A Review of FDA-Approved Medications for Opioid Use Disorder (MOUD)

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Project Echo First Responders

Brief Biography

- Corporate Medical Director Wexford health Sources
- Former Chief Medical Officer for the Indiana Department of Correction
- Former Medical Advisory Board for the American Correctional Association
- Former Corporate Medical Director Advanced Correctional healthcare
- Boarded in Family Medicine and Addiction Medicine as well as Healthcare Quality Management (ABQAURP)
- Beacon Addiction Medicine Consulting CMO

Disclosures

- None

Objectives

- Define substance use disorder
- Brief review around the myths of SUD
- Review epidemiological data on the Opioid epidemic and Overdose deaths
- Understand how the diagnosis of SUD/OUD is established
- Basic review of the data on effectiveness of MOUD
- Review the 3 FDA approved drugs for Opioid Use Disorder
- Emphasize that medically supervised withdrawal alone does NOT work
- Review our approach to SUD treatment including opioids using harm reduction
- Discuss the harm reduction model to treat Opioid use disorder as well as other substance use disorders
- Emphasize that OUD is a chronic illness and needs to be treated as such

According to the American Society of Addiction Medicine's definition:

• *Addiction is a **primary, chronic and relapsing*** brain disease *characterized by an individual pathologically pursuing reward and/or relief by substance use and other **behaviors.***

ACLU

The lifesaving impact of providing MAT:

“The risk of unnatural death — including overdose, suicide, and other preventable causes — was 87 percent lower for incarcerated people on MAT compared to incarcerated people with OUD not on MAT”.

“MOUD reduces the risk of death from an overdose by 75 percent in the weeks following release”

Opioid Use Disorder (OUD)

- Chronic, relapsing disease
- Changes the structure and functioning of the brain
    - Alters the risk/reward system

MOUD is the Standard of care for treating OUD

Harms: overdose, death, social isolation, behaviors controlled by opioid/drug seeking, criminal legal and child welfare system involvement

Why are People Denied Access to MOUD?

- Stigma surrounding OUD
- Misconceptions about MOUDs
- Stereotypes about people who use MOUD
- Belief in only “abstinence-based” treatments
- Failure to recognize MOUD as the standard of care
- Logistical obstacles in prescribing/administering MOUD
- Limited MOUD capacity in the community

Common Substance Abuse MYTHS

- **Myth #1: Drug addiction is a choice.** Drug *use* can be a choice, and prolonged use changes your body and brain chemistry. When that happens, the user no longer appears to have a choice—this is when use and misuse become addiction. ***The reward system sees the drug as life sustaining and essential as it sees oxygen, food, shelter etc., "holds the cortex hostage!" > 50% of substance use disorder is genetic***
- **Myth #2: If you have a stable job and family life, you're not addicted.** You may still have a job or career, a loving spouse and kids, and still have a drug or alcohol problem. Just ask any physician in recovery—many of them practiced for years without anyone recognizing their drug addiction. Holding down a job doesn't mean you're not addicted—it could mean that you have a tolerant spouse or boss, or you are in a career that puts up with excessive drug or alcohol use. ***Like any chronic illness, there are different severity levels***
- **Myth #3: Addicts are bad people. People with SUD** aren't "bad" people trying to get "good," they're sick people trying to get well. They don't belong to a particular race or exist only in certain parts of the country. They are lawyers, farmers, soldiers, mothers and grandfathers who struggle with drug dependence on a daily basis. They are proof that addiction doesn't discriminate—but, thankfully, neither does recovery ***Once the disorder develops, control is lost and people often exhibit survival actions sometimes completely out of character for them.***
- **Myth #4: More than anything else, drug addiction is a character flaw:** ***SUD is a brain disease***. Every type of drug of abuse has its own individual mechanism for changing how the brain functions. But regardless of which drug a person is addicted to the effects are similar: they range from changes in the molecules and cells that make up the brain, to mood changes, to changes in memory processes and in such motor skills as walking and talking. ***The drug becomes the single most powerful motivator in a drug abuser's existence***. This comes about because drug use has changed the individual's brain and its functioning in critical ways.
- **Myth #5: Detox is all you need. You aren't addicted after you finish detox. They can just knock you out so you can detox while you sleep.** Detox is difficult and it's just the beginning. Detox is the first step towards recovery, but addiction is a chronic illness—like diabetes, asthma or hypertension, it needs to be managed throughout the lifespan. There is no "cure." ***DETOX (medically supervised withdrawal) ALONE DOES NOT WORK***
- **Myth #6: You need to be religious in order to get sober. Recovery** doesn't require you to believe in God or subscribe to any organized religion Treatment that meets the client's needs is most effective. ***A higher power can be anything including the 12- step group***
- **Myth #7: You need to hit "rock bottom."** There is no such thing a universal "rock bottom." Each person has different limits. This is a dangerous idea that keeps people using or avoiding help because "I haven't him rock bottom" or allows family members to wait to intervene till someone "hits rock bottom." Help can be obtained at any time and early intervention is best. ***You can get off the elevator on any floor!***

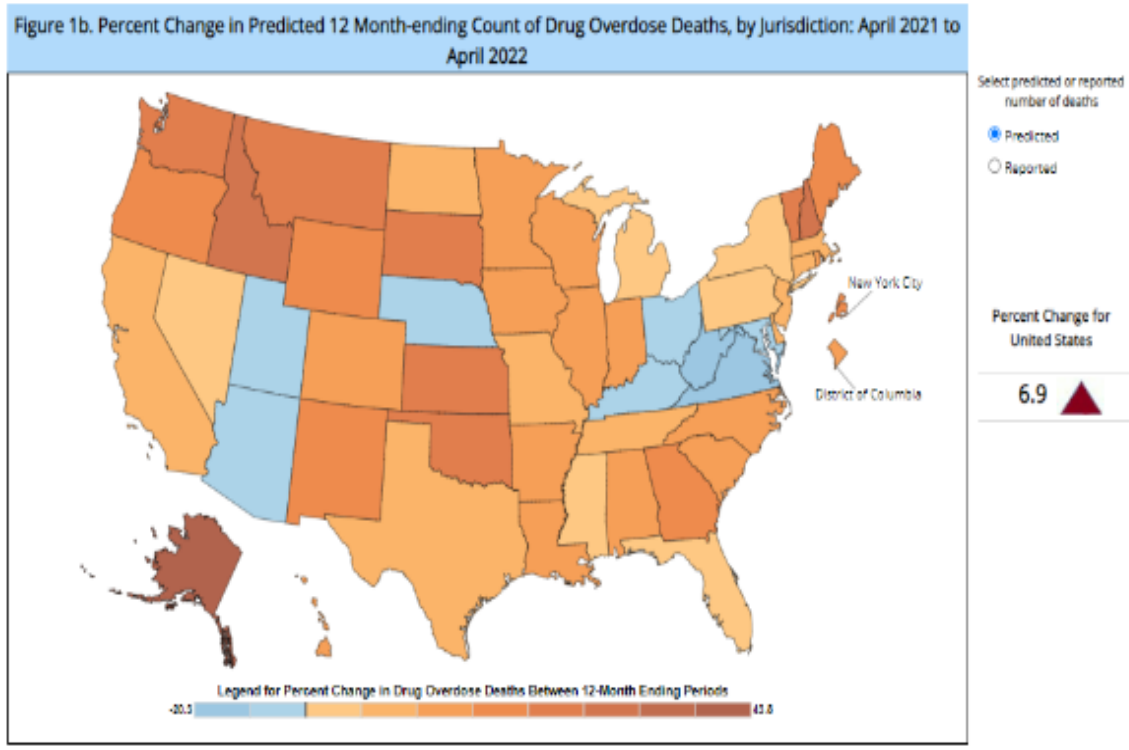
Deni Carise, Ph.D. Chief Clinical Officer, Phoenix House See more at: http://www.phoenixhouse.org/news-and-views/our-perspectives/ten-popular-myths-drugs-addiction-recovery/#sthash.Ntly2mhz.dpuf and NIDA "Exploring Myths about Drug Abuse" by Alan I. Leshner, Ph.D

