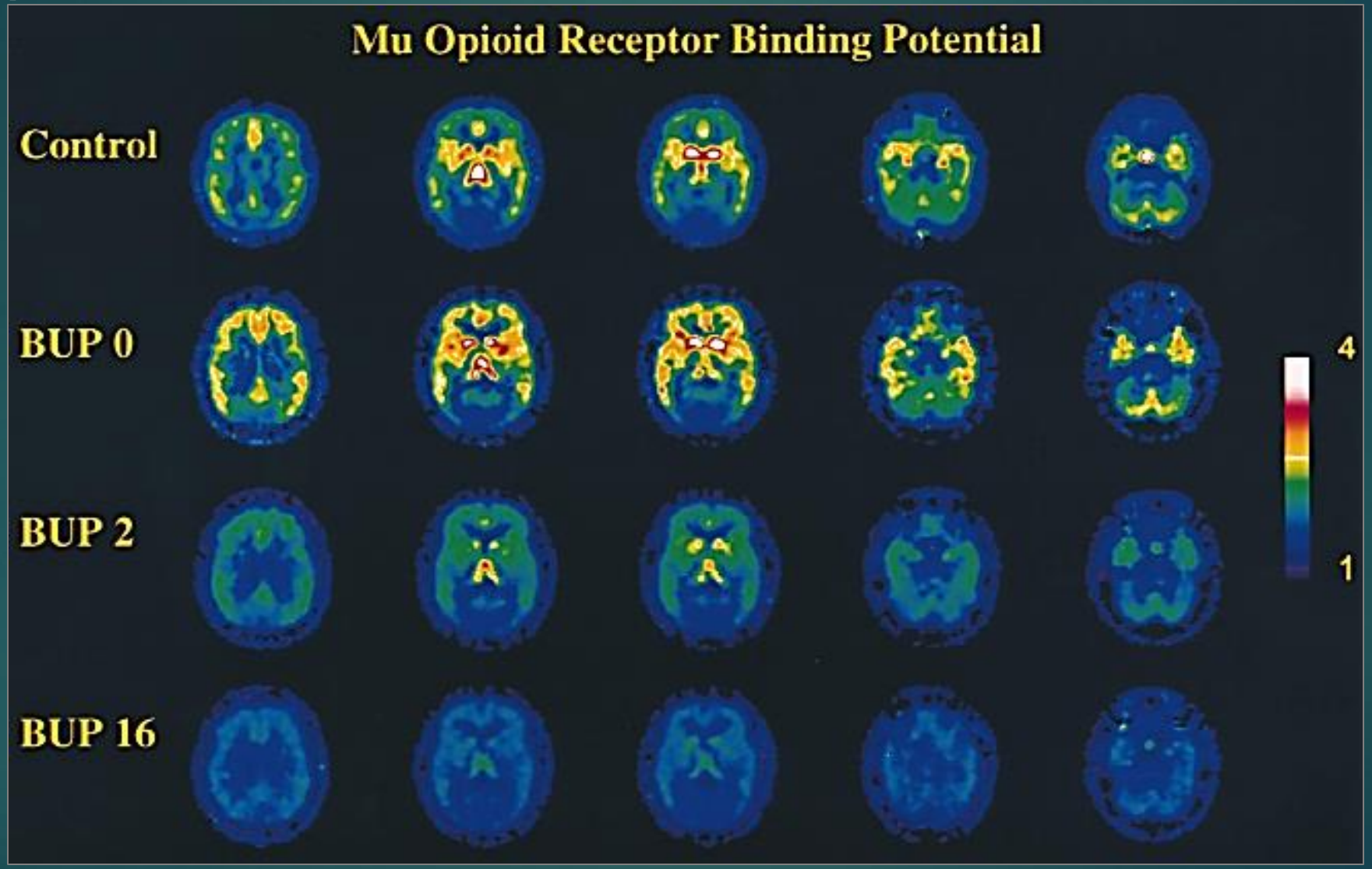
Mu Receptor

Bup dissociation is slow

Therefore, Full Agonists can't bind

Slide created by Tom Pichot, MD

Opioid Blockade



Binding Potential (Bmax/Kd)

Zubieta et al. Neuropsychopharmacology 23:326–334, 2000

Buprenorphine Summary

- High affinity partial mu opioid agonist (higher than naloxone, fentanyl)
- Long half-life when used to prevent overdose and cravings
- Analgesic properties are shorter lived (4-6 hours)
- "Ceiling effect" on respiratory depression

Pharmacology Highlights Buprenorphine

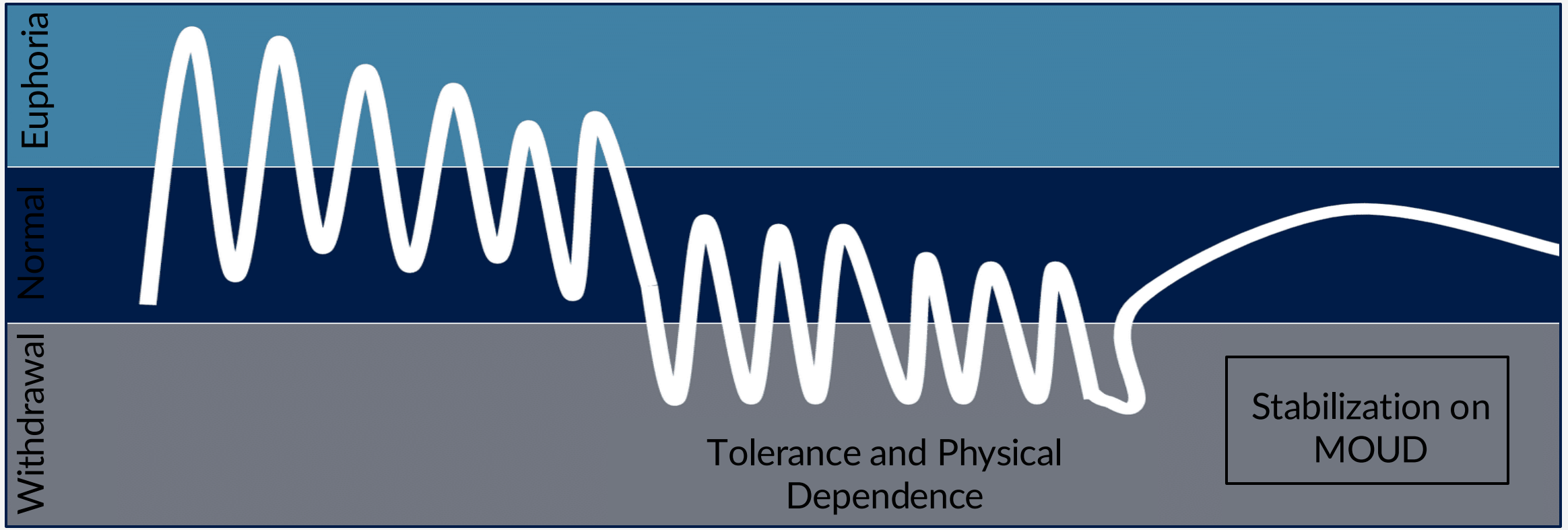
- Generally given sublingually
  - Moderate (~30%) bioavailability
  - ~0%-5% when swallowed
- Can also be given IV at a much lower dose (0.3mg) due to 100% bioavailability

Pharmacology Highlights Buprenorphine

- Comes as mono (buprenorphine) and combo (bup-naloxone) products
- Naloxone is inert sublingually, may occur with high doses of combo
- Combo products preferred to prevent diversion and discourage misuse by injection
  - If injected, naloxone competes with buprenorphine to limit euphoria and overdose
- Use the combination products

Goldsworthy, 2008

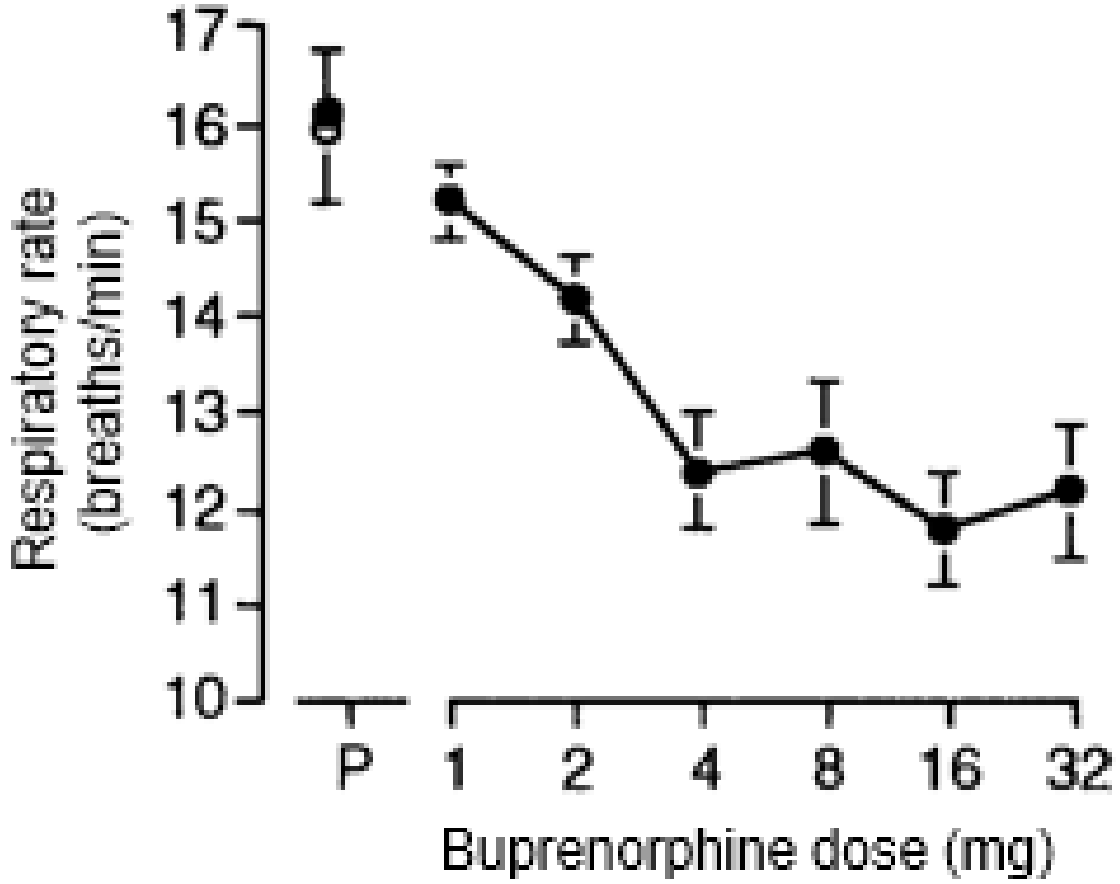
Natural History Of Opioid Use Disorder



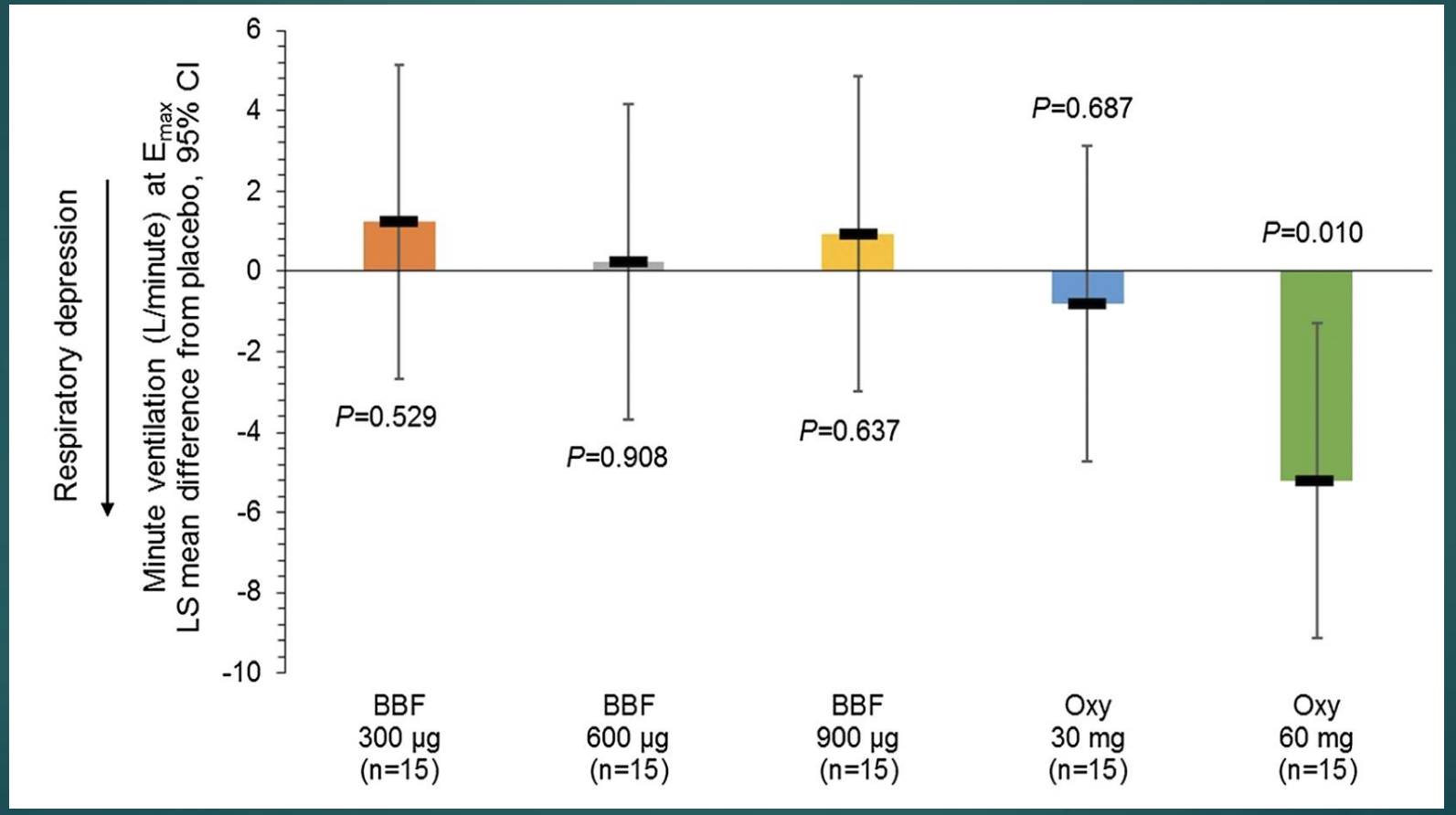
Adapted From Dole et al., 1996. DOI: 10.1001/archinte.1966.00290160004002

