Opioid Use Disorder Precipitated withdrawal

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Disclosures

None

Project ECHO®

Indiana University

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

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

Opioid Use Disorder (OUD)

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

MOUD is the Gold Standard of care for treating OUD

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

Why are People Denied Access to MOUD?

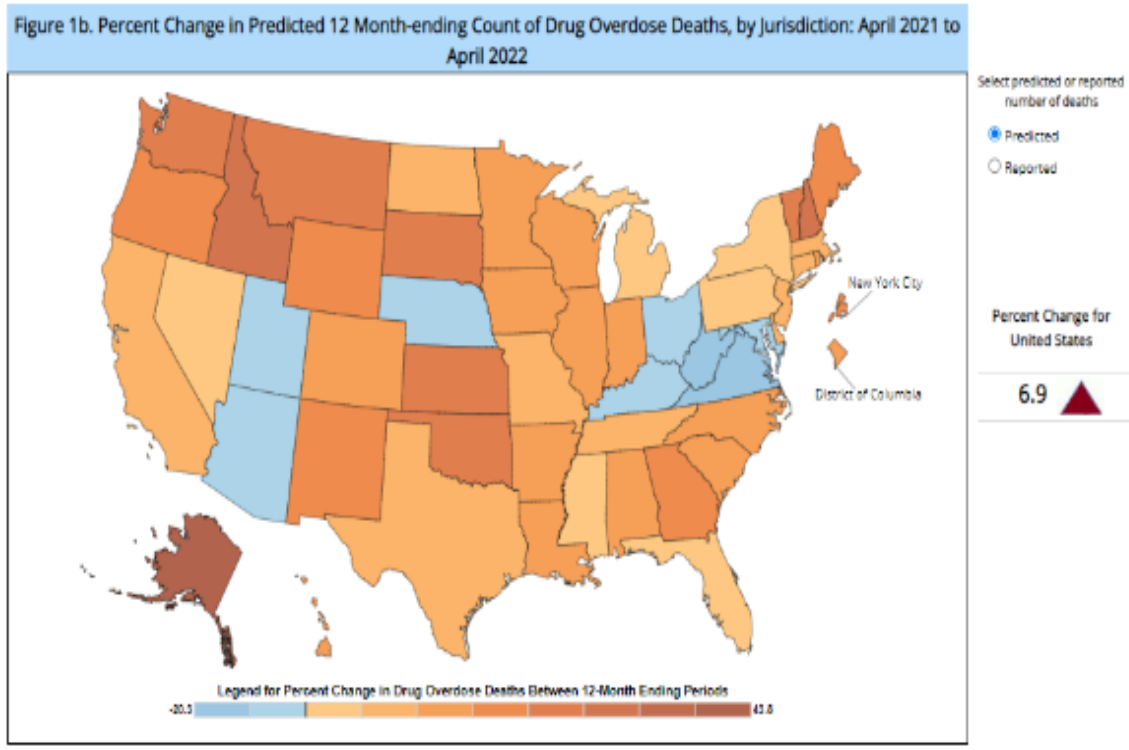
- Stigma surrounding OUD
- Misconceptions about MOUDs
- Stereotypes about people who use MOUD
- Belief in only “abstinence-based” treatments
- Failure to recognize MOUD as the standard of care
- Logistical obstacles in prescribing/administering MOUD
- Limited MOUD capacity in the community
- Fear amongst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