12 month-ending provisional number of drug overdose deaths

20% increase

Provisional Drug Overdose Deaths from 12 months ending in April 2022

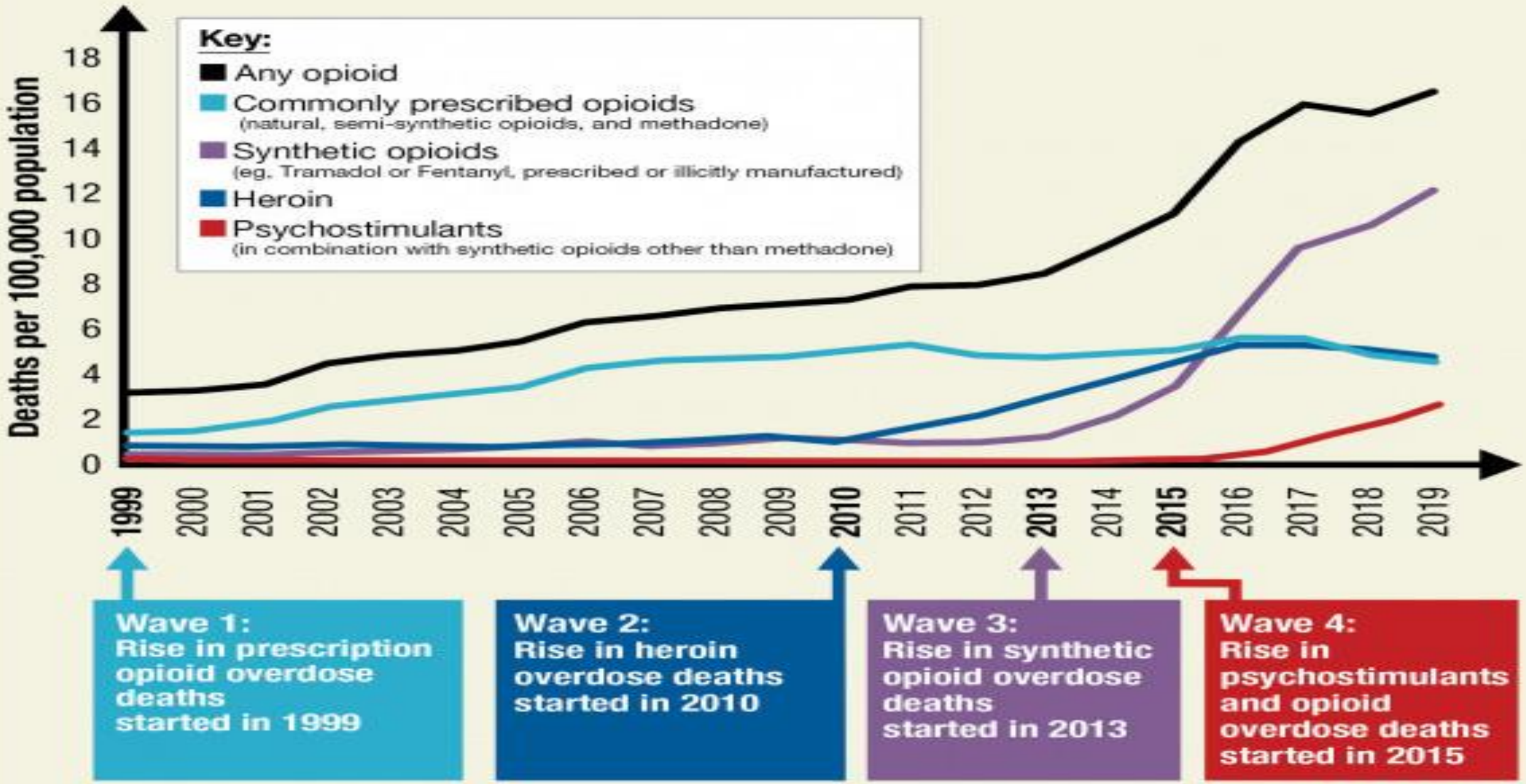
September 14, 2022 by NCHS



New provisional data show that the number of drug overdose deaths occurring in the United States increased by almost 7% from the 12 months ending in April 2021 to the 12 months ending in April 2022, from 101,167 to 108,174.

FIGURE 1

Timeline of Opioid-related Overdose Deaths

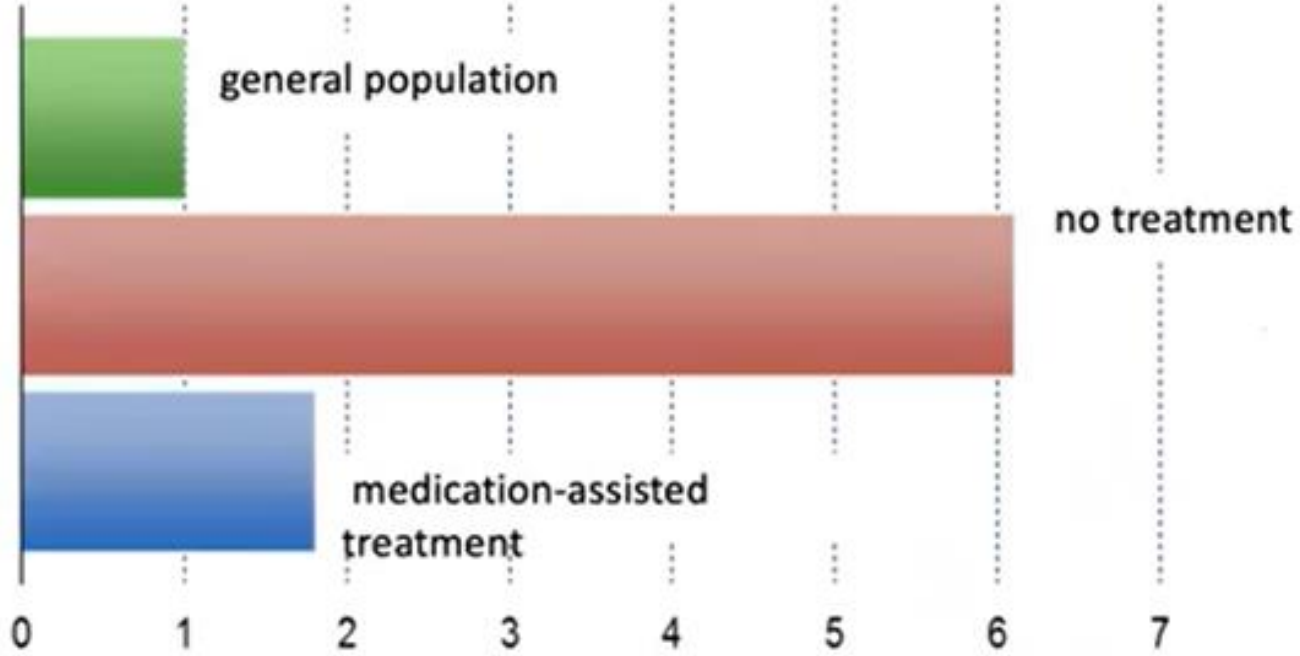


Source: National Vital Statistics Systems Mortality File and the National Institute on Drug Abuse.


Real Oxycodone
Fake Oxycodone
M
30

Benefits of Medications for OUD: Decreased Mortality

Death Rates:

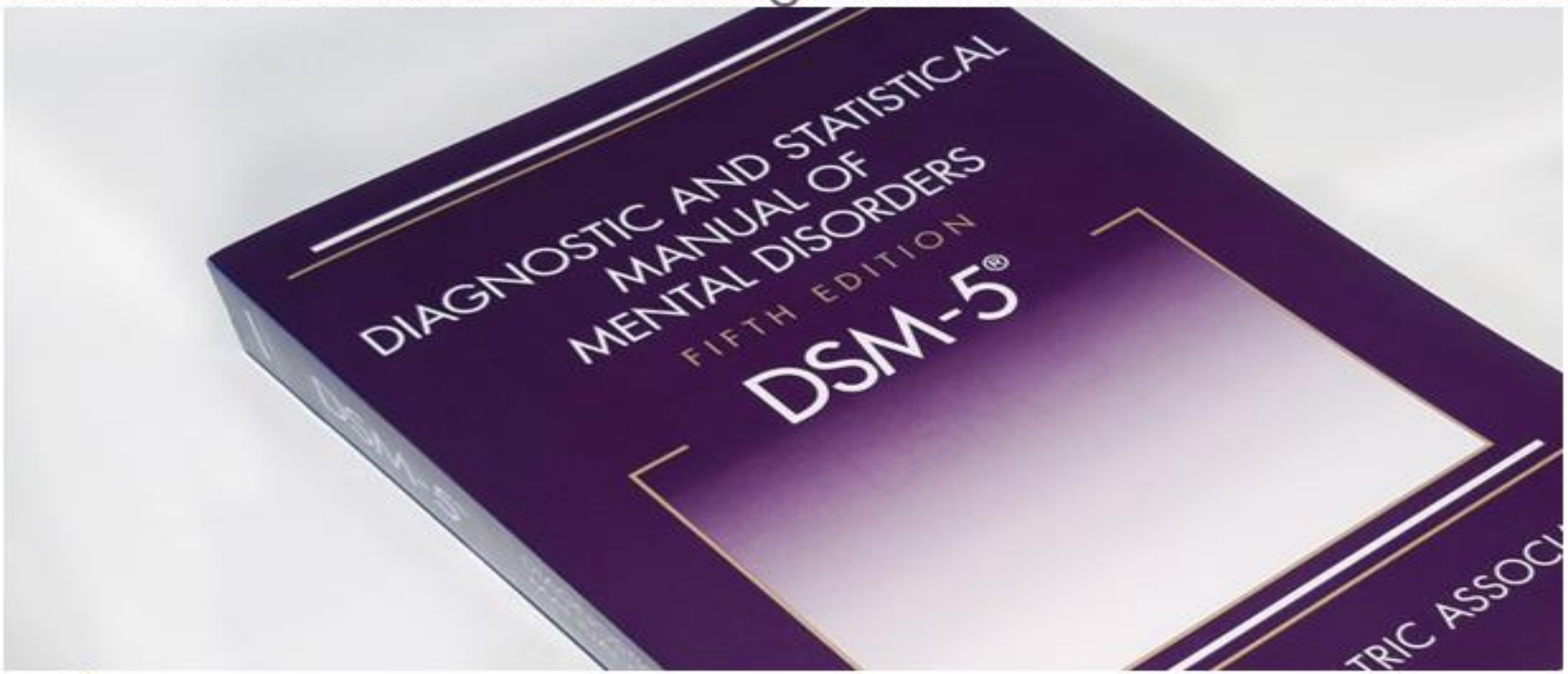


Fentanyl 100 x more potent than morphine and 50 x more potent than heroin

Diagnosis of OUD

- Universal screening for SUD/OUD
- Can be diagnosed by MH or primary care
- Primary care Addictionologists and Psychiatric Addictionologists
- DSM 5 criteria