Pharmacology Highlights Buprenorphine

- Walsh, 1994



Pharmacology Highlights Buprenorphine



Webster, 2020

Ceiling Effect

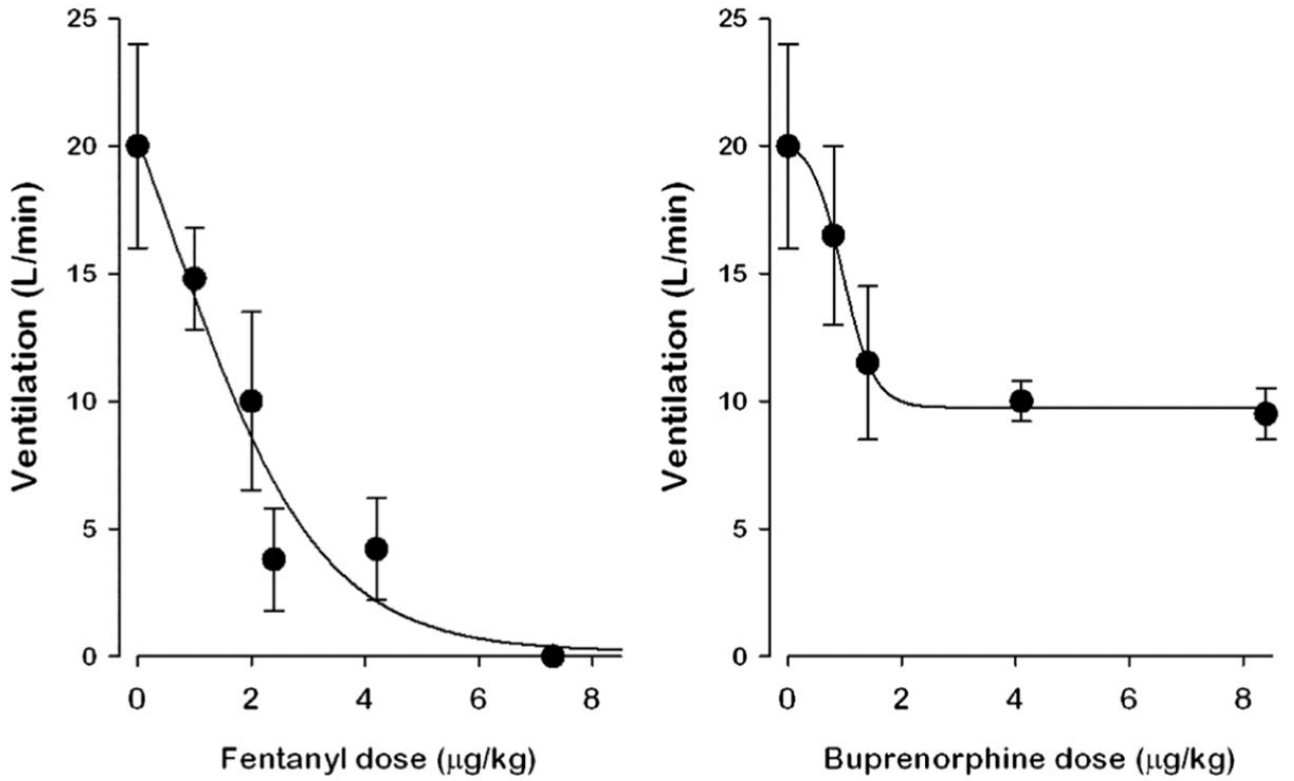
British Journal of Anaesthesia 96 (5): 627–32 (2006)
doi:10.1093/bja/ael051 Advance Access publication March 17, 2006

BJA

Buprenorphine induces ceiling in respiratory depression but not in analgesia

A. Dahan[1]*, A. Yassen[2], R. Romberg[1], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Danhof[2]

A

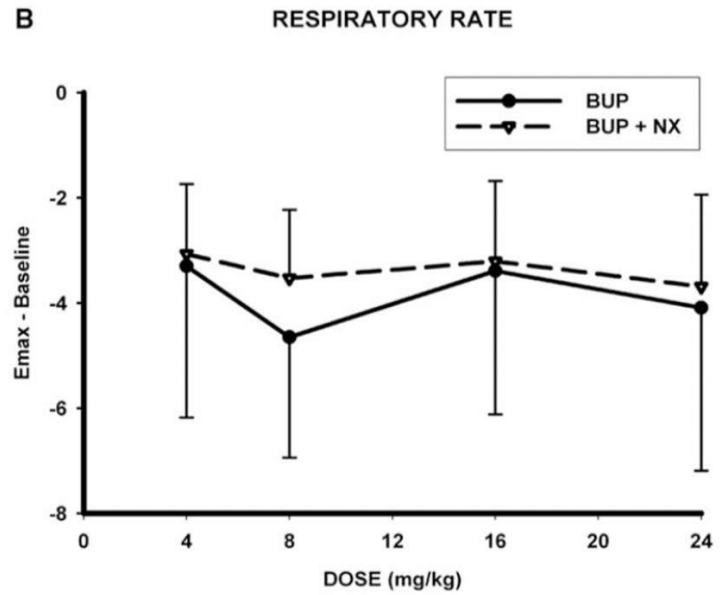


Pharmacokinetics and Pharmacodynamics of Multiple Sublingual Buprenorphine Tablets in Dose-Escalation Trials

Domenic A. Ciraulo, MD, Robert J. Hitzemann, PhD, Eugene Somoza, MD, Clifford M. Knapp, PhD, John Rotrosen, MD, Ofra Sarid-Segal, MD, Ann Marie Ciraulo, RN, David J. Greenblatt, MD, and C. Nora Chiang, PhD

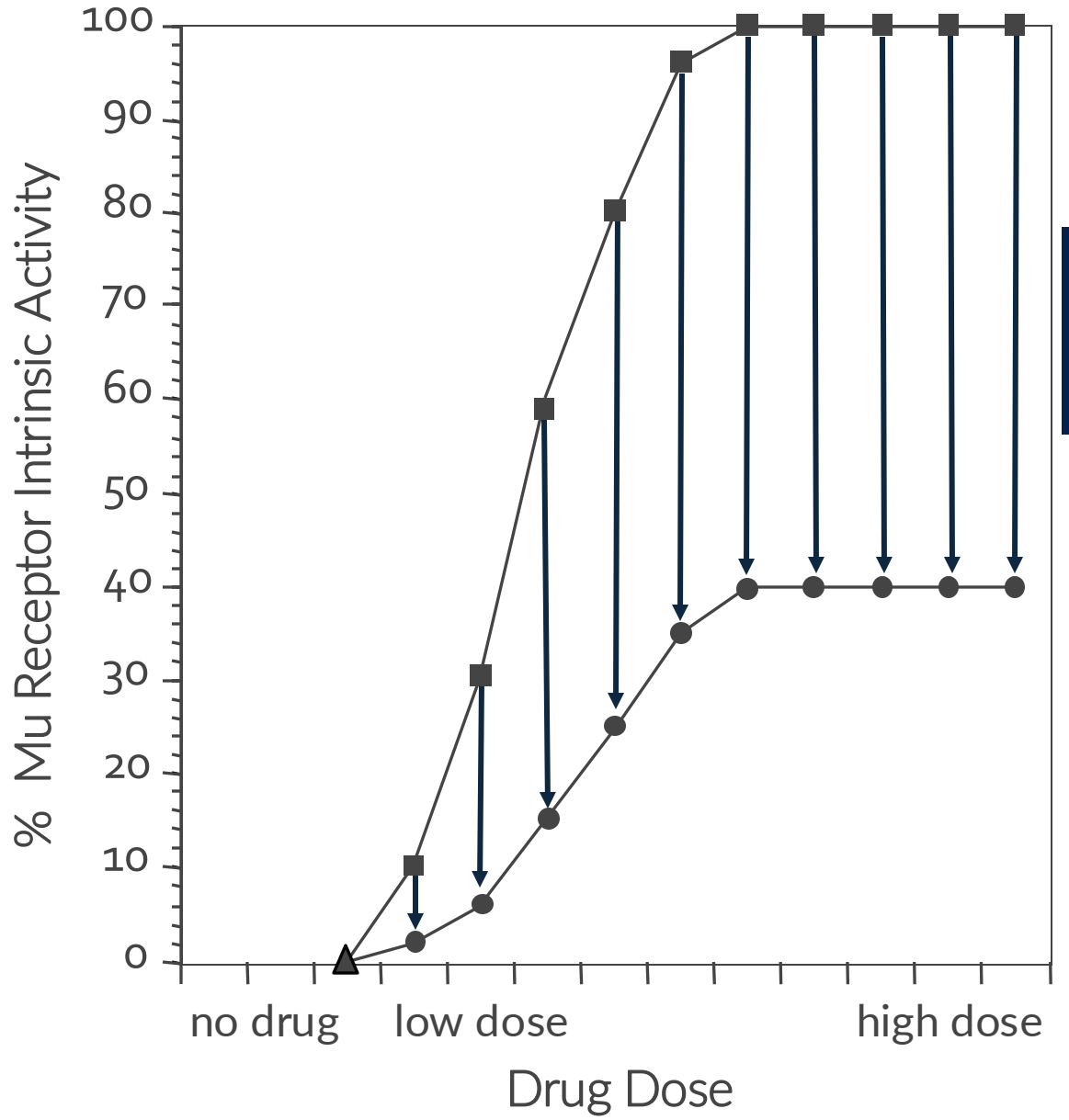
38 subjects

B



Precipitated Acute Withdrawal

Buprenorphine will precipitate withdrawal when it displaces full agonist off the Mu receptors.



Full Agonist
(e.g. heroin, methadone, oxycodone)

A Net Decrease in Receptor Activity if a Partial Agonist Displaces Full Agonist

Partial Agonist
(e.g. buprenorphine)

Pharmacology Highlights Buprenorphine

- **2% of IV opioid users report buprenorphine use "to get high"**
- **Of those using diverted buprenorphine, 72-80% report use for symptom management, e.g., withdrawal, and suppression of cravi**ng
- May be public health signal that treatment needs not being met
  - need for improved access/expansion of treatment
- Part of addiction long-term care can be urine drug testing for bup with metabolites

Goldsworthy, 2008
Cicero, 2018
Daniulaityte, 2019
Genberg, 2013
Robbins, 2021

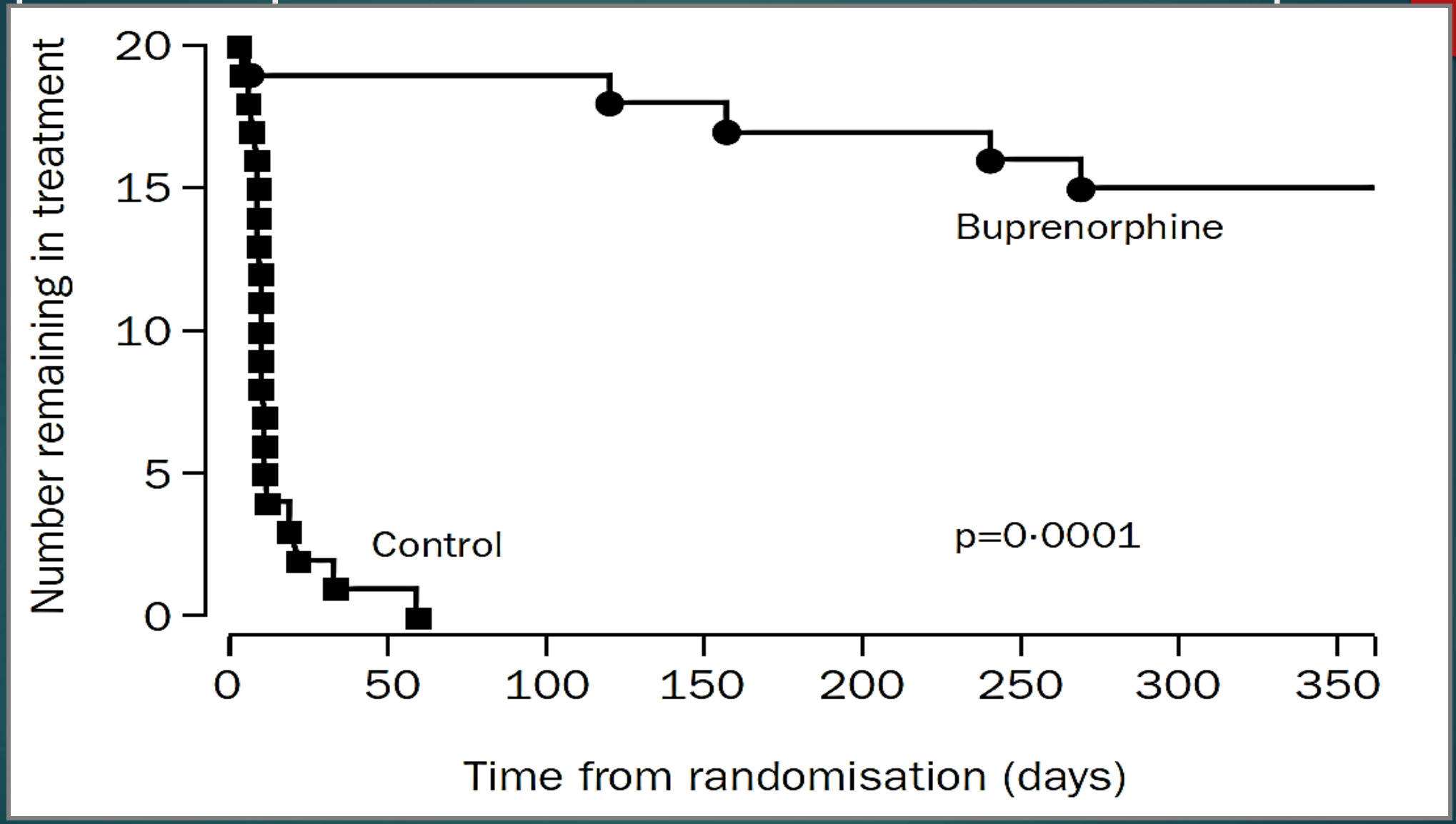
MEDICATIONS are the MOST EFFECTIVE Treatment for OUD

- **Opioid use disorder does not respond to the same treatments as** alcohol **use disorder**.
- **Non-medication therapies generally DO NOT WORK**: ~80 – 90+% annual relapse rate. Incarceration with forced abstinence, also does not work. Both increase the risk of lethal overdose post-discharge. Only 28% of residential programs provide MOUD.
- 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 recovery of ~10 to 80%, but average ~40-50%.

Kakko, 2003

*Poor data collection from most of these programs.