12 month-ending provisional number of drug overdose deaths

7% increase

Provisional Drug Overdose Deaths from 12 months ending in April 2022

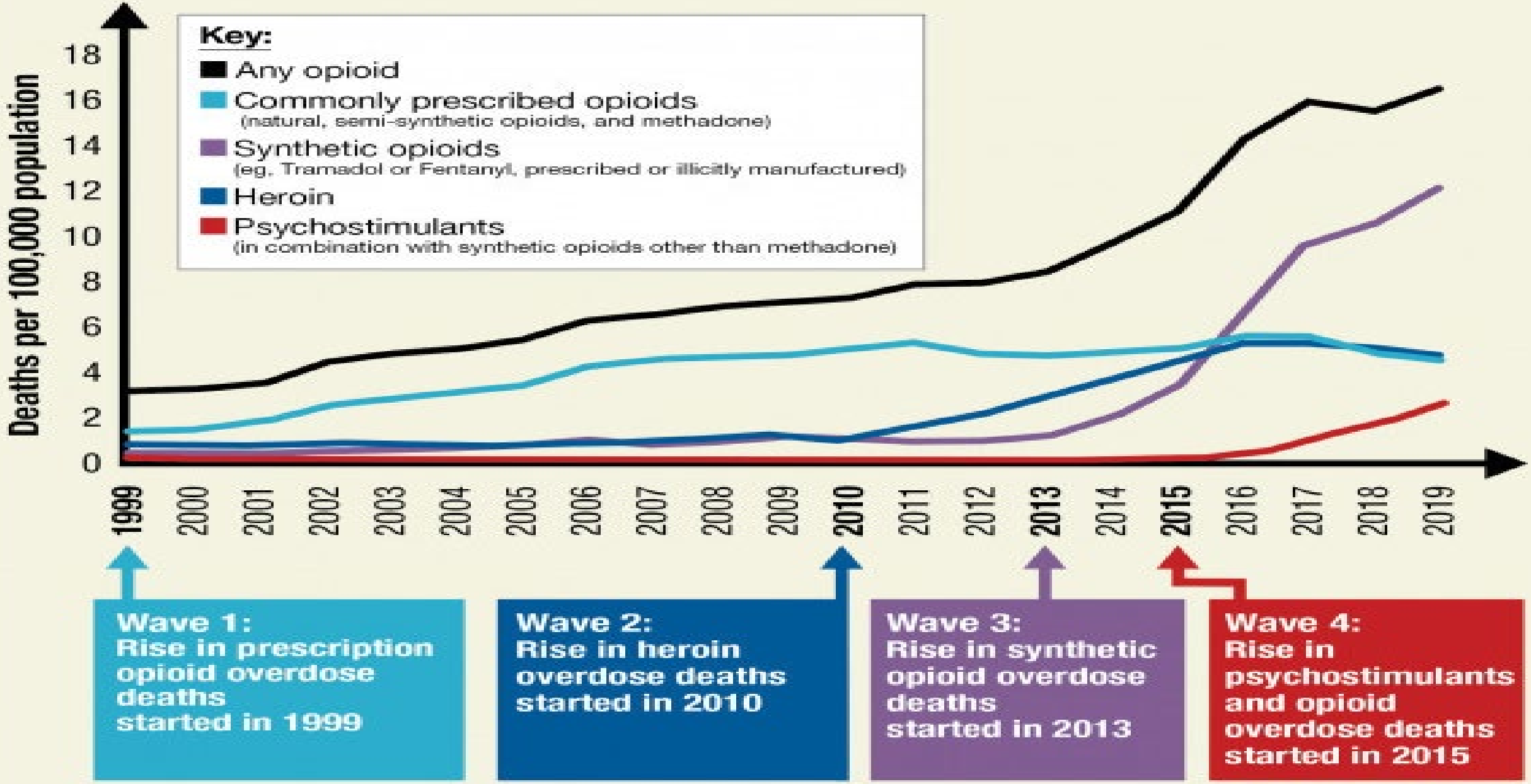
September 14, 2022 by NCHS



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

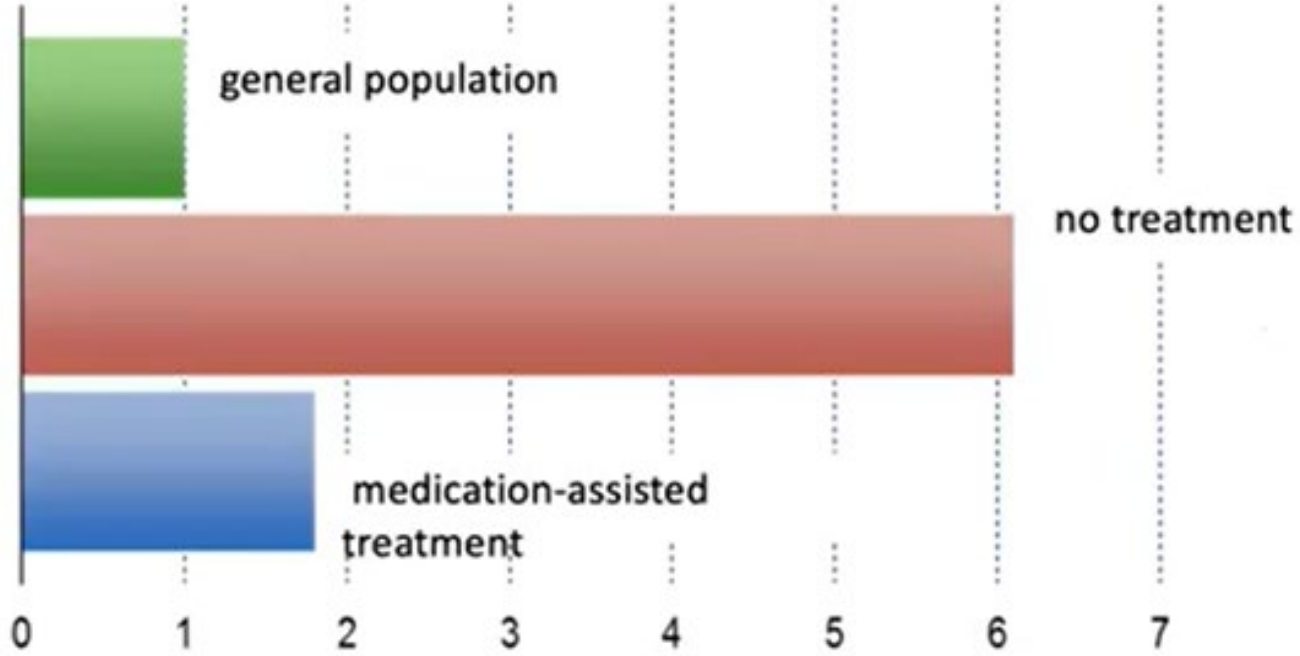
Timeline of Opioid-related Overdose Deaths