Diagnosing SUD



DSM-5 Opioid Use Disorder

- Taking the opioid in larger amounts and for longer than intended
- Wanting to cut down or quit but not being able to do it
- Spending a lot of time obtaining the opioid
- Craving or a strong desire to use opioids
- Repeatedly unable to carry out major obligations at work, school, or home due to opioid
- Continued use despite persistent or recurring social or interpersonal problems caused or made worse by opioid use
- Stopping or reducing important social, occupational, or recreational activities due to opioid
- Recurrent use of opioids in physically hazardous situations
- Consistent use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using opioids
- *Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (Does not apply for diminished effect when used appropriately under medical supervision)
- *Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (Does not apply when used appropriately under medical supervision)

Mild = 2-3 criteria; Moderate = 4-5 criteria; Severe = 6+ criteria

Risk factors for OUD

- **Chronic opioid use with chronic pain syndrome**
- **Untreated Psychiatric disorders including ADHD, anxiety and depression**
- **History of Benzodiazepine and/or Alcohol use disorder**
- **Early use especially adolescents. Group most vulnerable 25-34**
- **Exposure to sexual, physical or emotional abuse**
- **Growing up in a household that normalized drug use**
- **Incarceration**
- **Genetic predisposition especially when combined with psychosocial factors >50% genetic**
- **Occupational exposure**

Some complications of opioid use disorder

- Overdose
- Increased mortality (6-20x higher than general population)
- Infections
  - Cellulitis/abscess
  - Osteomyelitis
  - Septic emboli
  - Endophthalmitis
  - Endocarditis
  - HIV
  - HCV
    - 32% become positive for HCV within 1 year of IDU
    - 53% positive within 5 years

Treatment of Substance Use Disorder including Opioid Use Disorder

- Treat as the chronic illness that it is
- Understand that like any chronic illness , relapse can be part of the disease
- We continue to treat patients that are obese and sedentary with insulin to treat their diabetes
- We treat patients with lung cancer who still smoke or have smoked for years
- We treat heart disease despite failure to adhere to lifestyle modification
- We continue to treat poorly compliant patients

Why should SUD be any different?

Approach to SUD treatment

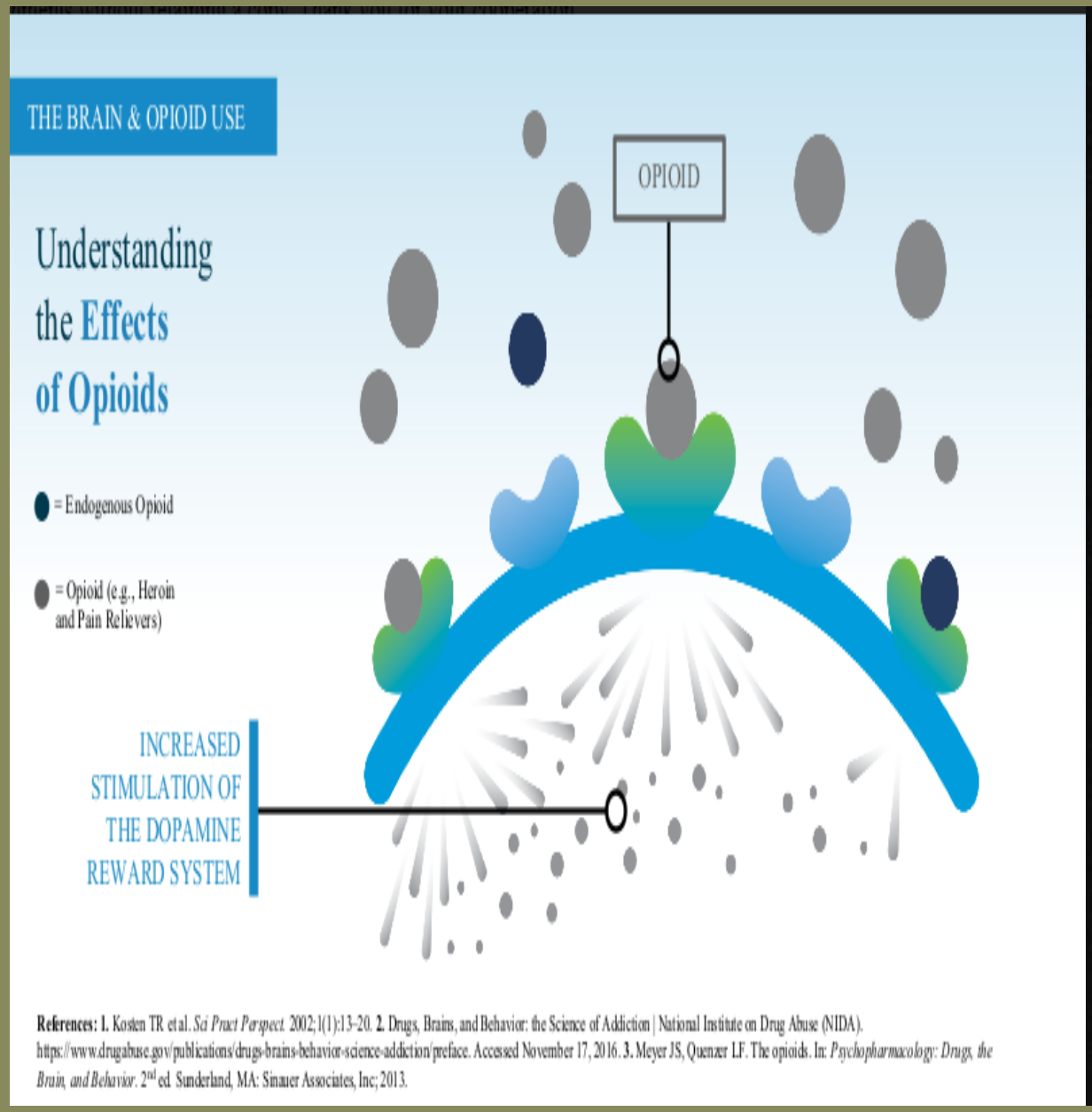
Works to elicit **ANY POSITIVE CHANGE** based on individual patient need, circumstance, and readiness to change

Meet the patient where they are at, and though motivational interviewing and brief interventions encourage them along the recovery spectrum

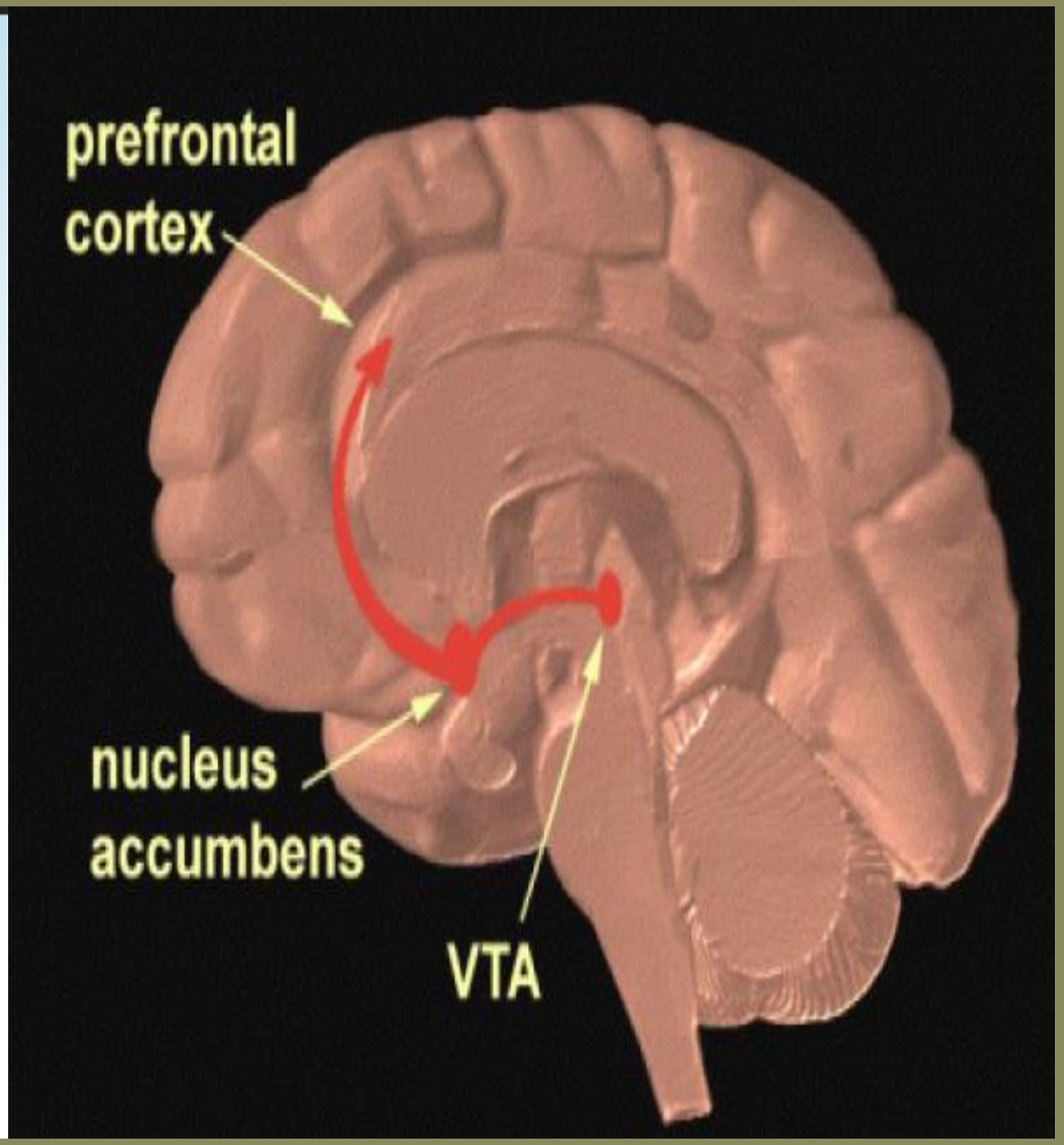
Harm reduction…. Paradigm change in addiction treatment Treat Substance Use Disorder as a chronic illness

Applies evidence-based interventions to reduce negative consequences:

- **Medication Assisted Treatment**
- Naloxone rescue kits
- Syringe exchange programs
- PrEP (Pre-exposure prophylaxis for HIV)
- PEP (Post-exposure prophylaxis for HIV)
- Fentanyl test strips
- HEP C testing /HIV testing & education on prevention/treatment



References: 1. Kosten TR et al. *Sci Pract Perspect.* 2002;1(1):13-20. **2.** Drugs, Brains, and Behavior: the Science of Addiction | National Institute on Drug Abuse (NIDA). https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/preface. Accessed November 17, 2016. **3.** Meyer JS, Quenzer LF. The opioids. In: *Psychopharmacology: Drugs, the Brain, and Behavior.* 2nd ed. Sunderland, MA: Sinauer Associates, Inc; 2013.