Buprenorphine: Maintenance vs Taper



Kakko J et al. *Lancet* 2003

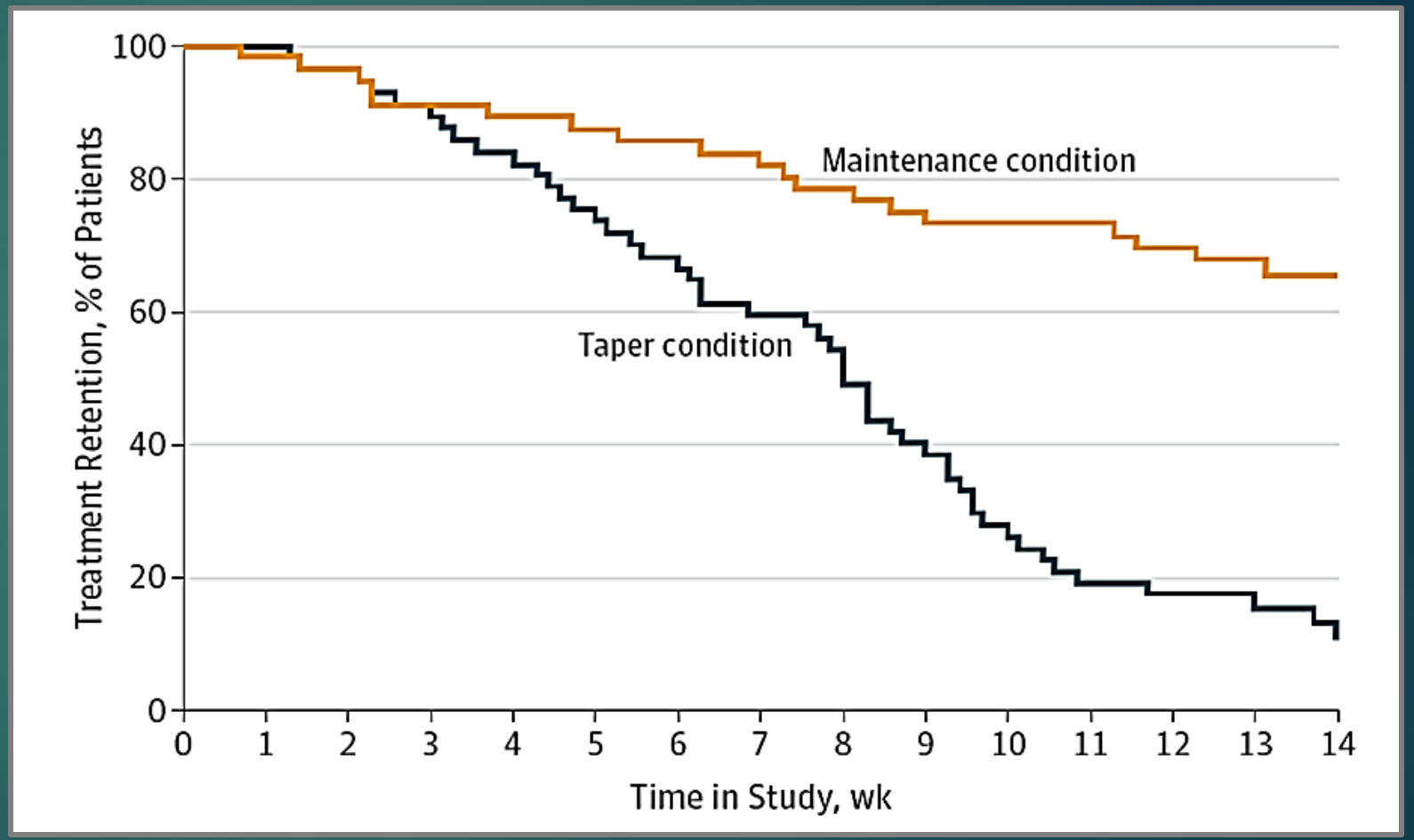
Buprenorphine Maintenance vs Taper Prescription OUD

Completion 14 wk trial:

- Taper: 11%
- Maintenance: 66%

Mean % urine negative:

- Taper: 35%
- Maintenance: 53%



Fiellin DA et al. JAMA Intern Med. 2014.

High Threshold vs Low Threshold Care

- PWUD face numerous barriers to engage in services:
  - Registration threshold (accessing care and staff)
  - Competence threshold (ability to communicate needs)
  - Efficiency threshold ("What about those who need 1000 cups of coffee before they start to speak about their needs?")
  - TRUST
- Low-threshold care aims to reduce barriers ('thresholds') through less stringent eligibility criteria to broaden potential reach

Edland-Gryt M. Int J Drug Policy. 2013 May;24(3):257-64.; Mofizul Islam M. Int J Drug Policy. 2013 May;24(3):220-2.

Creating a System of Low Threshold Care

- SUD Initiative Mission: *To improve the quality, clinical outcomes and value of addiction treatment for all patients with SUD. To accomplish this mission, patients must have access to* ***evidence based treatment*** *that is* ***readily available*** *and standardized across the system.*
- **Core Principles**:

1. Chronic Care Model
2. Patient Centered Approach
3. Evidence Based Treatment
4. Treatment Available on Demand without Barriers
5. Quality Standards Across Settings

Low threshold, outcome based treatment

- Collaborate with patient to set treatment goals
- Ask about the role/function and effects of drug use in daily lives
- Clinicians and patients should decide on an appropriate level of care
- Offer pharmacologic treatment, provide information, evidence
- Don’t discharge patient with return to use, other use.

What are the benefits of low threshold, outcome centered care?

- A continuum of care with no gaps
- Enhanced engagement and treatment retention
- Improved patient and staff satisfaction
- Compassion, " I felt that my life had value"!
- Hope
- Best part of my practice!
- Life saving!

Creating a System of Low Threshold Care

- SUD Initiative Mission: *To improve the quality, clinical outcomes and value of addiction treatment for all patients with SUD. To accomplish this mission, patients must have access to* ***evidence based treatment*** *that is* ***readily available*** *and standardized across the system.*
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3. Evidence Based Treatment
4. Treatment Available on Demand without Barriers
5. Quality Standards Across Settings

New System of Care



- Inpatient Consult Team
- Integrated treatment in primary care
- Recovery coaches
- ED initiated treatment
- Mentoring & support to specialty clinics trauma, ID, OB)
- ***Bridge clinic, low threshold, outcome centered care***

How Do Patients Get to Bridge?

Why is This Unique?

- On demand, urgent access, individualized
- Warm welcomes, warm hand offs
- Engagement is primary goal
- Same day pharmacotherapy
- Emphasis on education and support, regardless of stage, reduction of harmful consequences and motivational enhancement
- Follow up outreach for no shows, transitions
- ***No one is discharged***

Don't forget naloxone rescue!

But naloxone rescue without treatment engagement only delays death!

Bridge programs with warm hand-offs improve follow through

Low threshold care, diminish barriers

Long term engagement with motivational enhancement

Contingency management (meth and opioids)

The Philadelphia Inquirer

New Jersey first state to authorize paramedics to provide addiction-treatment drug to overdose victims

Buprenorphine Induction: Early Stabilization

Overall Goals: To find the buprenorphine dose at which the patient experiences:

- Suppression of opioid withdrawal symptoms
- Marked reduction or discontinuation of non-prescribed opioids
- Decreased opioid cravings
- Provide effective blockade to decrease risk of lethal overdose
- Minimal/no side effects (avoid precipitated withdrawal)

Goals of Induction

- Achieve Buprenorphine Maintenance
  - Decreased Mortality
  - Improved outcomes

GOALS OF USING MOUD

- Prevent overdose and death
- Reduce cravings and withdrawal symptoms
- Block the euphoric effect of other opioids
- Restore the normal reward pathway
- Interrupt the cycle of seeking, using, and recovering from drug use
- Improve rates of engagement in treatment

Menu of Buprenorphine Inductions[1]

- Standard Induction
- High-Dose Induction
- Low-Dose induction, previously microdosing/microinduction

Greenwald, M. K., Herring, A. A., Perrone, J., Nelson, L. S., & Azar, P. (2022). A neuropharmacological model to explain buprenorphine induction challenges. *Annals of Emergency Medicine*.

Emergency Department

- First point of contact prior to admission, 1/80 patients
- Effective, low-barrier setting
- High-Dose Inductions Recommended

Greenwald, M. K., Herring, A. A., Perrone, J., Nelson, L. S., & Azar, P. (2022). A neuropharmacological model to explain buprenorphine induction challenges. *Annals of Emergency Medicine*.

Buprenorphine in the ED

- EDs can act as a very important entry point for MOUD, 1/80 patients seen has an opioid use disorder, “it’s where the patients are”
- One of multiple entry points
  - Jails
  - PCPs

Buprenorphine in the ED

- 75% of patients initiated in ED and given RX still on buprenorphine at 30 & 60 days
  - No precipitated withdrawal[1]
- 30% follow up in one week
  - 1 case of withdrawal[2]
- 78% were engaged in addiction care at 30 days
  - Reduction of illicit drug use from 5.4 days per week to 2.3 days[3]

Lane, 2020
LeSaint, 2020
D'Onofrio, 2015

Precipitated Withdrawal

- Rapid onset of withdrawal symptoms within 1-hour of administration of buprenorphine (described for SL-BUP)

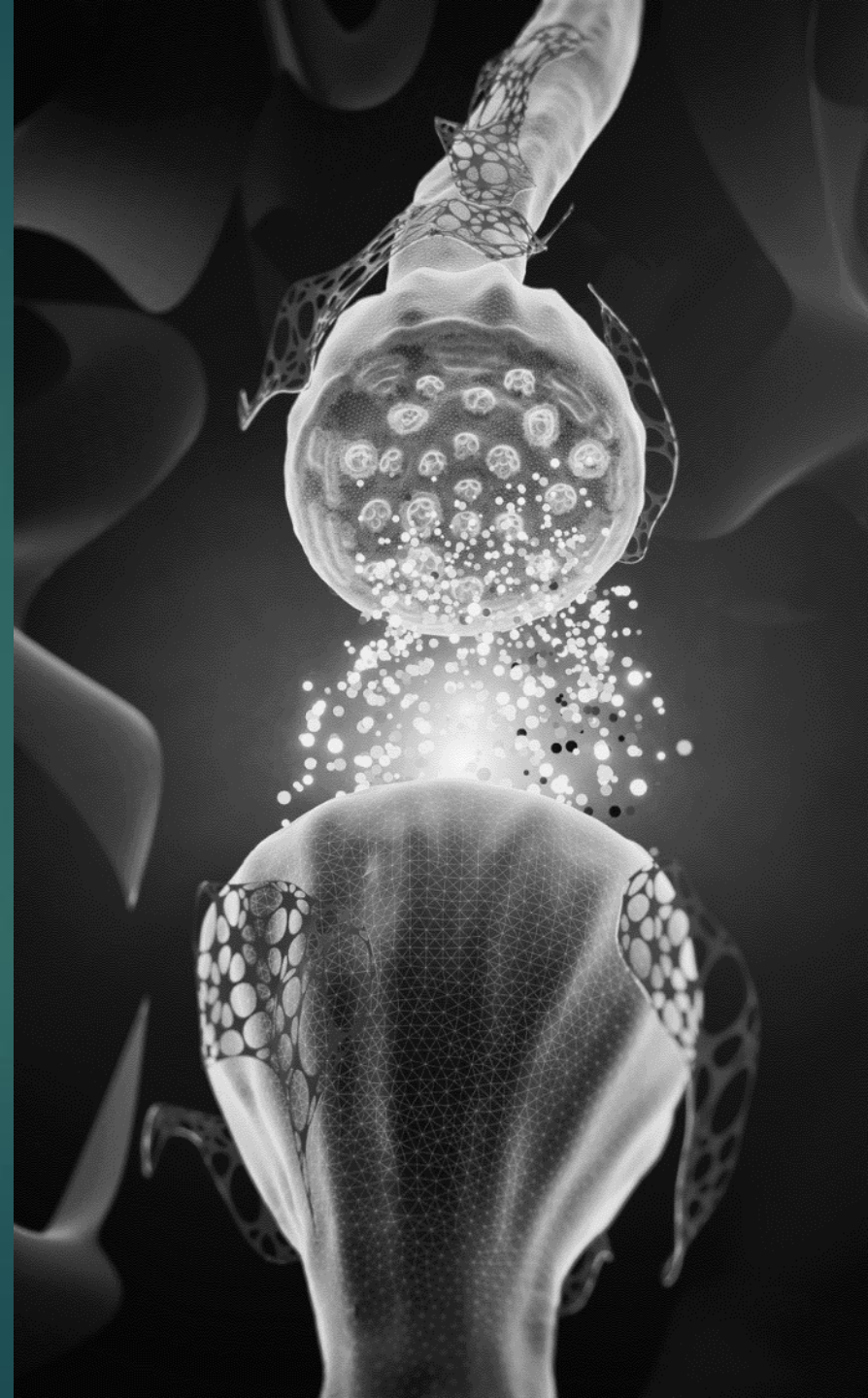
- Assessment is based on rapidity of onset of withdrawal symptoms and clinical factors, similar to when a patient receives full naloxone rescue. COWS scores reflect this rapid deterioration and skyrocket to moderate/severe levels.

  (e.g., timing since last use, duration and use of opioid agonist(s))

Rosado, Alcohol Depend 2007;90(2-3):261-269 https://doi.org/10.1016/j.drugalcdep.2007.04.006
Comer S, et al. National practice guideline for the use of medications in the treatment of addiction involving opioid use. American Society for Addiction Medicine. 2015;66.

Precipitated Withdrawal

- Occurs when a full opioid agonist (i.e. fentanyl, morphine, heroin) is replaced with a partial opioid agonist (buprenorphine) with a higher affinity to the mu receptor
- Symptoms are the same as naloxone induced opioid withdrawal with acute onset.



SOURCE: SAMHSA Buprenorphine Quick Start Guide
DOI: 10.1001/jamanetworkopen.2023.6108

Lessons Learned: Treatment of PW

- More Buprenorphine 24-32 mg (Use mono **product with large dosing)**
- **Ancillary Medications**
  - Muscle aches and pains: Acetaminophen, NSAIDs: Ibuprofen, ketorolac
  - Abdominal cramps and diarrhea: Dicyclomine, Loperamide
  - Nausea: Antiemetics
  - Elevated blood pressure, tachycardia and/or anxiety/restlessness: Clonidine
- Consider IV Fluids & small doses of lorazepam
- Best to find a dark quieter place or send home if possible

After Hospital Admission

- Opioids Not Required on Admission
  - Start buprenorphine when withdrawal develops
- Opioids Continued on Admission
  - Cannot use a standard induction

Acutely Ill, Hospitalized Patients

- Can’t tolerate withdrawal
  - Acute psychiatric conditions
  - Post-op/trauma-related acute pain
  - Cardiac Stress
- Don’t want to tolerate withdrawal
  - Ambivalence about MOUD
  - On methadone, want to switch to buprenorphine
  - History of precipitated withdrawal

Weimer, M. B., Guerra, M., Morrow, G., & Adams, K. (2021). Hospital-based buprenorphine micro-dose initiation. *Journal of Addiction Medicine*, *15*(3), 255-257.

Hospital is Critical Opportunity

- OUD in hospitalized patients quadrupled
  - Annual rate of hospital discharges documenting OUD without opioid overdose quadrupled during 1993–2016
- OUD in hospitalized pts increased 8% annually
  - During 2003–2016.

Peterson, C., Xu, L., Florence, C., & Mack, K. A. (2019). Opioid-related US hospital discharges by type, 1993–2016. *Journal of substance abuse treatment*, *103*, 9-13.