MAT/MOUD

Evidence-based:

- Decrease illicit opioid use
- Reduce transmission of Hepatitis C and HIV
- Decrease criminal behavior
- Reduce sexual risk behaviors (e.g., trading sex for money/drugs)
- Improve social functioning
- Retain people in treatment
- Decrease overdose and death (even if they use on MOUD)
- Increase employment
- Decrease in domestic violence

Medications for Opioid Use Disorder (MOUD)

Methadone	Buprenorphine ± Naloxone	Naltrexone
Full mu opioid receptor agonist	Partial mu opioid receptor agonist	Mu opioid receptor antagonist (blocker)
	 	 
Oral (often solution)	Sublingual (tab, film), IV, IM, subcutaneous injection, transdermal patch	Intramuscular injection (extended release) or Oral

MAT components: focus on OUD

1. Medication management with **FDA approved agents**
    - Opioid full agonists → **methadone**
    - Opioid partial agonists → **buprenorphine**
    - Opioid antagonists → **naltrexone**

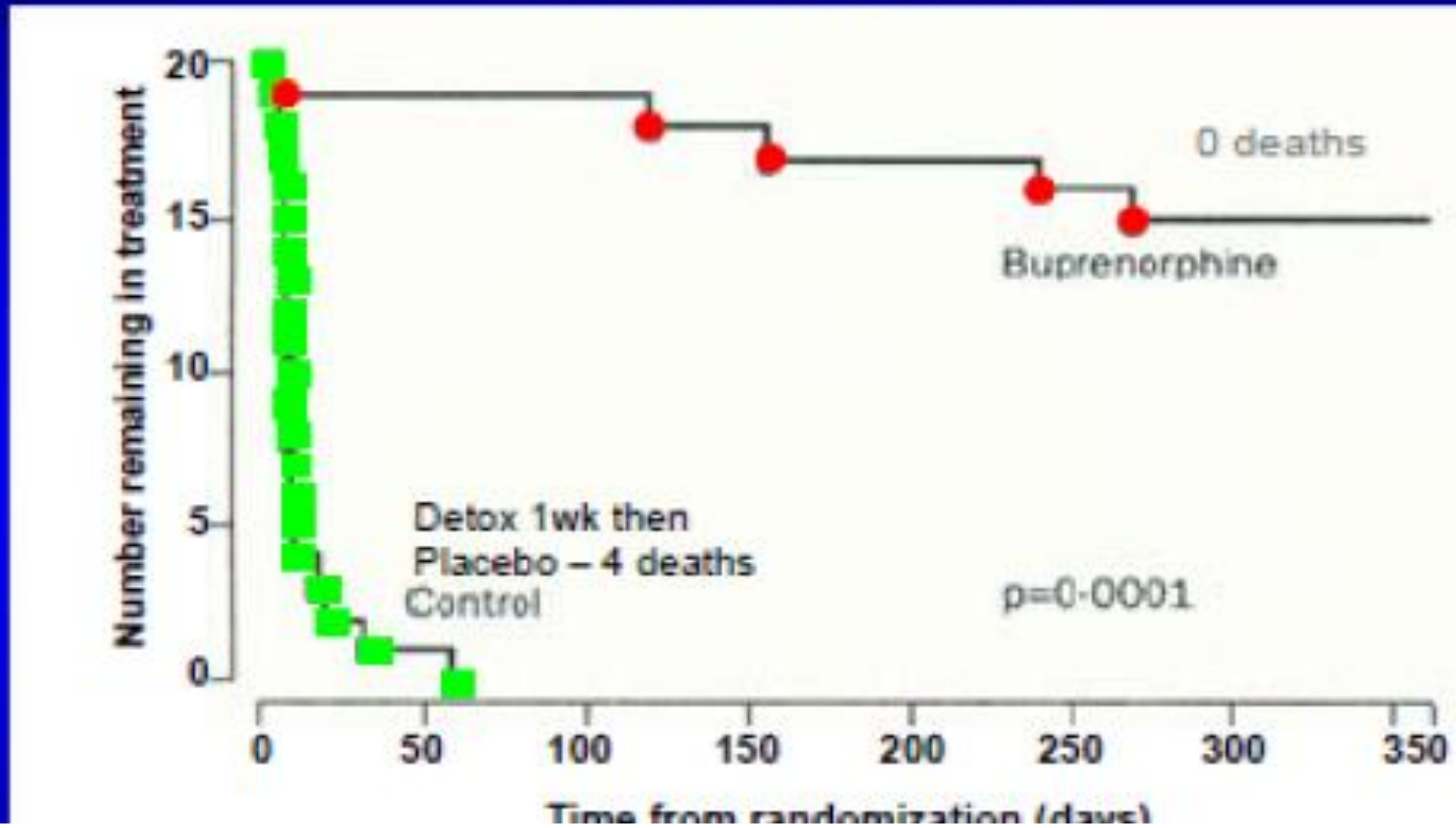
2. Evidence-based **psychosocial treatments**
    - Motivational Interviewing
    - Manualized therapies (e.g. Seeking Safety)
    - Harm reduction psychotherapy

3. Treat **co-occurring psychiatric disorders** and address comorbid medical illness whenever possible

MOUD in Pregnancy

Both ACOG (American College of Obstetricians and Gynecologists) as well as ASAM (American Society of Addiction Medicine) strongly recommend that a pregnant patient stay on the OAT they are on. (Methadone or Buprenorphine) If the patient is in agreement and has an OUD, they should be induced onto an agonist or partial agonist.

Buprenorphine Maintenance vs Detox. RCT of cumulative retention in treatment



Methadone (schedule 2 controlled substance)

- **Synthetic, slow acting full mu-opioid receptor agonist**
  - **Half-life 24-36 hours**
  - **Blocks euphoric effects of self administered opioids**
  - **Eliminates or strongly reduces cravings for opioids**
- **Used for treatment of substance use disorder since 1960's. Officially approved for MAT 1972**
- **Only available through licensed Opioid Treatment Programs (OTP) approved and accredited by SAMHSA/HHS**
- **Dispensed @ OTP daily initially**
  - **Patients can progress to receiving "take-home doses"**
  - **Average 80 to 120mg/day**

Cardiac concerns related to QT interval especially with overdose

Naltrexone/ANTAGONIST

- Oral agent Revia . ASAM does NOT recommend it routine use for MAT except in select groups where you can ensure compliance.(50mg once daily)
- Monthly Injection of 380mg IM (Vivitrol) Currently approx. $1500 dollars a month.
- ***Must be completely withdrawn from Opioids*** . No use for 7-14 days depending on the half life of the drug used
- Can induce withdrawal if using opioids
- Blocks opioid receptors (high affinity)
- If stop using Naltrexone, would have lost opioid tolerance putting them at risk for Overdose
- Will have to use alternatives to opioids for pain management
- If patient is successful at overcoming the receptor blockade , they are at high risk for overdose
- Not a controlled substance
- No abuse potential
- ***Works for opioids and alcohol***

Major Features of Buprenorphine

ISMA
INDIANA STATE MEDICAL ASSOCIATION

Treats withdrawal, craving, & overdose

Safe & effective for treating OUD

Partial agonist:

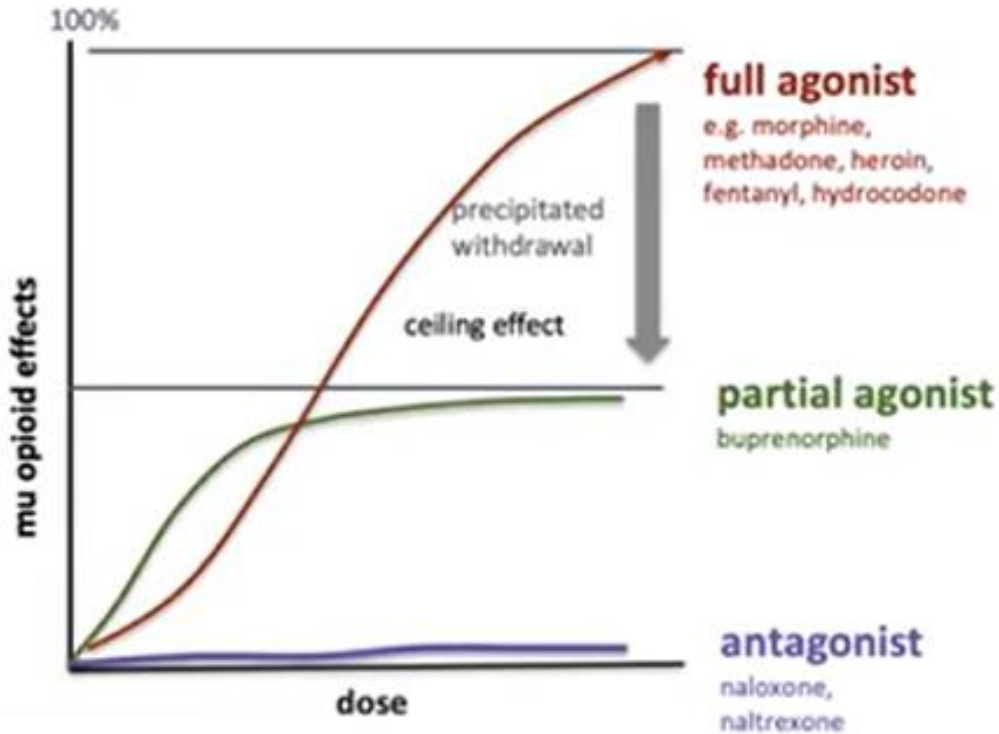
- Ceiling effect:
  - respiratory depression
  - sedation
- No ceiling effect:
  - analgesia

High affinity:

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

Long acting: Half-life ~ 24-36 Hours

Any clinician can order bup to be *administered* in the ED,



Buprenorphine is VERY safe

"R.A.I.S.E. the Standard"

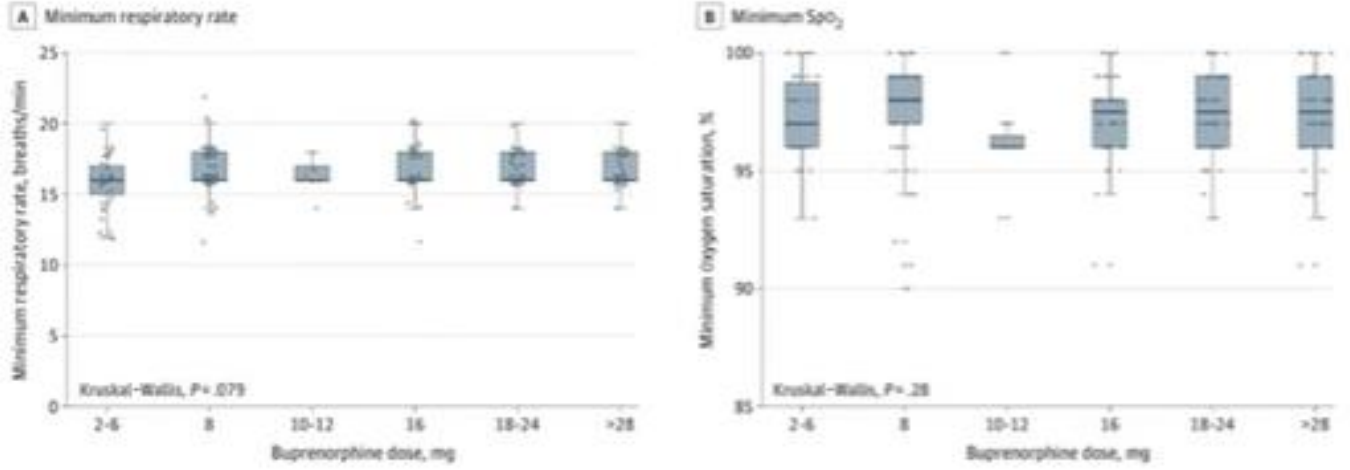
JAMA Network Open

Original Investigation | Substance Use and Addiction

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

Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D'Onofrio, MD, MS

Figure 2. Minimum Respiratory Rate and Oxygen Saturation (SpO_2) Following Initial Dose by Buprenorphine Dose



Boxes correspond to 25th and 75th percentiles, with lines in boxes denoting medians. Dots denote outliers. Error bars denote 95% CIs. Kruskal-Wallis test compares distributions of respiratory rate and oxygen saturation across buprenorphine dose categories.

Dose categories
Mg (*N*)

2-6 (55)
8 (136)
10-12 (22)
16 (106)
20-24 (122)
≥ 28 (138)

Ceiling On Respiratory Depression

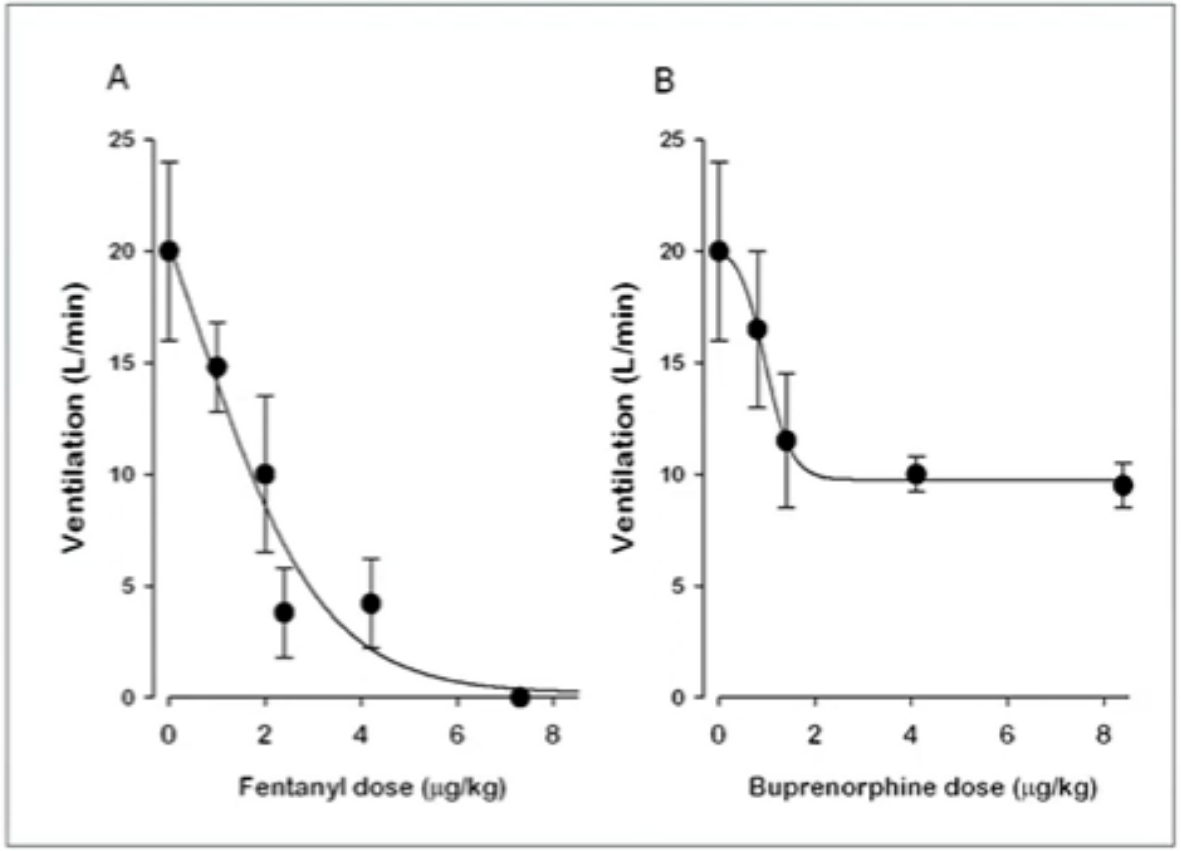
Andrew King

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]



Removal of DATA Waiver (X-Waiver) Requirement

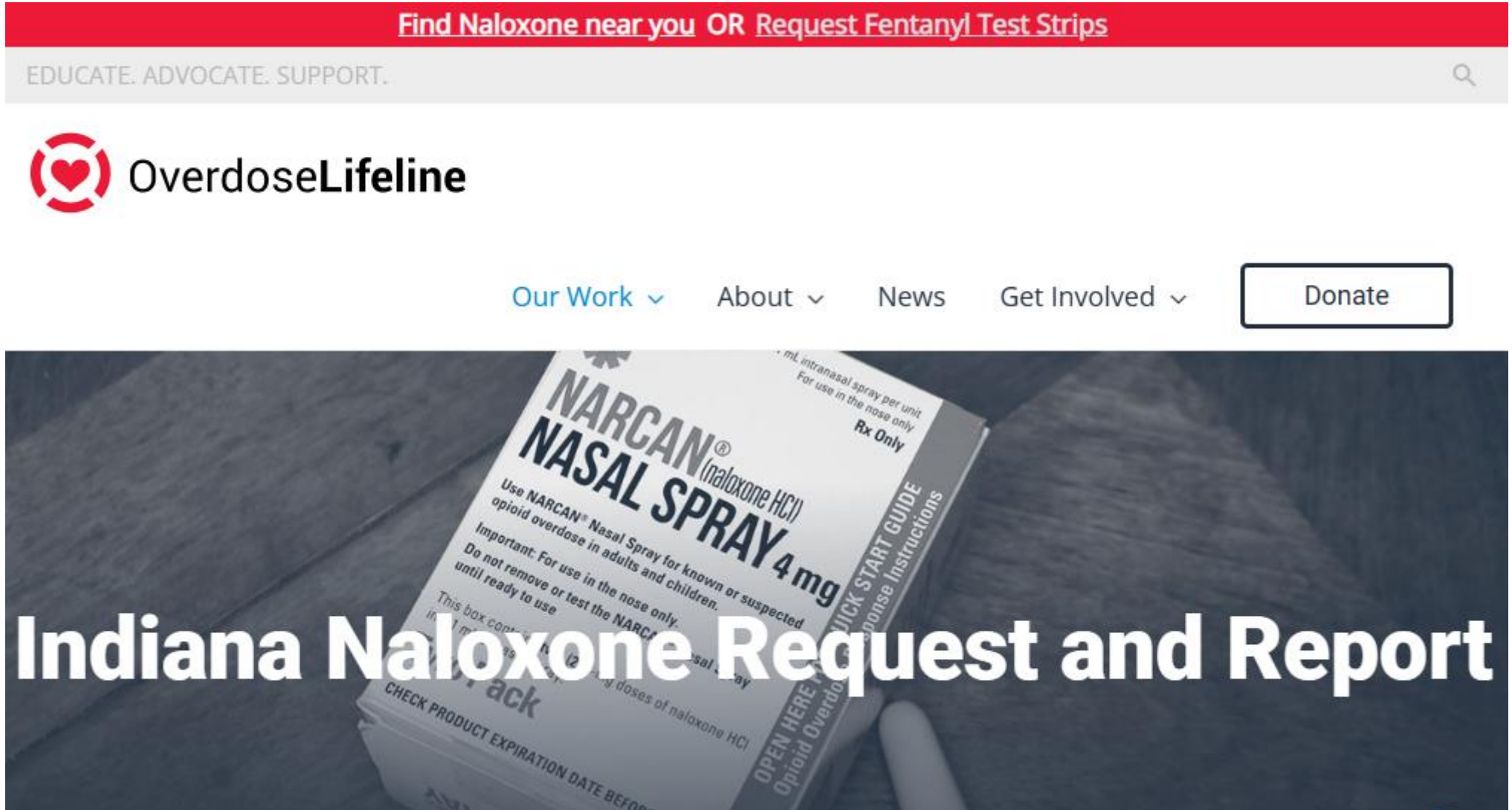
Section 1262 of the Consolidated Appropriations Act, 2023 (also known as Omnibus bill), removes the federal requirement for practitioners to submit a Notice of Intent (have a waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder (OUD). With this provision, and effective immediately, SAMHSA will no longer be accepting NOIs (waiver applications).