Low-Dose Buprenorphine Initiation

- Names
  - Bernese Method
    - Microdose or Micro Induction
  - Low-Dose Initiation/induction
    - Low doses don't precipitate withdrawal[1]
    - Precipitated withdrawal is a function of the starting dose of buprenorphine (not buprenorphine itself)

1. Mendelson, J.; Jones, R.T.;Welm, S.; Batki, S.L. Buprenorphine and naloxone interactions in methadone maintenance patients. Biol. Psychiatry **1997, 41, 1095–1101.**

Low-Dose Buprenorphine Initiation

- Start with a small dose that doesn't precipitate withdrawal
- Continue Opioids to prevent withdrawal, and taper as tolerated
- Titrate up as tolerated

Quirk K, Stevenson M. Buprenorphine Microdosing for the Pain and Palliative Care Clinician. J Palliat Med. 2022 Jan;25(1):145-154. doi: 10.1089/jpm.2021.0378.

Low-Dose Buprenorphine Initiation

- Transmucosal
  - Sublingual
    - Start: 0.5mg (1/4 film or tablets), 0.25mg
    - Duration: Reach 12mg dose by day 3, typically 4-7 days
  - Buccal
    - Start: 225mcg film
    - Duration: Reach 8mg SL films by day 5, 16mg by day 7
- Transdermal
    - Start: 20mcg/hr patch (or less)
    - Duration: Reach 8 mg dose by day 2, 16mg by day 3

Quirk K, Stevenson M. Buprenorphine Microdosing for the Pain and Palliative Care Clinician. J Palliat Med. 2022 Jan;25(1):145-154. doi: 10.1089/jpm.2021.0378.

Barriers to Transdermal Inductions

- Lack of awareness of faster transdermal protocols
- Patches FDA-approved for Pain not OUD
- Patches are expensive
  - 1 Film = few dollars vs. 1 Patch = few hundred dollars
- Not covered by outpatient insurance

Sokolski, Eleasa, et al. "Rapid Low-dose Buprenorphine Initiation for Hospitalized Patients With Opioid Use Disorder." *Journal of Addiction Medicine* (2023): 10-1097.

Barriers to Transmucosal Forms

- Many protocols take longer to get to 8mg dose
- Lowest available SL dose is 2mg
  - Requires cutting (complicated and imprecise)
    - Content uniformity only shown in films cut in half
      - high-performance liquid chromatography analysis
    - Inpatient pharmacies may not approve ¼ films
      - Buccal preparations remain an option but will be covered in inpatient settings

- Solutions
  - Consider Manufacturing Smaller SL Doses
  - Preformulated medication packaging
  - More research on faster protocols

Research

- Speed
  - We don’t want to prolong people on illicit opioids
  - Fastest uptitration speed (for OUD)
  - Highest Starting Dose
- Routes (that lead to most adherence)
- RCT in progress
  - Clinical Practice outpacing research

Standard Induction

Day 1

DAY 1

Checklist

Check the boxes next to each step to help you track your progress. Be patient — you're close to feeling better!

Before taking your first dose, stop taking all opioids for 12-36 hours. You should feel pretty lousy, like having the flu. These symptoms are normal. You will feel better soon.

- ❑ Before your first dose of medication, you should feel **at least three** of the following:
  - ❍ Very restless, can't sit still
  - ❍ Twitching, termors, or shaking
  - ❍ Enlarged pupils
  - ❍ Bad chills or sweating
  - ❍ Heavy yawning
  - ❍ Joint and bone aches
  - ❍ Runny nose, tears in your eyes
  - ❍ Goose flesh (or goose bumps)
  - ❍ Cramps, nausea, vomiting or diarrhea
  - ❍ Anxious or irritable
- ❑ Complete the SOWS. You need your SOWS score to be ≥17 before taking your first dose of buprenorphine.

Schedule

- ❑ **Take 4 mg** of buprenorphine under the tongue (tablet or film strip). (Half of an 8 mg tablet, or two 2 mg tablets). Usually one film strip.
- ❑ Put the tablet or film under your tongue. Do not swallow it. Buprenorphine does not work if swallowed.
- ❑ Wait an hour.
  - If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - If you continue to have withdrawal symptoms, take a second dose under your tongue (4 mg).
  - If you are feeling worse than when you started, you might have precipitated withdrawal. Call and talk with your provider about treatment options.
- ❑ Call your provider or office staff to check in.
- ❑ Wait 1-2 hours.
  - If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - If you continue to have withdrawal symptoms, take a third dose under your tongue (4 mg).
- ❑ Call your provider or office staff to check in.
- ❑ Wait 1-2 hours.
  - If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - If you continue to have withdrawal symptoms,

DAY 1 Dose Summary

Dose	Amount	Time
1st dose (if needed)	4 mg	
2nd dose (if needed)	mg	
3rd dose (if needed)	mg	
4th dose (if needed)	mg	
Total mg on Day 1	mg	

Do not take more than 16 mg total of buprenorphine on Day 1.
If you have taken up to 16mg of buprenorphine and still fee bad, call your doctor right away.

Congratulations! You are through Day 1. See instructions for Day 2 on the next page. You're doing great.

Standard Induction

Day 2

DAY 2

Total from Day 1

What was the total amount of buprenorphine you took yesterday (Day 1)?

Total buprenorphine taken on Day 1	mg

If your Day 1 total was 4 mg:

- ❑ If you feel fine, take 4 mg this morning; however, if you feel some withdrawal symptoms, start with 8 mg this morning.
- ❑ Later in the day, see how you feel. If you feel okay, do not take more. If you still feel withdrawal, take another 4 mg dose.
- ❑ Talk with your provider or office staff.

If your Day 1 total was 8 mg:

- ❑ If you feel fine, take 8 mg this morning; however, if you feel some withdrawal symptoms, start with 12 mg this morning.
- ❑ Later in the day, see how you feel. If you feel okay, do not take more. If you still feel withdrawal, try another 4 mg dose.
- ❑ Talk with your provider or office staff.

If your Day 1 total was 12 mg:

- ❑ If you feel fine, take 12 mg this morning. You might want to split the dose into a morning dose (6 mg) and afternoon dose (6 mg).
- ❑ If you feel some withdrawal symptoms, start with 16 mg this morning.
- ❑ Later in the day, see how you feel. If you feel okay, do not take more. If you still feel withdrawal, try another 4 mg dose.
- ❑ Talk with your provider or office staff.

DAY 2 Dose Summary

Dose	Amount	Time
1st dose (if needed)	mg	
2nd dose (if needed)	mg	
Total mg on Day 2	mg	

Standard Induction

Self-Start Guide

- A resource provided by California Bridge. Access the full guide: https://bridgetotreatment.org/wp-content/uploads/CA-BRIDGE-PATIENT-MATERIALS-Buprenorphine-Self-Start.pdf

CA BRIDGE

Buprenorphine Self-Start

Guidance for patients starting buprenorphine outside of hospitals or clinics

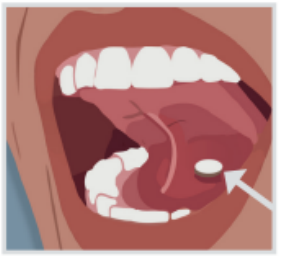
1. Plan to take a day off and have a place to rest.
2. Stop using and wait until you feel very sick from withdrawals (at least 12 hours is best, if using fentanyl it may take a few days).
3. Dose one or two 8mg tablets or strips UNDER your tongue (total dose of 8-16mg).
4. Repeat dose (another 8mg-16mg) in an hour to feel well.
5. The next day, take 16-32mg (2-4 tablets or films) at one time.

If you have started bup before:

- If it went well, that's great! Just do that again.
- If it was difficult, talk with your care team to figure out what happened and find ways to make it better this time. You may need a different dosing plan than what is listed here.

If you have never started bup before:

- Gather your support team and if possible take a "day off."
- You are going to want space to rest. Don't drive.
- Using cocaine, meth, alcohol or pills makes starting bup harder, and mixing in alcohol or benzos can be dangerous.



Place dose under your tongue (sublingual).

If you have a light habit: *(For example, 5 "Norco 10's" a day)*

- Consider a low dose: start with 4mg and stop at 8mg total.
- **WARNING:** Withdrawal will continue if you don't take enough bup.

If you have a heavy habit: *(For example, injecting 2g heroin a day or smoking 1g fentanyl a day)*

- Consider a high dose: start with a first dose of 16mg.
- For most people, the effects of bup max out at around 24-32mg.
- **WARNING:** Too much bup can make you feel sick and sleepy.

Low-Dose Induction

- "Microdosing"
- Gradual introduction of small doses of buprenorphine with ongoing use of full agonist opioids, allowing for buprenorphine to slowly build up in your system.
- Start with maximum 1 mg of buprenorphine.
- Pick a protocol based on preference, formulary, timing.
- Avoid prolonged protocols (> 7 days).

Low-Dose Induction

When to Consider

Transitioning from methadone

Difficulty with buprenorphine induction in the past.

Transition from full agonist opioids for pain to buprenorphine

Intentional, daily, fentanyl consumption with high tolerance

SOURCE: CA Bridge, bridgetotreatment.org

DOI: 10.1097/CXA.0000000000000072; 10.1111/dar.13394

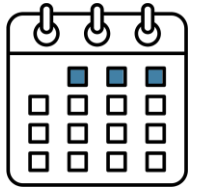
Low-Dose Induction

When to Reconsider

- Person doesn't want to continue full agonist opioids during transition
- High risk of respiratory depression
- Already in significant withdrawal
- Difficulties with health literacy or medication adherence
- Unable to self-administer
- Unable to dose frequently (i.e., incarcerated, work schedule)
- Patient preference for standard induction
- It can delay induction

SOURCE: CA Bridge, bridgetotreatment.org

Low-Dose Induction – 3 Day

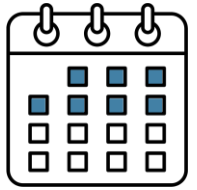


Prescribe 2 mg buprenorphine films #6, 8 mg buprenorphine films #4 for 3-day supply

- Day 1: 0.5 mg (1/4 of 2 mg strip) SL buprenorphine q3 hours (4 mg total daily dose), continue full opioid agonists.
- Day 2: 1 mg (1/2 of 2 mg strip) SL buprenorphine q3 hours (8 mg total daily dose), continue full opioid agonists.
- Day 3: 8-16 mg (1-2 8 mg strips) SL buprenorphine once daily and 4 mg SL q6h prn withdrawal (max 32 mg total daily dose), wean or stop full opioid agonists.

SOURCE: CA Bridge, bridgetotreatment.org

Low-Dose Induction – 7 day



Prescribe 2 mg buprenorphine SL strips # 15, 8 mg buprenorphine SL strips #4 for 7-day supply.

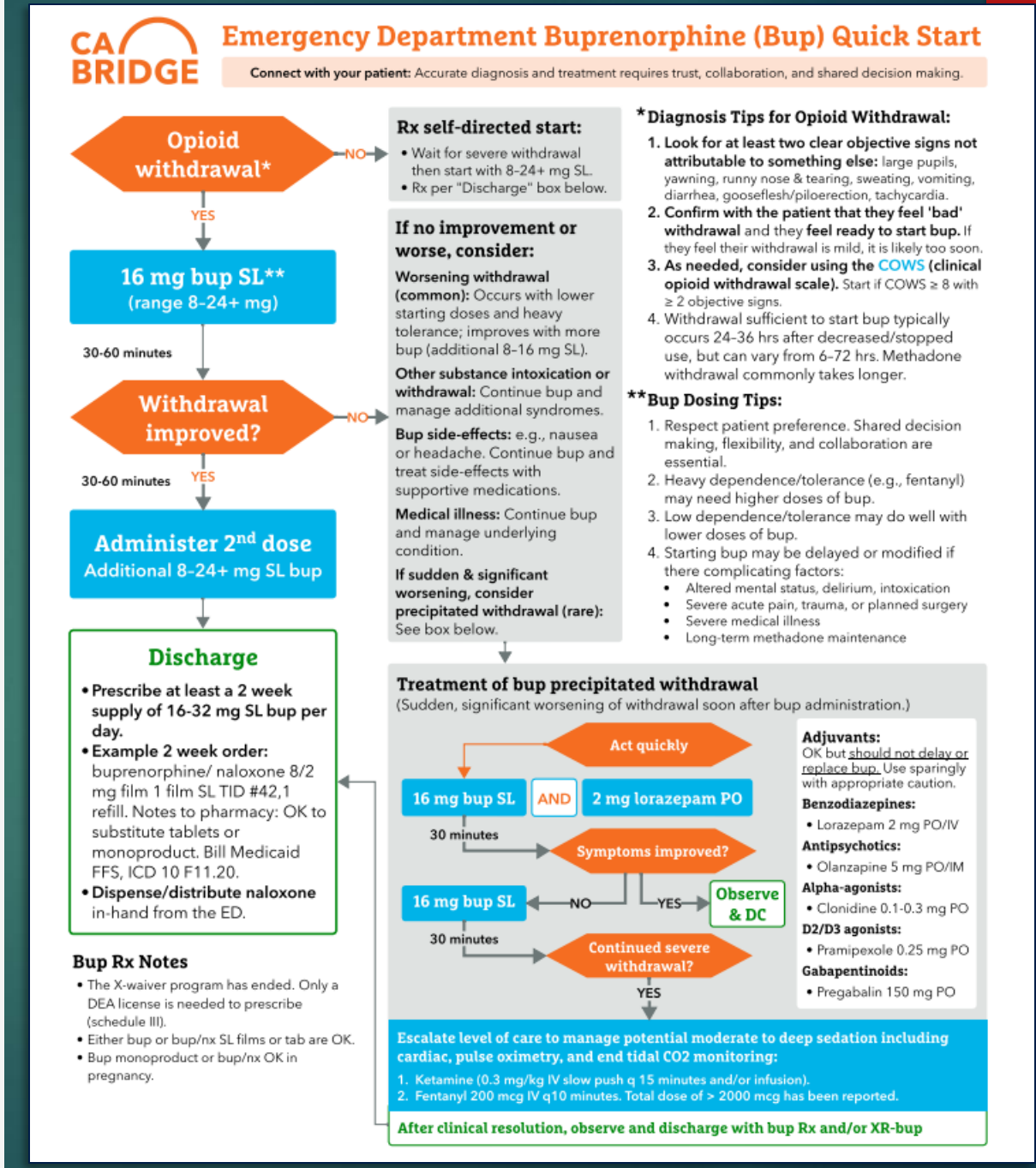
- Day 1: 0.5 mg (1/4 of 2 mg strip) buprenorphine SL daily (0.5 mg total daily dose), continue full opioid agonist.
- Day 2: 0.5 mg (1/4 of 2 mg strip) buprenorphine SL BID (1 mg total daily dose), continue full opioid agonist.
- Day 3: 1 mg (1/2 of 2 mg strip) buprenorphine SL BID (2 mg total daily dose), continue full opioid agonist.
- Day 4: 2 mg buprenorphine SL BID (4 mg total daily dose), continue full opioid agonist.
- Day 5: 3 mg (1+1/2 of 2 mg strip) buprenorphine SL BID (6 mg total daily dose), continue full opioid agonist.
- Day 6: 4 mg (2 of 2 mg strip) buprenorphine SL BID (8 mg total daily dose), continue full opioid agonist.
- Day 7: 6 mg (3 of 2 mg strip) buprenorphine SL BID (12 mg total daily dose), continue full opioid agonist.
- Day 8: 16 mg (2 of 8 mg strip) buprenorphine qday and 4mg (1/2 of 8 mg strip) q6h prn withdrawal (max 32 mg total daily dose), wean or stop full opioid agonists.