- ***All practitioners who have a current DEA registration that includes Schedule III authority, may now prescribe buprenorphine for Opioid Use Disorder in their practice if permitted by applicable state law and SAMHSA encourages them to do so***

Co-prescribe Narcan intranasal

- Naloxone – short acting medication to remove opioid from opioid receptor, reverses opioid overdose
- Co-Prescribing naloxone (NARCAN) is a best practice
- Train Patient, care givers on use of naloxone to reverse overdose

State of Indiana provides Narcan (naloxone) Overdose Lifeline



Buprenorphine and Pain

- BUP is a long-acting agent and can be given as once daily in most people
- Analgesic effects only last 6-8 hours so may need to split dosage or even temporarily increase dosage for acute pain such as a broken bone
- In patients currently on Opioids, buprenorphine is started through a process of induction

Suboxone

- Transmucosal (first pass metabolism) Can take 20 min to dissolve
- Naloxone in sublocade to prevent IV drug use
- Generic and cost effective
- By far the most common form of MOUD being used nationally inside and outside of corrections
- Initial dosages were studied prior to fentanyl entering the market . Most common in the community is between 16-24mg a day. Can go up to 32 mg
- Don’t recommend stopping if using other drugs such as THC or Stimulants
- Standard dosage ***used to be*** 12-16 mg
- Macro and Micro dosing with long acting opioids

Bup Diversion

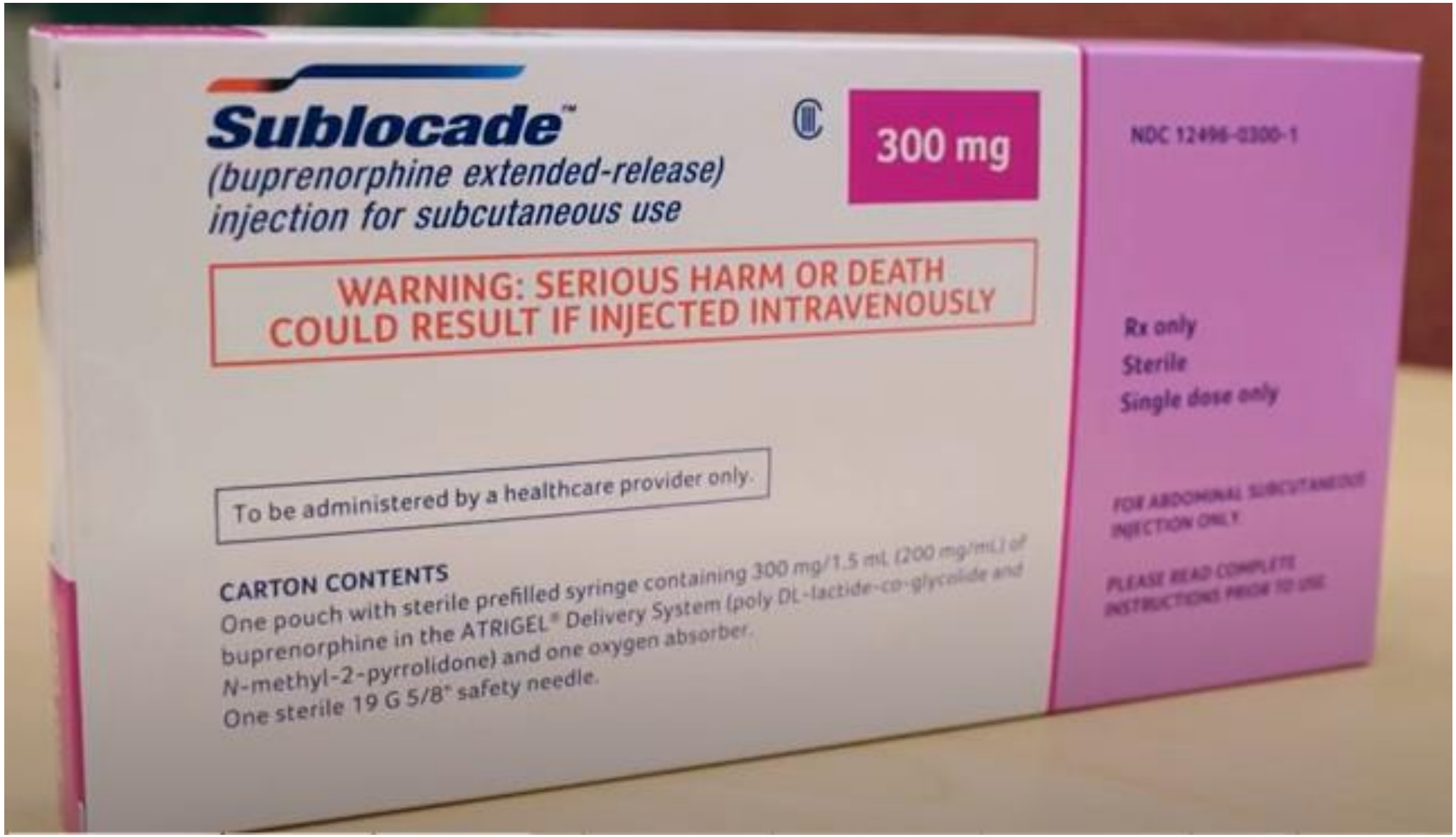
2% of IV opioid users report buprenorphine use "to get high"

72-80% report use of "diverted" BUP for symptom management

→ Would prefer rx by a licensed provider

→ May be public health signal that treatment needs not being met

→ Need for improved access/expansion of treatment


Sublocade™
(buprenorphine extended-release)
injection for subcutaneous use
C
300 mg
NDC 12496-0300-1
WARNING: SERIOUS HARM OR DEATH
COULD RESULT IF INJECTED INTRAVENOUSLY
Rx only
Sterile
Single dose only
To be administered by a healthcare provider only.
CARTON CONTENTS
One pouch with sterile prefilled syringe containing 300 mg/1.5 mL (200 mg/mL) of
buprenorphine in the ATRIGEL® Delivery System (poly DL-lactide-co-glycolide and
N-methyl-2-pyrrolidone) and one oxygen absorber.
One sterile 19 G 5/8" safety needle.

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

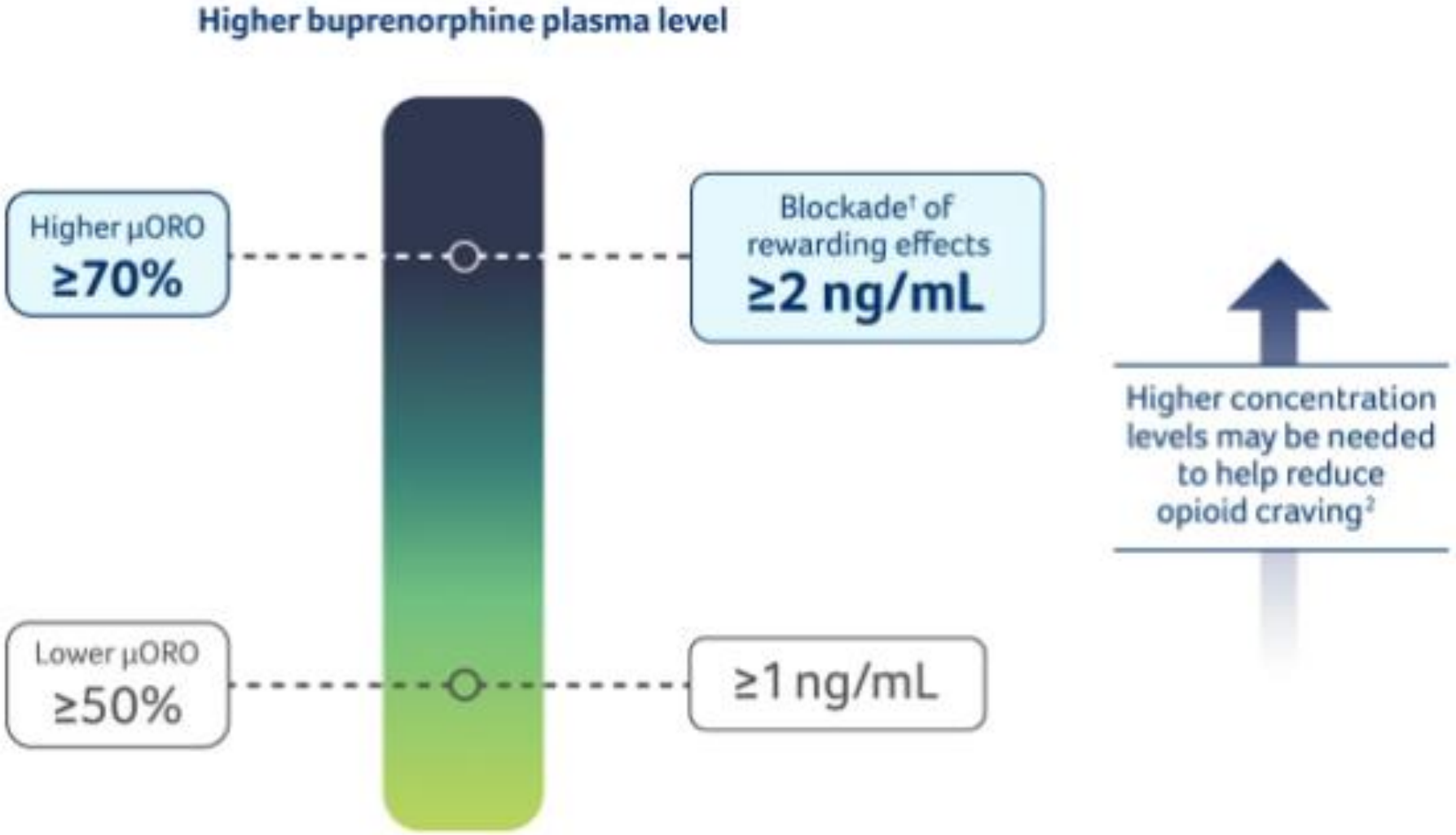
- Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously.

Pros with sublocade

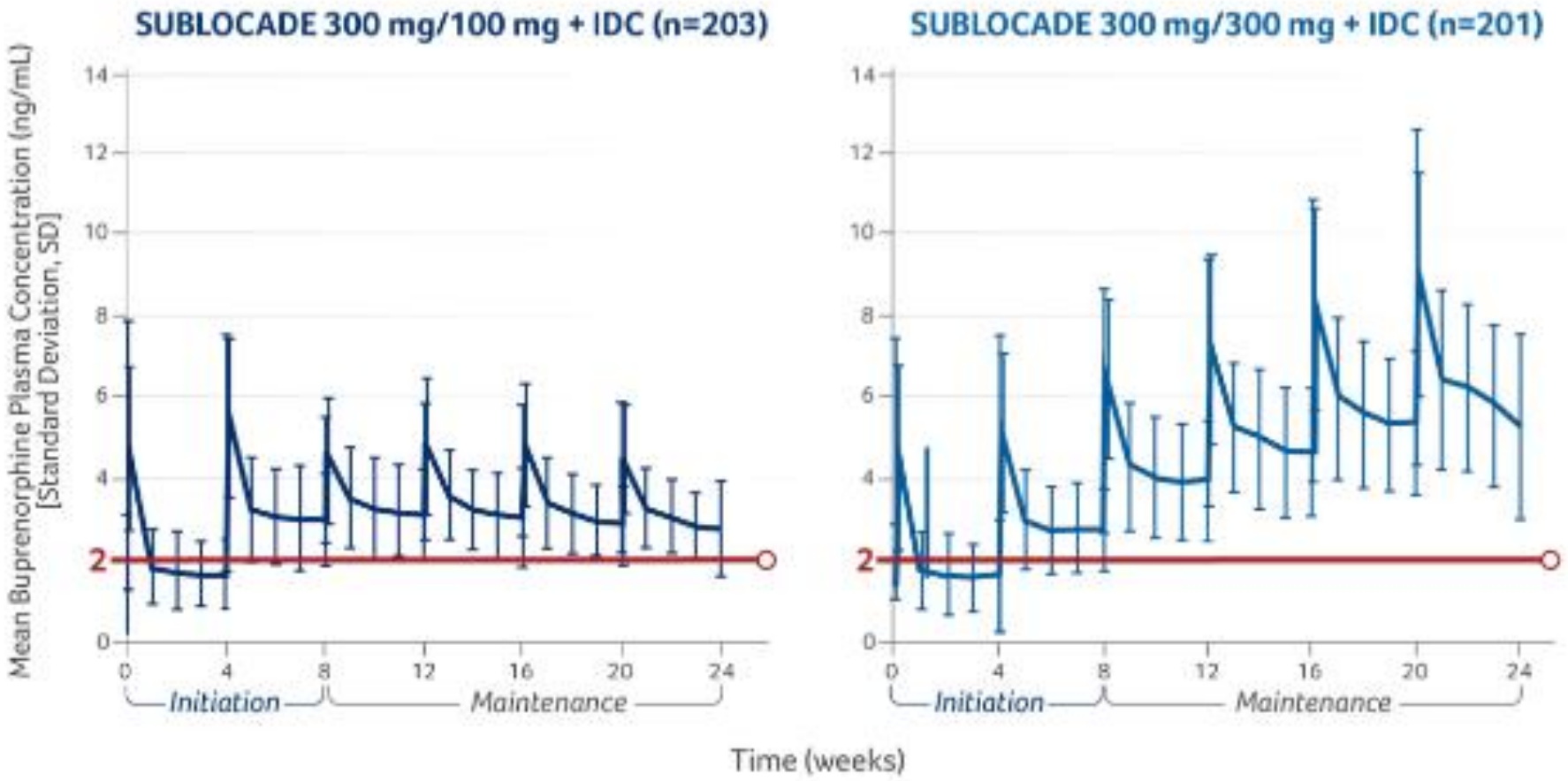
- Once monthly dosing
- Little to no diversion potential
- Little compliance concern
- If a patient stops the injections, the taper will be slow

Sublocade Cons

- Expensive (however covered by many insurance companies and Medicaid)
- Can be painful (large needle)
- Bump can stay around for months
- Injection site reaction
- First month can be rough and may need supplemental buprenorphine (especially weeks 2-4)
- Must be given at a REMS certified clinic.
- Dangerous if given into the blood stream


Higher buprenorphine plasma level
Higher μORO
≥70%
Blockade[1] of rewarding effects
≥2 ng/mL
Higher concentration levels may be needed to help reduce opioid craving[2]
Lower μORO
≥50%
≥1 ng/mL

Mean weekly buprenorphine concentration levels[3]



1 | SUBLOCADE Administration[1]

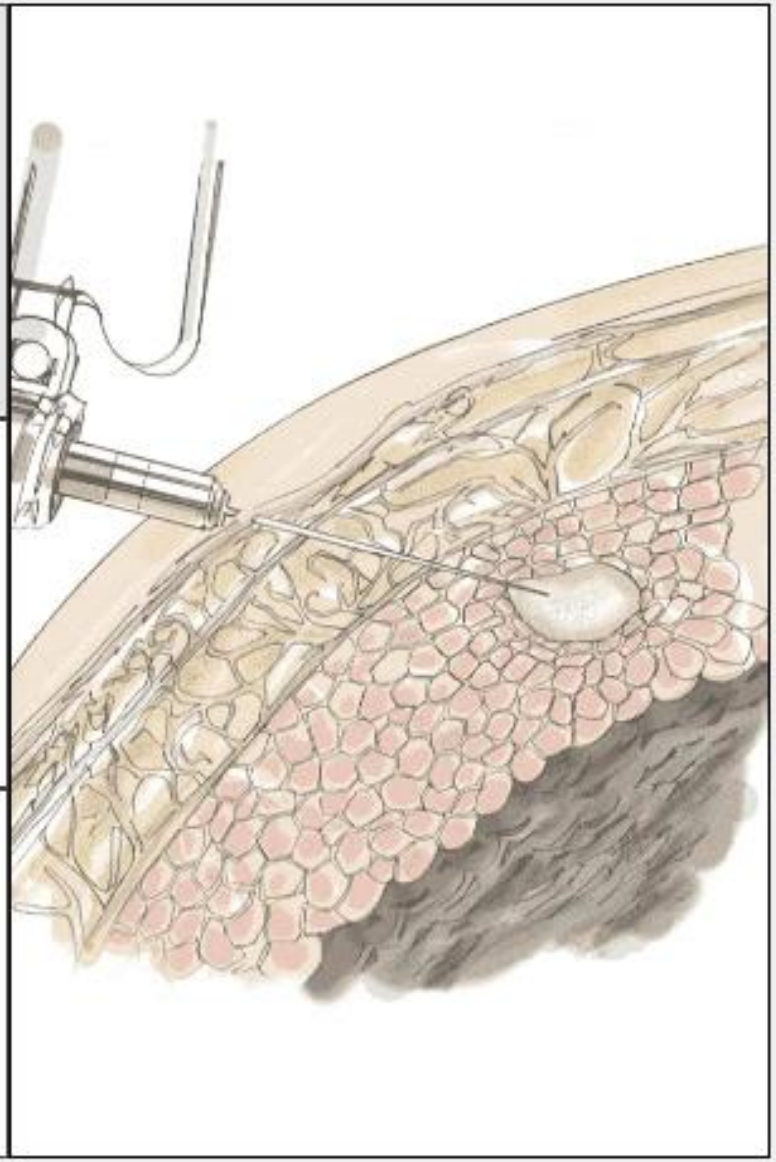
SUBLOCADE is administered as an injection into the abdominal subcutaneous tissue (total volume: 0.5 mL for 100 mg and 1.5 mL for 300 mg)