SOURCE: CA Bridge, bridgetotreatment.org
DOI: 10.2147/SAR.S109919

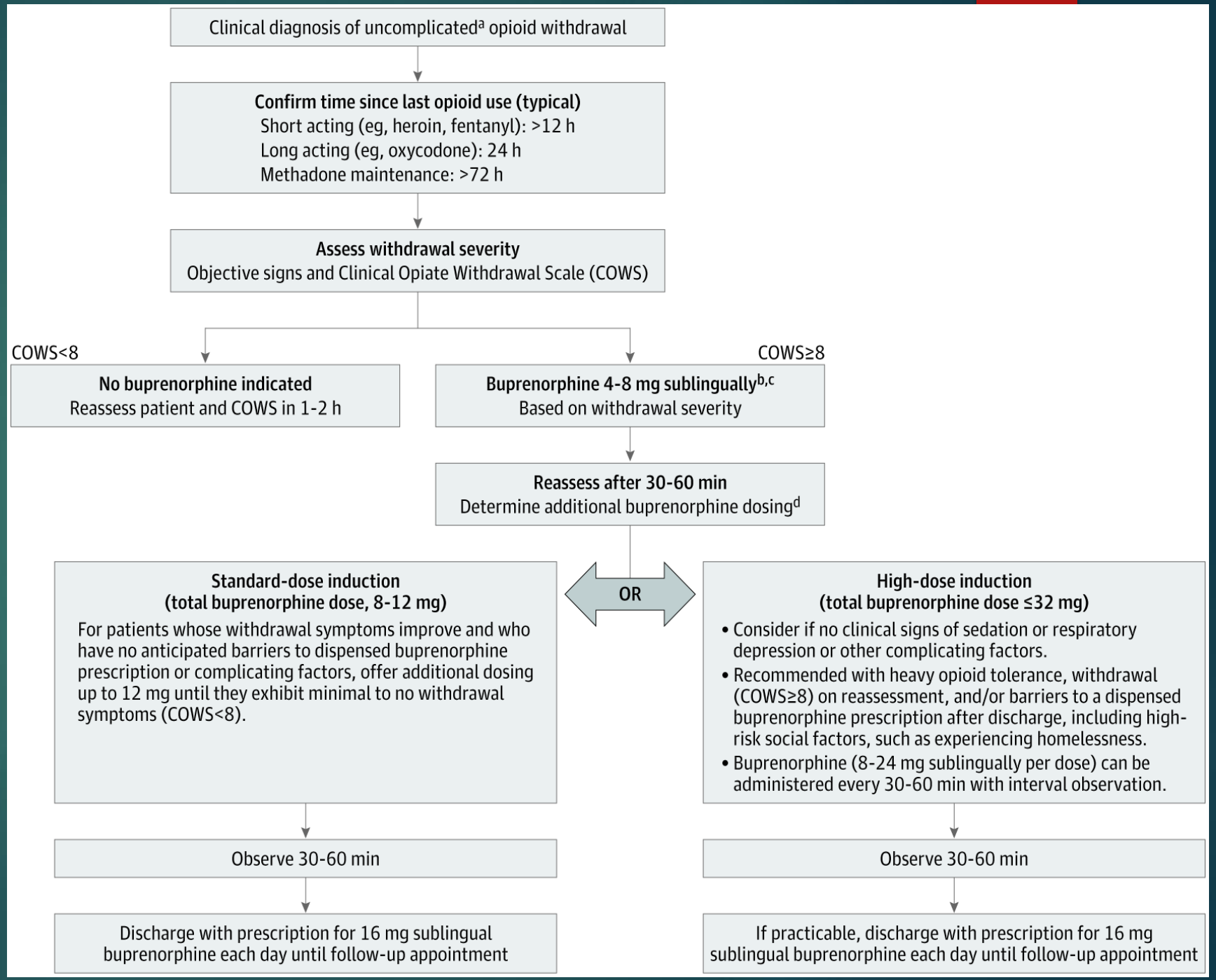
High-Dose Induction

Emergency Department Buprenorphine Quick Start Guide

- A resource provided by California Bridge. Access the full guide: https://bridgetotreatment.org/resource/buprenorphine-bup-hospital-quick-start/



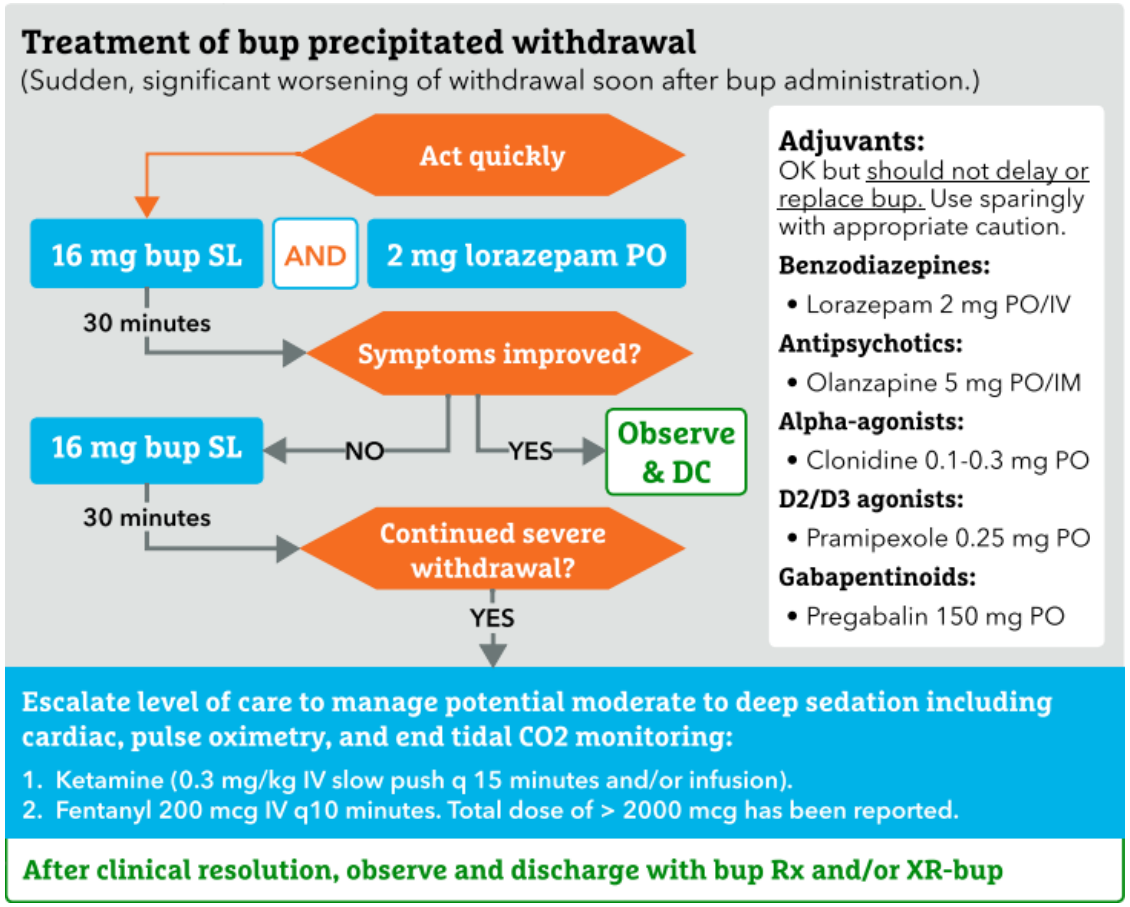
High-Dose vs. Standard Induction



SOURCE: DOI: 10.1001/jamanetworkopen.2021.17128

Precipitated Withdrawal Management

High-dose Induction



SOURCE: CA Bridge

Brixadi® (Buprenorphine)

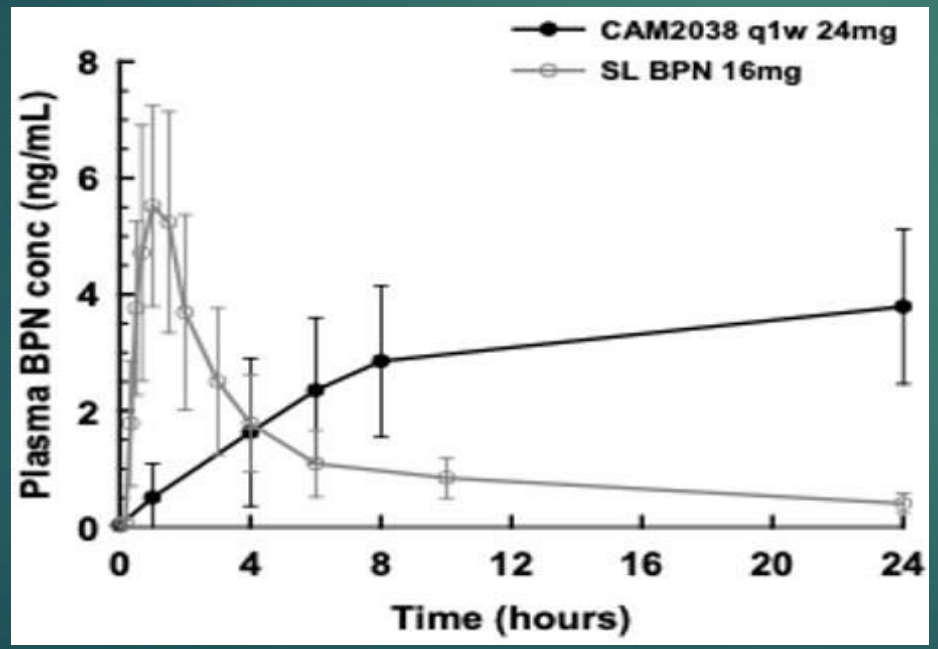
- Approved for the **treatment of moderate to severe OUD** for either:
  - Patients who have initiated treatment with a single dose of a transmucosal buprenorphine product
  - Patients who are already being treated with buprenorphine
- There is no naloxone contained in this medication.

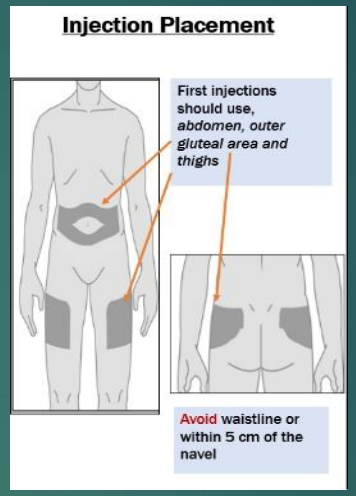
SOURCE: Brixadi® Package Insert

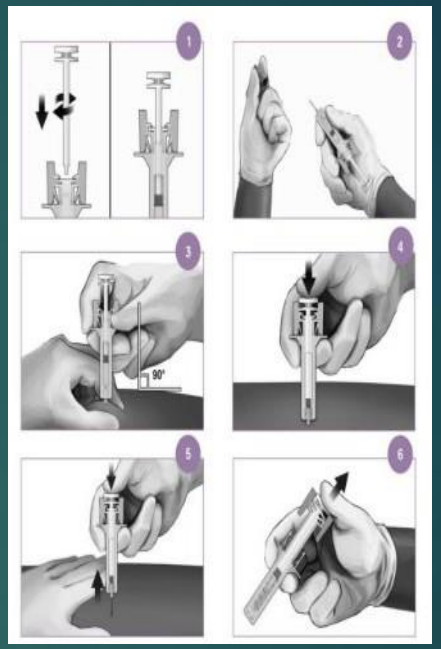
ED INNOVATION

ED-INitiated BupreNOrphine VAlidaTION Network Trial

Pharmacokinetics of XR- & SL- Buprenorphine







Upon injection **CAM2038** forms into a viscous liquid crystalline gel, producing a sustained, non-fluctuating levels of buprenorphine in the blood **avoiding the peaks and troughs of daily dosing**

3UG1DA015831

PCSS Providers Clinical Support System

JAMA Network | Open

Research Letter | Substance Use and Addiction

Incidence of Precipitated Withdrawal During a Multisite Emergency Department–Initiated Buprenorphine Clinical Trial in the Era of Fentanyl

Gail D'Onofrio, MD, MS; Kathryn F. Hawk, MD, MHS; Jeanmarie Perrone, MD; Sharon L. Walsh, PhD; Michelle R. Lofwall, MD; David A. Fiellin, MD; Andrew Herring, MD

Introduction

Buprenorphine treatment is associated with decreased mortality and morbidity,[1] yet the treatment gap remains wide. Emergency departments (EDs) offer an effective, low-barrier setting in which to initiate buprenorphine.[2] Retrospective case series[3] have raised concerns about increased incidence of precipitated withdrawal (PW) when buprenorphine is initiated in persons using fentanyl, a high-potency μ-opioid agonist with high affinity and slow dissociation from the μ receptor. With long-term use, its high lipophilicity leads to bioaccumulation and prolonged metabolite excretion. As confidence in standard buprenorphine inductions has eroded, alternative strategies, such as low-dose buprenorphine, have emerged, often prompting continued use of illicit opioids. Thus, there is a need for high-quality evidence from prospective studies using uniform surveillance and operational definitions of PW. We report the incidence of PW as part of an ongoing randomized clinical trial[4] comparing traditional sublingual buprenorphine with CAM2038, a 7-day extended-release injectable form of buprenorphine, conducted in sites with high prevalence of fentanyl.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Buprenorphine induction in the ED remains safe and effective, even with fentanyl present

Results: Patient Characteristics

Total Enrolled to Date (n=1200)

- Male 67%
- Age (Mean) 38
- Race: 56% White, 30% Black, Multiracial 2% American Indian
- Urine Drug Screen
  - 84% Multiple Drugs
  - 76% Fentanyl
  - 33% Cocaine
  - 46% Marijuana
  - 45% Opiates

Patients with PW (n=9)

- Male 67%
- Age (Mean) 38
- Race: 2 (22%) White, 4 (60%) Black, 2 (22%) Multiracial 1 (10%) American Indian
- Urine Drug Screen
  - 68% Multiple Drugs
  - 100% Fentanyl
  - 67% Cocaine
  - 44% Marijuana
  - 22% Opiates

High-Dose Buprenorphine (>12mg)Induction for Treatment of Opioid Use Disorder

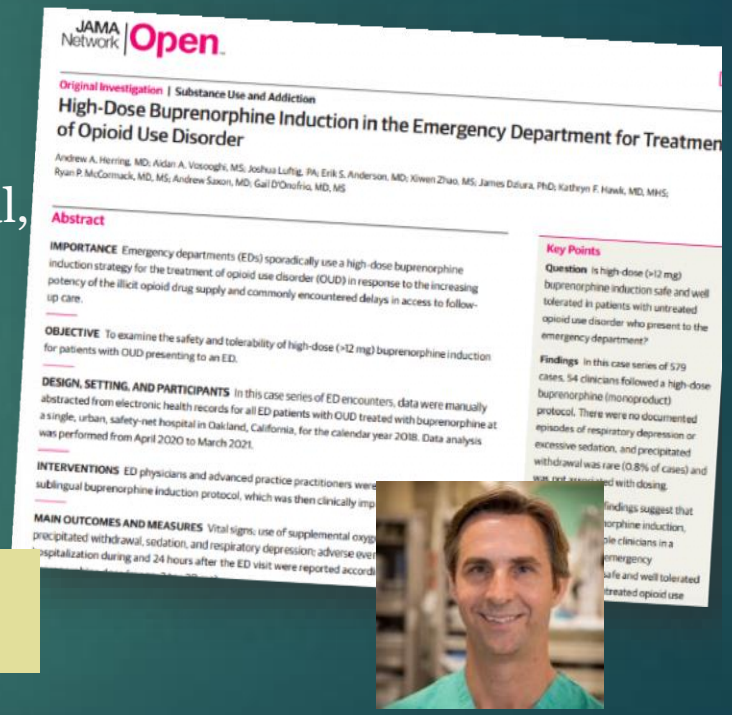
CTN 0069-A1

Accelerated induction achieves therapeutic buprenorphine levels in < 3-4 hours vs typically 2-3 days… extended-release increases safety during the crucial gap between ED & follow-up care… particularly in context of COVID limitations

Retrospective case series –

2018 calendar year at a single site – Highland Hospital, Oakland CA.

- 391 unique patients (579 encounters)
- No cases of respiratory depression or sedation
- 5 cases of precipitated withdrawal not dose related


JAMA Network Open

Original Investigation | Substance Use and Addiction

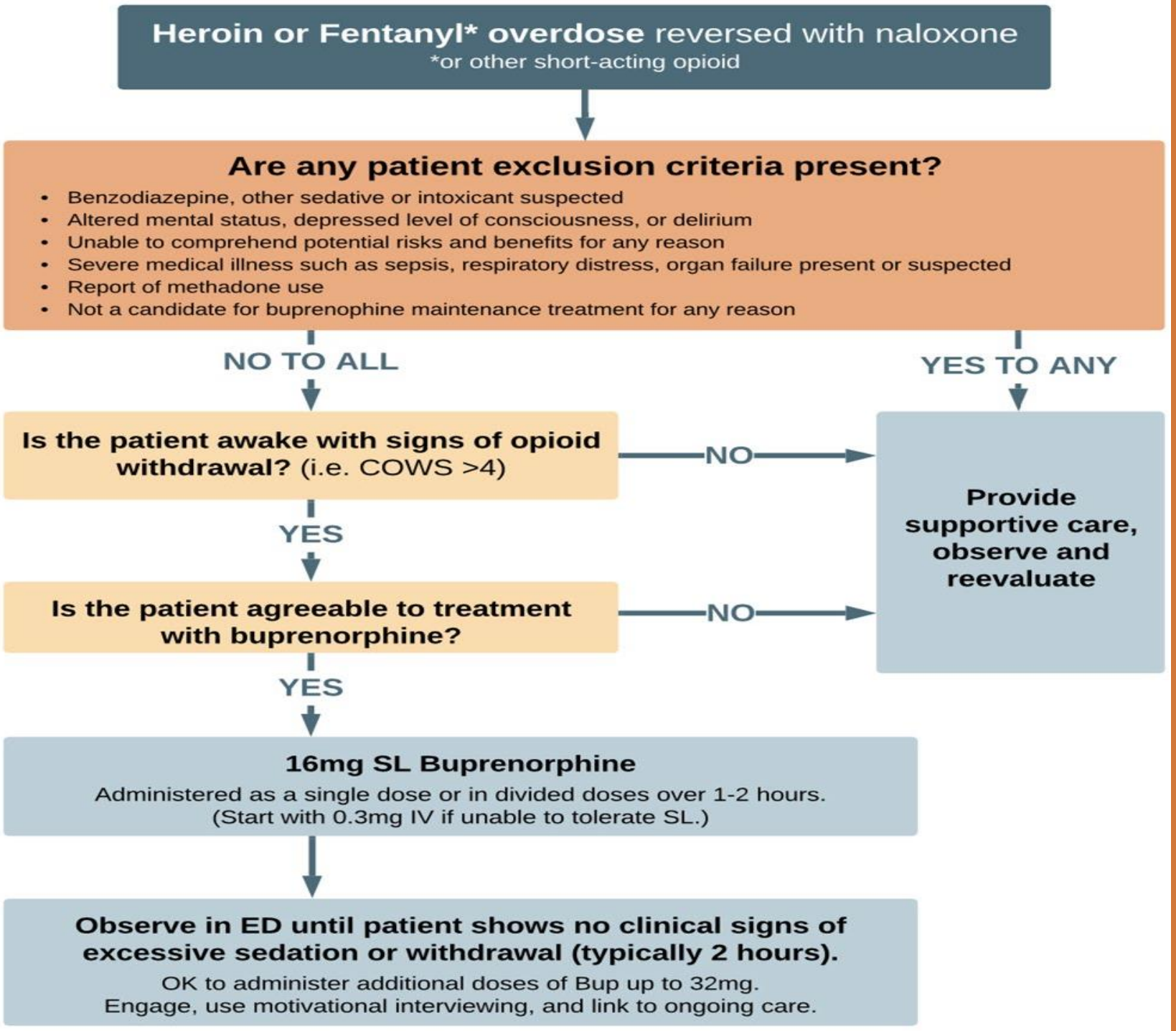
High-Dose Buprenorphine Induction in the Emergency Department for Treatmen of Opioid Use Disorder

Abstract

Key Points

High dose buprenorphine induction was safe and well tolerated in untreated OUD patients

Herring, JAMA Netw Open. 2021 July

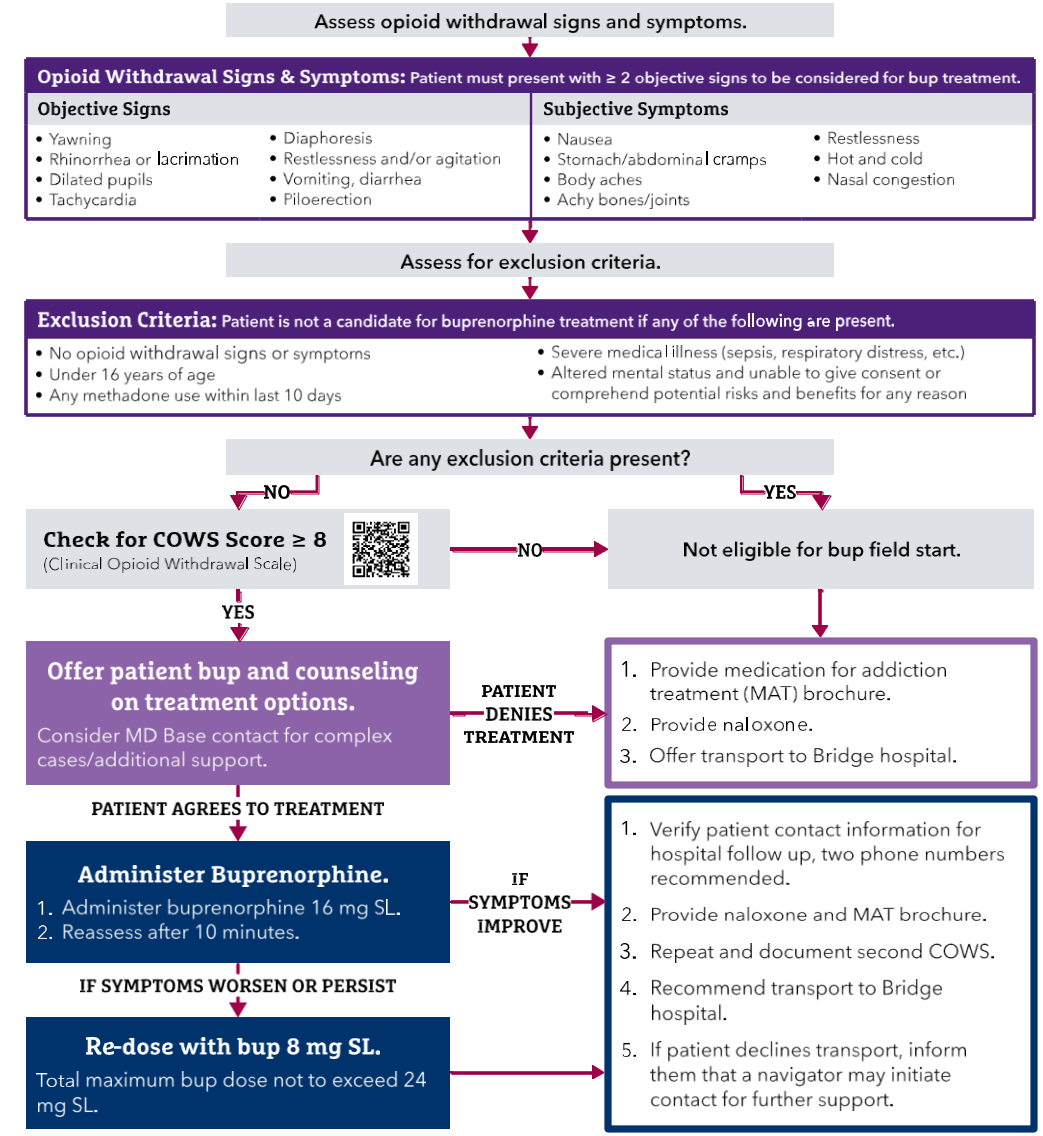


Bup Induction after Overdose

Emergency Medical Services: Buprenorphine (Bup) Field Start Protocol

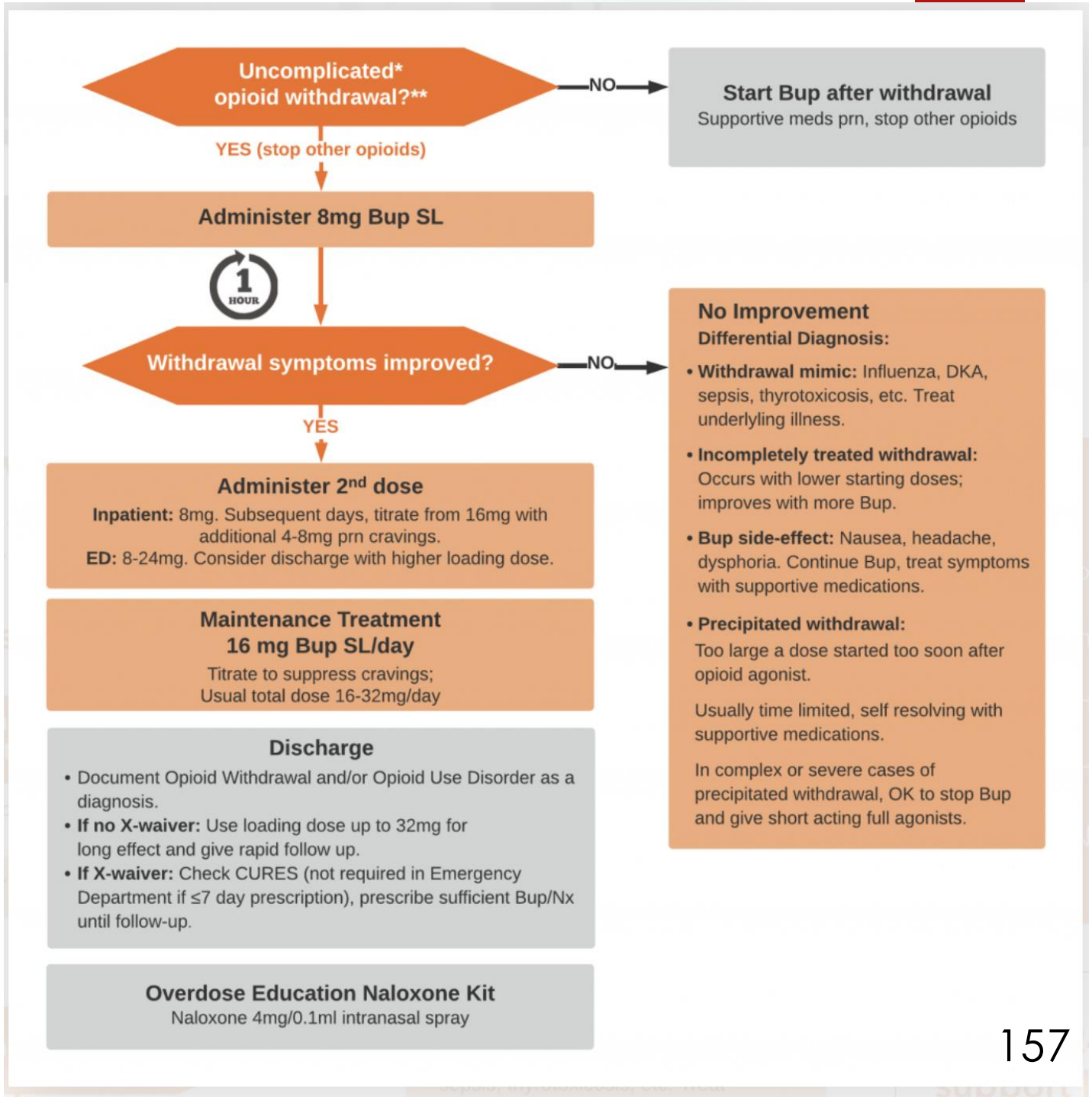
BRIDGE
Treatment. Equity. Connection.

This treatment protocol can be used for patients experiencing opioid withdrawal symptoms and for patients recently administered naloxone.