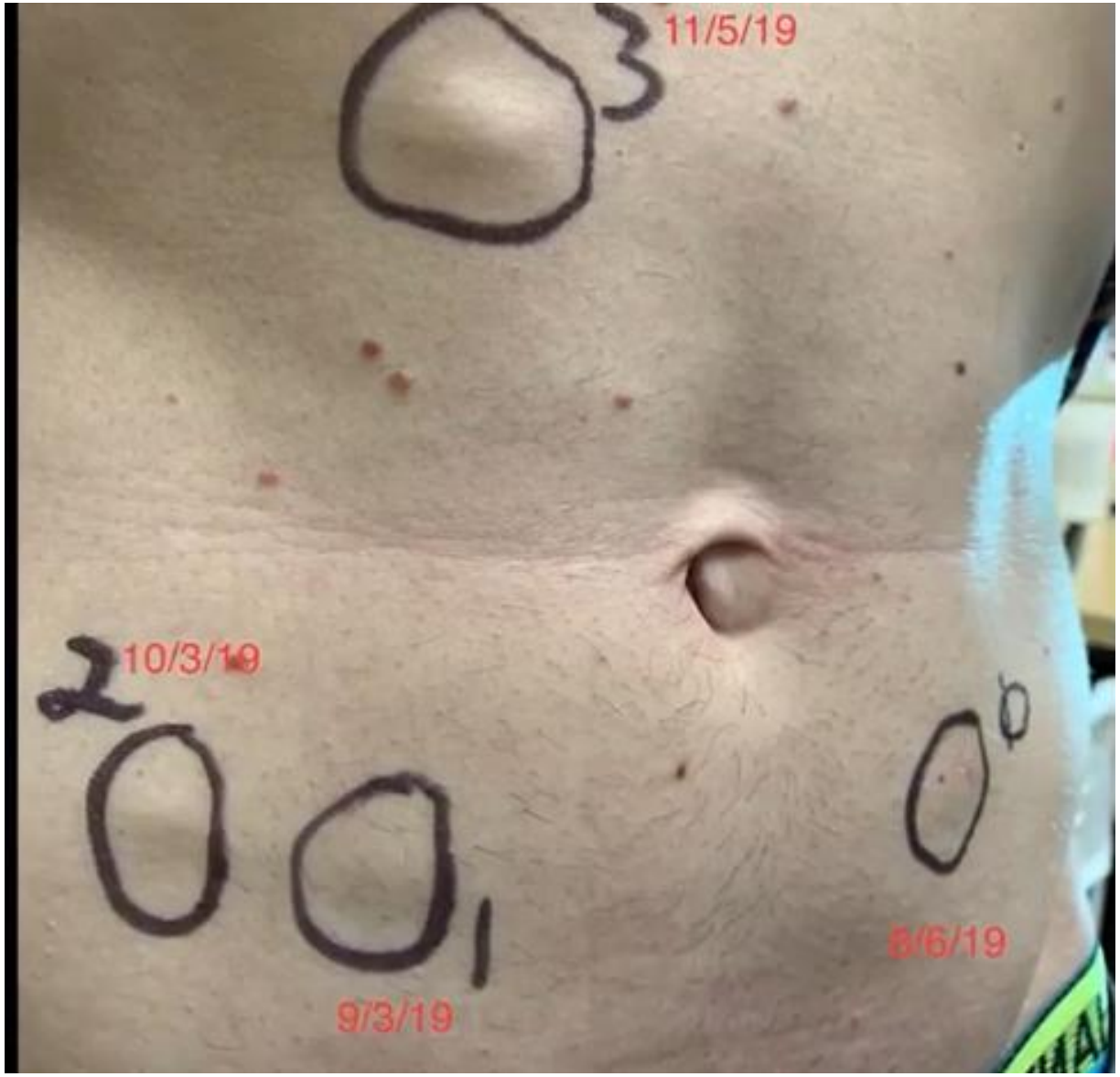
2 | Depot Formation[1]

SUBLOCADE is injected as a liquid, and upon contact with body fluids, the ATRIGEL® delivery system forms a solid depot containing buprenorphine

3 | Continuous Release[1]

After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot




11/5/19
3
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Brand name	Probuphine	Sublocade	Brixadi (US) or buvidal (Europe/ Australia)
Molecular name		RBP-6000	CAM2038
Pharmaceutical	Previously Braeburn, currently Titan	Indivior	Braeburn Pharmaceuticals/Camurus
Indicated population	Stable transmucosal buprenorphine dose of 8 mg or less for three months or longer	Initiated transmucosal buprenorphine (8–24 mg) for a minimum of 7 days.	Initiation of treatment in patients not already receiving buprenorphine or switching from transmucosal buprenorphine
Route of administration	Subcutaneous implant	Subcutaneous injection	Subcutaneous injection
Duration of effect	6 months	1 month	1 week or 1 month
Dosage	320 mg (Four 80 mg implants)	100 and 300 mg	8, 16, 24 and 32 mg (weekly) or 64, 96 and 128 mg (monthly)
Long-acting technology	Ethylene vinyl acetate (EVA) polymer	18% (weight/weight) buprenorphine base in the ATRIGEL Delivery System	Prolonged release FluidCrystal injection depot technology
Location	Upper arm	Abdomen	Buttock, thigh, stomach (abdomen) or upper arm
FDA-approval	2016	2017	2018 (tentative)
Plasma concentrations (ng/mL)	C_{max} 3.23 C_{trough} 0.72	C_{max} 4.88 (100 mg) 10.12 (300 mg) C_{trough} 2.48 (100 mg) 5.01 (300 mg)	C_{max} Weekly 4.35–8.23 Monthly 3.81–6.59 C_{trough} Weekly 0.26–0.54 Monthly 0.45–0.93
Provider burden	+++ Live training program Procedural competency	++ Supervised injection Monthly injections	++ Supervised injection Weekly or monthly injections
Special Handling Requirements	Requires implant procedure Need for removal or replacement every 6 months	Needs Refrigeration Injection only under skin around umbilicus	No special requirements

A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management.

Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment.

Patients should be offered or referred to psychosocial treatment, based on their individual needs.

Rationale:

- Requirements for psychosocial treatment can present barriers to access to treatment for some patients
- Research has shown that methadone and buprenorphine treatment reduce mortality even without psychosocial treatment.

MOUD

- Use as long as the Benefits outweigh the Risk similar to other chronic diseases
- Long term maintenance therapy ***(minimum 18 months)***

- Detox: is not treatment, (medical management of withdrawal)

" Detoxification from heroin is good for many things – but staying off heroin is not one of them"

Walter Ling

Replacing One Drug For Another?

Buprenorphine Abuse?

→ Brain chemistry and structure of OUD is changed

→ Those changes require a medication to stabilize the disease

→ Diabetes - insulin is a stabilizing medication

→ Dosage of meds used does not get them high

→ Restores balance in the brain's circuits

→ Misuse among opioid-dependent people is low

→ "Street use" of bup is usually self-treatment for OUD without access to MOUD

Summary

Substance use disorder is a chronic disease and should be treated as such

OUD overdose deaths continue to escalate and we need to treat it as a medical problem

Meet the patient where they are at and move them along the recovery continuum with brief interventions/motivational interviewing

MOUD is evidence based, very effective and is the community standard

Universal screening for OUD should be performed

DOJ guidelines say it is a violation of ADA not to treat a patient's OUD

When a true substance use disorder develops, the reward system holds the cortex hostage and views the drug/alcohol as essential for survival

Diagnosis should be made using the DSM 5 criteria

Summary

- **Treatment needs to continue as long as the benefits outweigh the risks (definitely > 18 months)**
- **Buprenorphine is a very safe drug.**
- **Naltrexone is FDA approved for AUD and OUD but the patient must be completely withdrawn from opioids and best to be off ETOH for at least a week**
- **Opioid related overdose deaths continue to rise in spite of expansive use of MOUD now due to Fentanyl and the addition of stimulants (primarily Crystal Methamphetamines)**
- **Buprenorphine combo product is generic and safe. An X-Waiver is no longer required for prescribing. Just need a DEA (schedule 3)**
- **Methadone needs to be prescribed in an OTP however we can treat up to 72 hours to bridge a patient**
- **Treating Substance use disorder is very rewarding with success rates that often exceed other chronic illnesses**

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MOTIVATIONAL INTERVIEWING

R	**RESIST** telling them what to do: *Avoid telling, directing, or convincing your friend about the right path to good health.*
U	**UNDERSTAND** their motivation: *Seek to understand their values, needs, abilities, motivations and potential barriers to changing behaviors.*
L	**LISTEN** with empathy: *Seek to understand their values, needs, abilities, motivations and potential barriers to changing behaviors.*
E	**EMPOWER** them: *Work with your friends to set achievable goals and to identify techniques to overcome barriers.*

Resources/References

- Medication-Assisted Treatment of Opioid Use Disorder Pocket Guide

  https://store.samhsa.gov/system/files/sma16-4892pg.pdf

  ▶ ASAM practice guideline

  ▶ Buprenorphine Waiver Management (X Waiver or DATA 2000)

  https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/training-materials-resources/buprenorphine-waiver

  Prescribe to Prevent

  https://prescribetoprevent.org/

1. Tanum L, Solli KK, Latif ZE, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. JAMA Psychiatry 2017; 74:1197.

2. Fischer G, Gombas W, Eder H, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. Addiction 1999; 94:1337.

3. Sublocate package insert