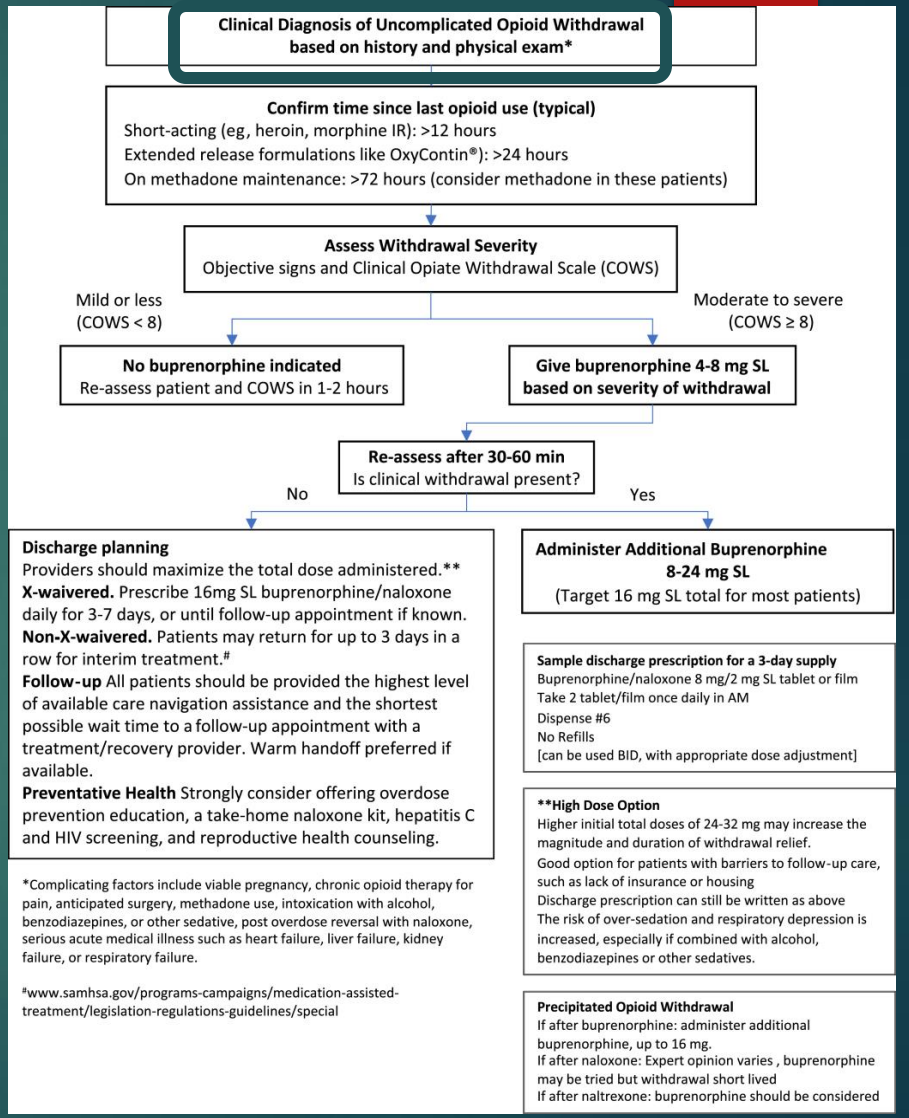
This project was supported by the CARESTAR Foundation.

April 2024


Uncomplicated* opioid withdrawal?**
NO
Start Bup after withdrawal
Supportive meds prn, stop other opioids
YES (stop other opioids)
Administer 8mg Bup SL
1 HOUR
Withdrawal symptoms improved?
NO
YES
No Improvement
Differential Diagnosis:
• Withdrawal mimic: Influenza, DKA, sepsis, thyrotoxicosis, etc. Treat underlyling illness.
• Incompletely treated withdrawal: Occurs with lower starting doses; improves with more Bup.
• Bup side-effect: Nausea, headache, dysphoria. Continue Bup, treat symptoms with supportive medications.
• Precipitated withdrawal:
Too large a dose started too soon after opioid agonist.
Usually time limited, self resolving with supportive medications.
In complex or severe cases of precipitated withdrawal, OK to stop Bup and give short acting full agonists.
Administer 2nd dose
Inpatient: 8mg. Subsequent days, titrate from 16mg with additional 4-8mg prn cravings.
ED: 8-24mg. Consider discharge with higher loading dose.
Maintenance Treatment
16 mg Bup SL/day
Titrate to suppress cravings;
Usual total dose 16-32mg/day
Discharge
• Document Opioid Withdrawal and/or Opioid Use Disorder as a diagnosis.
• If no X-waiver: Use loading dose up to 32mg for long effect and give rapid follow up.
• If X-waiver: Check CURES (not required in Emergency Department if ≤7 day prescription), prescribe sufficient Bup/Nx until follow-up.
Overdose Education Naloxone Kit
Naloxone 4mg/0.1ml intranasal spray

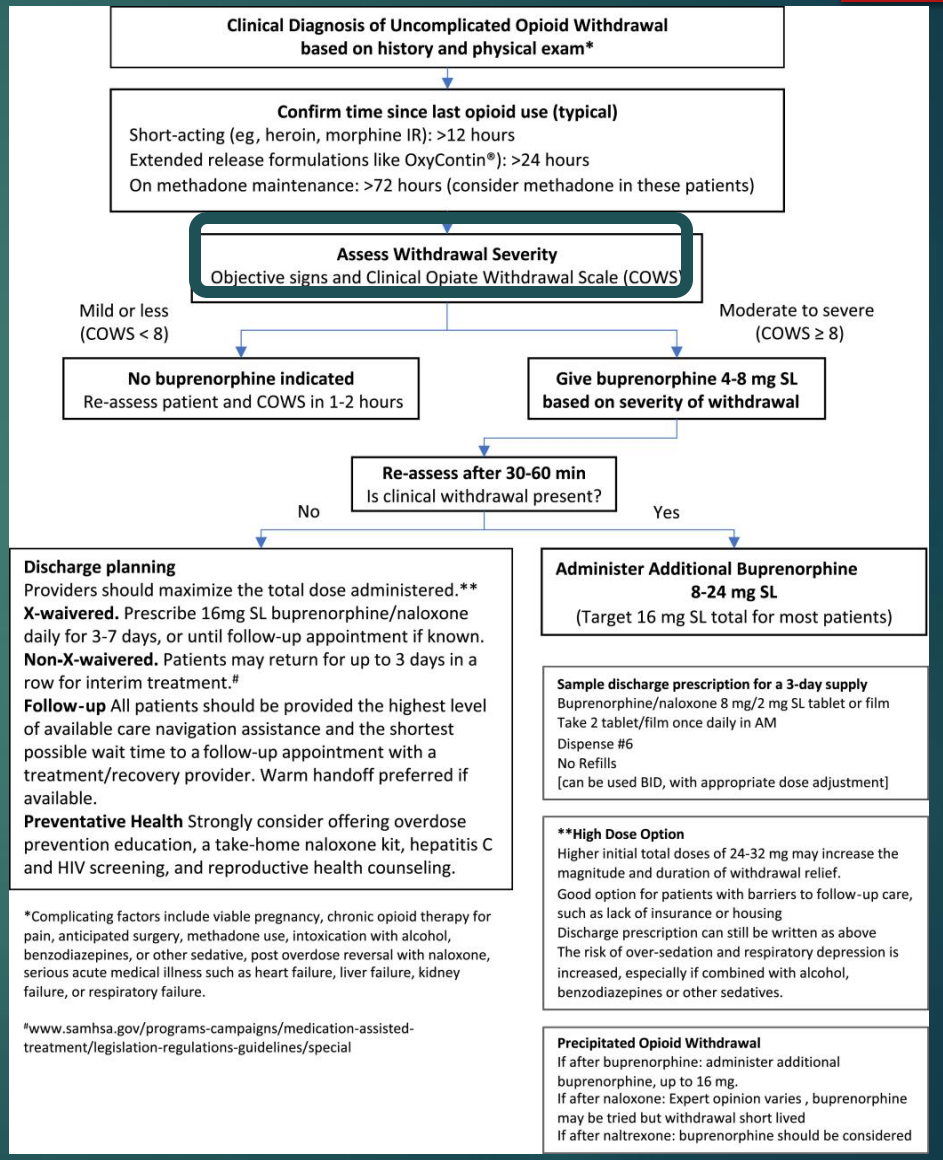
Buprenorphine in the ED

- Step 1
  - Diagnose Opioid Use Disorder
    - Screening
    - PDMP



Buprenorphine in the ED

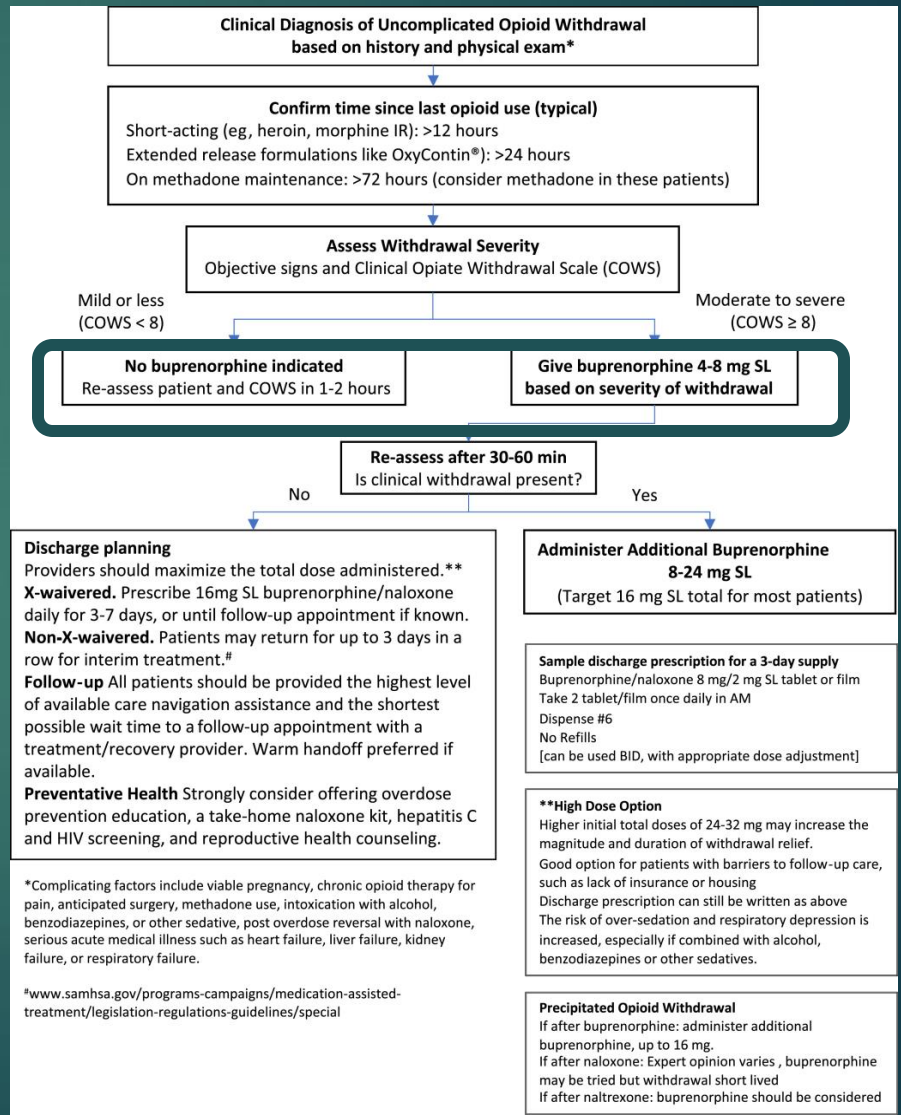
- Step 2
  - Calculate their Clinical Opioid Withdrawal Scale (COWS)
    - Pulse | Sweating | Restlessness | Pupil Size | Arthralgias | Rhinorrhea | GI upset | Tremor | Yawning | Anxiety or irritability | Gooseflesh
      - ≥8 mild-moderate withdrawal, typically ok for induction
      - ≥12 moderate suggested by some pathways



Herring, 2019
D'Onofrio, 2015
McLane, 2020

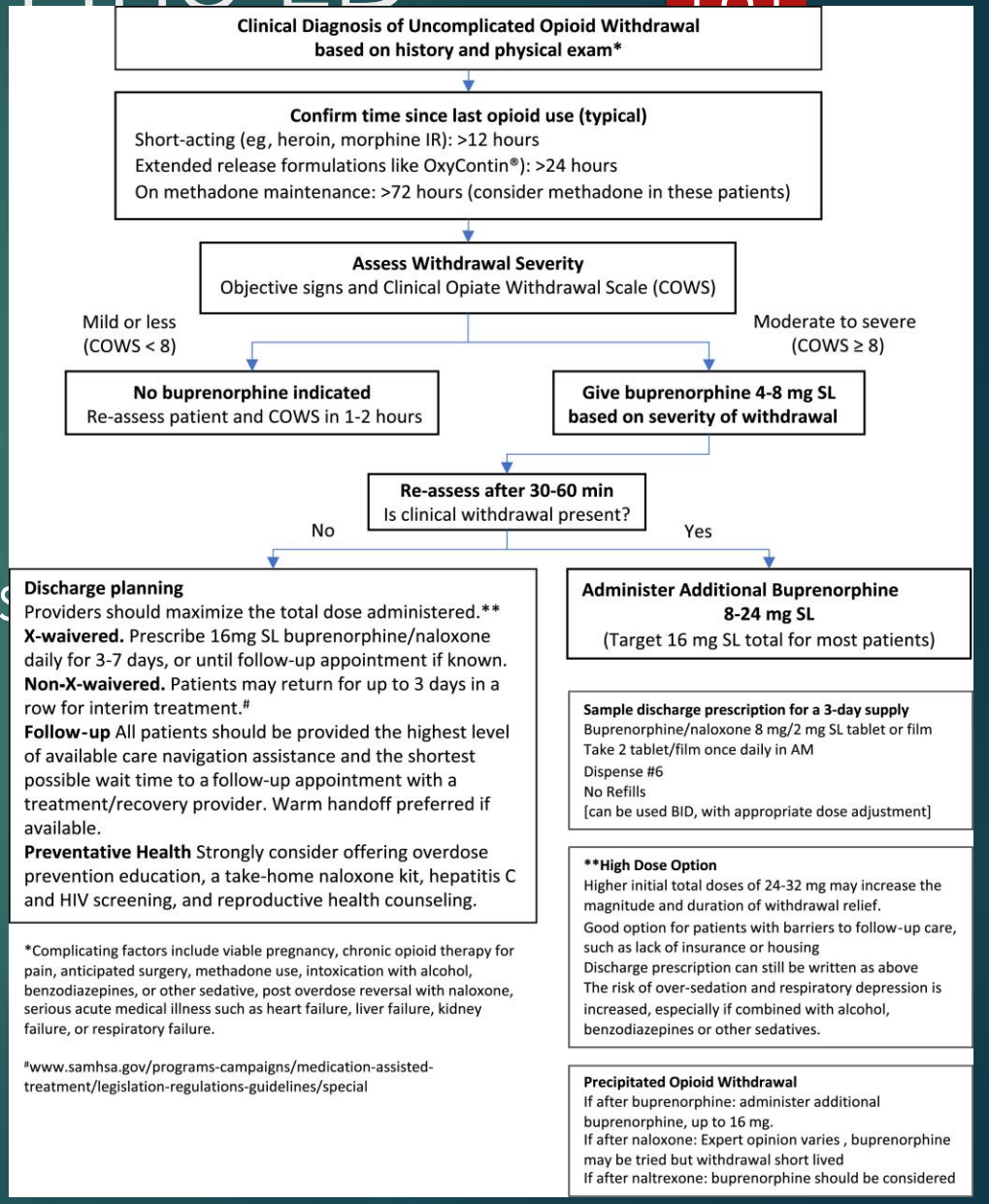
Buprenorphine in the ED

- Step 3
  - Choose your induction site
    - ED vs Home



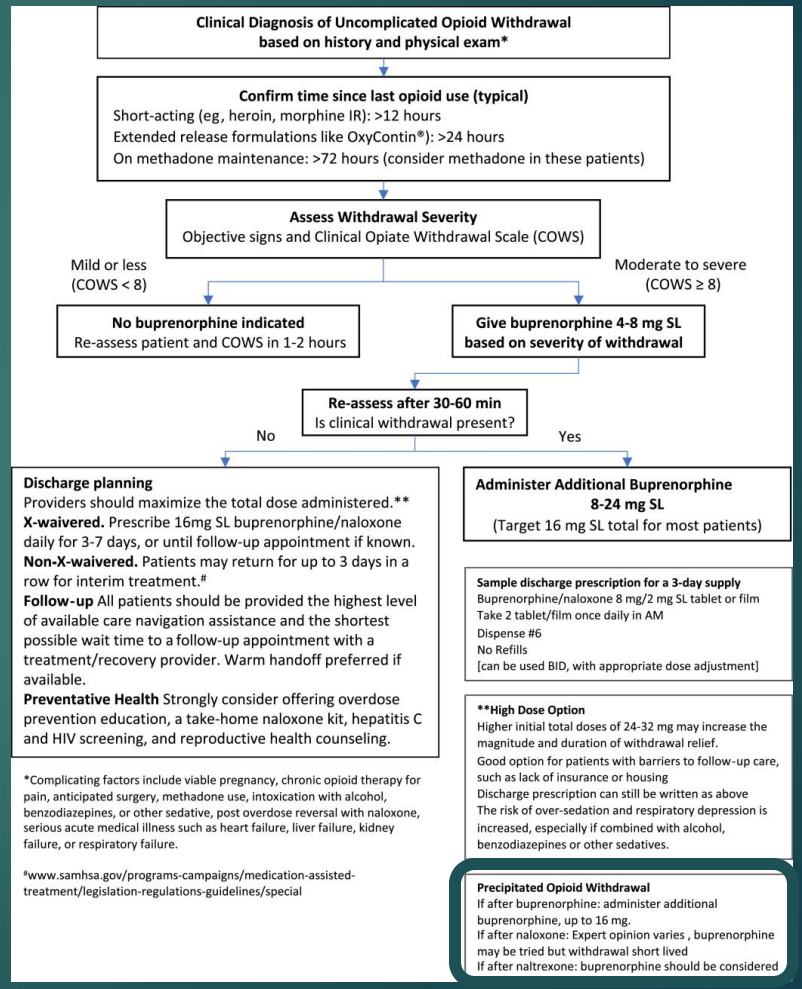
Buprenorphine in the ED

- Step 4
  - Reassess in 20-40 minutes
    - If improving, provide second bup dos
      total of 16mg
      - 12mg if given 4mg initially
      - 8mg if given 8mg initially



Buprenorphine in the ED

- Step 4b
  - If patient gets worse
    - May have precipitated withdrawal
      - If mild, patient may want to receive adjuncts and try home induction later
      - However, optimal treatment for precipitated withdrawal is…more bup
        - Titrate to effect
          - 8mg q 15 min
          - Nervous around 32mg

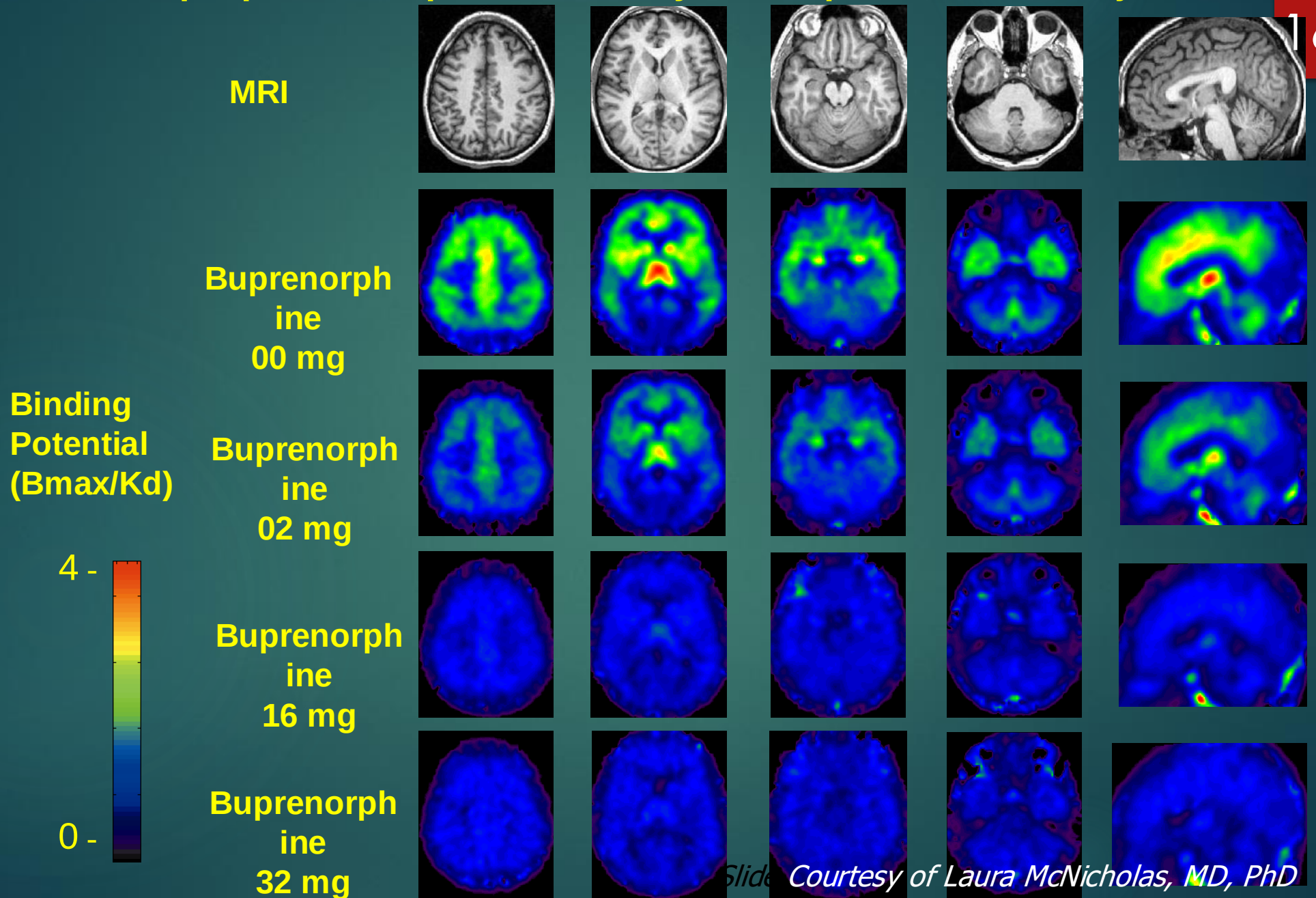


Quattlebaum, 2021

Buprenorphine in the ED

- Step 5
  - Discharge preparation
    - Place consult to recovery coach/social work/peer support
      - May want to do this earlier if patient is hesitant or requests
    - Provide take-home naloxone kit
    - Provide specific follow up instructions (TIME AND PLACE)
    - Prescribe 8-2mg buprenorphine-naloxone every 12 hours for as long as needed to get into local clinic

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



Slide Courtesy of Laura McNicholas, MD, PhD

Buprenorphine in the ED

- Naloxone precipitated withdrawal
  - Except in severe circumstances, aim to avoid this
    - 0.1 mg naloxone WHILE BVM (Bag Valve Mask) (NP airway and elevated head of bed)
    - Goal RR 10-12—respiration not conversation!
  - If in NPW(Naloxone Precipitated Withdrawal) , can treat and transition with buprenorphine
    - May start with 16mg
    - Add 8mg every 15min to effect
    - When stable, can DC as you would normal induction
    - Not for methadone overdoses

Treatment Course

- Discontinuation of MOUD is associated with relapse, overdose and mortality
  - Only 23% of those tapering off buprenorphine produce opioid negative urine during first follow up
- General conclusion: Discontinuation not recommended
  - But moving from SL to sub-q formulations possible
  - Eventually could try a taper to IM-naltrexone
    - Prevents death with return to use
- Remember and Remind Patients this is a Chronic Disease

Zweben, 2020

Special Populations

- Polysubstance/Sedative Use
  - Up to 30% of patients on opioid maintenance treatment also receive benzodiazepine prescriptions
  - Taking benzos and Z drugs with buprenorphine elevates risk of nonfatal overdose, but not as much as the group not on buprenorphine (OR 1.64 vs 2.23)
  - Advise patients to limit sedative use
    - Bup still safer than illicit opioids
    - Bup should not be withheld

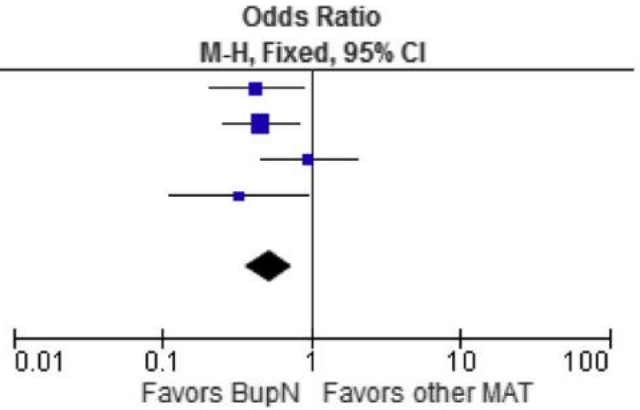
Xu, 2021

Pregnancy

FIGURE 2
Forest plot for need for neonatal abstinence treatment

Study or Subgroup	buprenorphine/naloxone Events	Total	any MAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gawronski 2014	37	58	74	92	25.7%	0.43 [0.20, 0.90]
Mullins 2019	30	85	59	108	41.7%	0.45 [0.25, 0.81]
Nechanska 2018 Norway	17	33	103	196	17.9%	0.96 [0.46, 2.01]
Wiegand 2015	8	31	16	31	14.7%	0.33 [0.11, 0.95]
Total (95% CI)		**207**		**427**	**100.0%**	**0.52 [0.36, 0.75]**
Total events	92		252			

Heterogeneity: Chi² = 3.85, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 3.55 (P = 0.0004)



CI, confidence interval; *MAT*, medication-assisted treatment; *M-H*, Mantel-Haenszel.

Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.

- When compared with methadone, mothers treated with buprenorphine have neonates needing fewer days of opioid agonist treatment

Link, 2020
Jones, 2010

Pregnancy

- No difference in outcomes for mother-baby pairs receiving buprenorphine vs buprenorphine-naloxone
- No need for pregnancy test result prior to dosing
- Does help with follow up and referral to correct clinic

Link, 2020
Jones, 2010

Management of Acute Pain

- Patients with OUD, especially those in recovery and on opioid agonist therapy or naltrexone, deserve pain relief on par with patients without OUD
  - Novel approaches required due to pharmacology of their OAT
    - Buprenorphine: high affinity partial agonism
    - Methadone: full agonism
    - Naltrexone: high affinity full antagonism

Management of Acute Pain

- Buprenorphine is a high affinity partial agonist
  - "Out-competes" most other opioids
- When possible, use non-opioid analgesia
  - Nerve blocks
  - NSAIDS
  - Acetaminophen
  - Immobilization
  - Ketamine

Management of Acute Pain

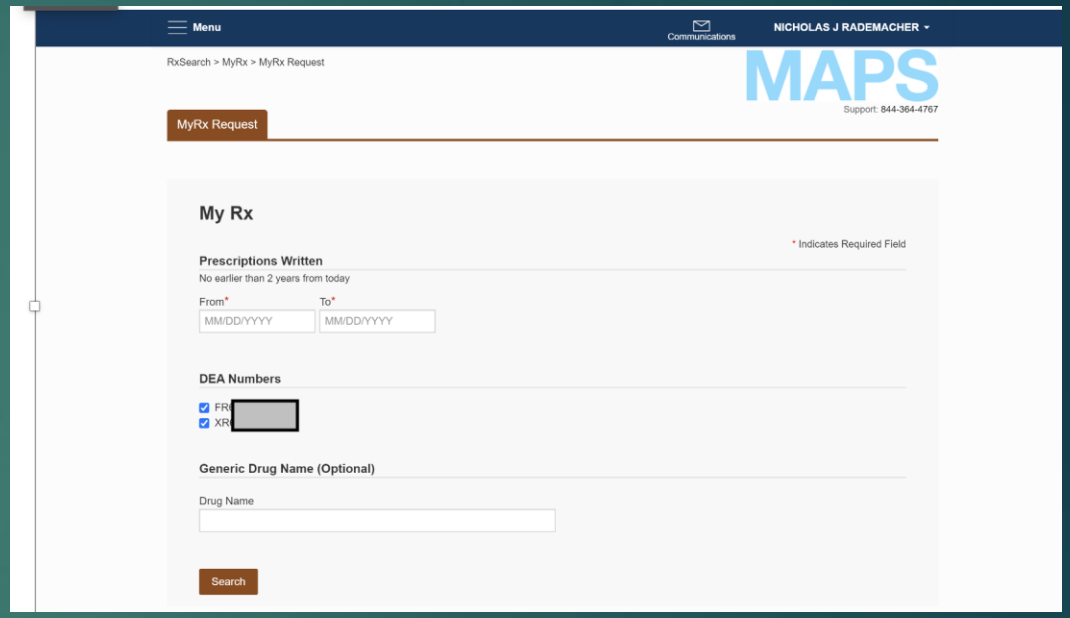
- If opioids are required
  - Select those also with high affinity
    - Fentanyl
    - Hydromorphone
  - Expect to use large doses
    - Not due to tolerance, although this contributes
    - Only a small amount of the opioid provided will outcompete buprenorphine
    - Titrate to effect

Management of Acute Pain

- The experience they have in the ED may influence their decision to remain engaged in opioid agonist treatment

Utilizing the PDMP

- DEA may request a current list of patients you have buprenorphine prescriptions to
  - In MT this is easily done in the PDMP
- PDMP can also be used to help with diagnosis of OUD
  - Also shows bup Rx, past or present
  - Will not show methadone used for OUD



Billing G 2213 code

- As of 2021 ED providers get paid just over $60 (1.9 RVUs) to "initiate medication for the treatment of opioid use disorder in the ED setting"
  - Assessment
  - Refer to ongoing care
  - Arranging access to supportive services

ASAM, 2021

Review

- OUD is a highly morbid chronic medical condition
- OUD is treatable with highly effective medications
- Survival neurocircuitry has been hijacked (would you lie, cheat, and steal to stay alive?)
- The ED is one of several very important entry points for those with OUD to receive MOUD
- Reimbursement now tied with effective interventions

What are the obstacles? Discussion, questions