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

Benefits of Medications for OUD: Decreased Mortality

Death Rates:



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

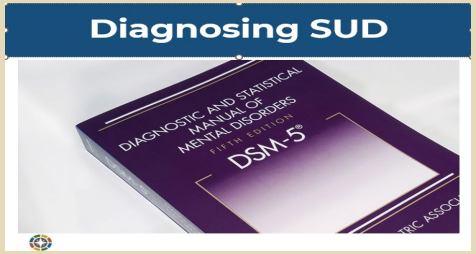

Real Oxycodone
Fake Oxycodone
M
30

Diagnosis of OUD

- Universal screening for SUD/OUD
- Can be diagnosed by MH or primary care using the DSM 5 criteria

Treatment of SUD/OUD is very rewarding with relapse rates similar to other chronic illnesses

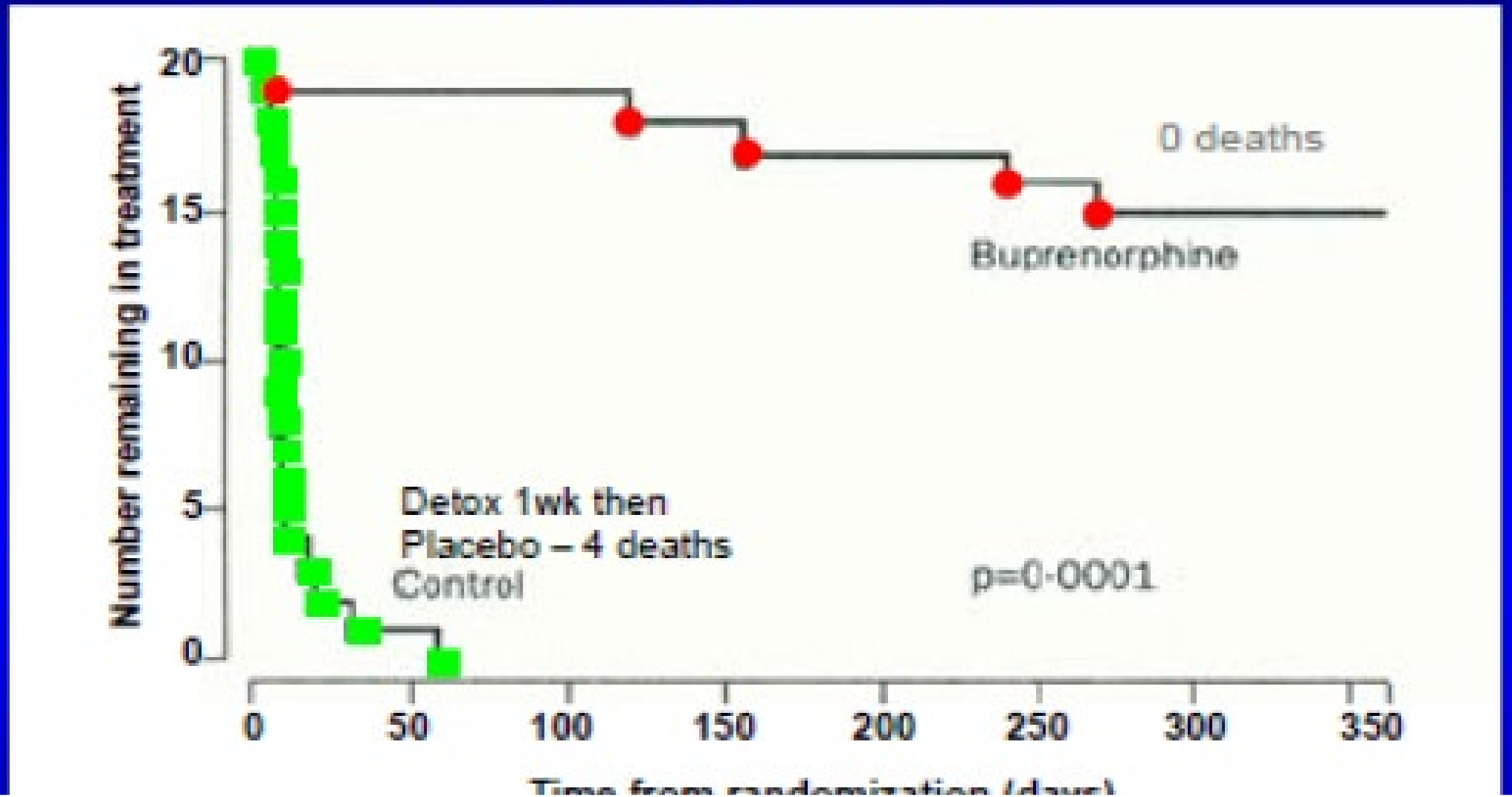
DSM-5 Opioid Use Disorder



- 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

Buprenorphine Maintenance vs Detox. RCT of cumulative retention in treatment



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

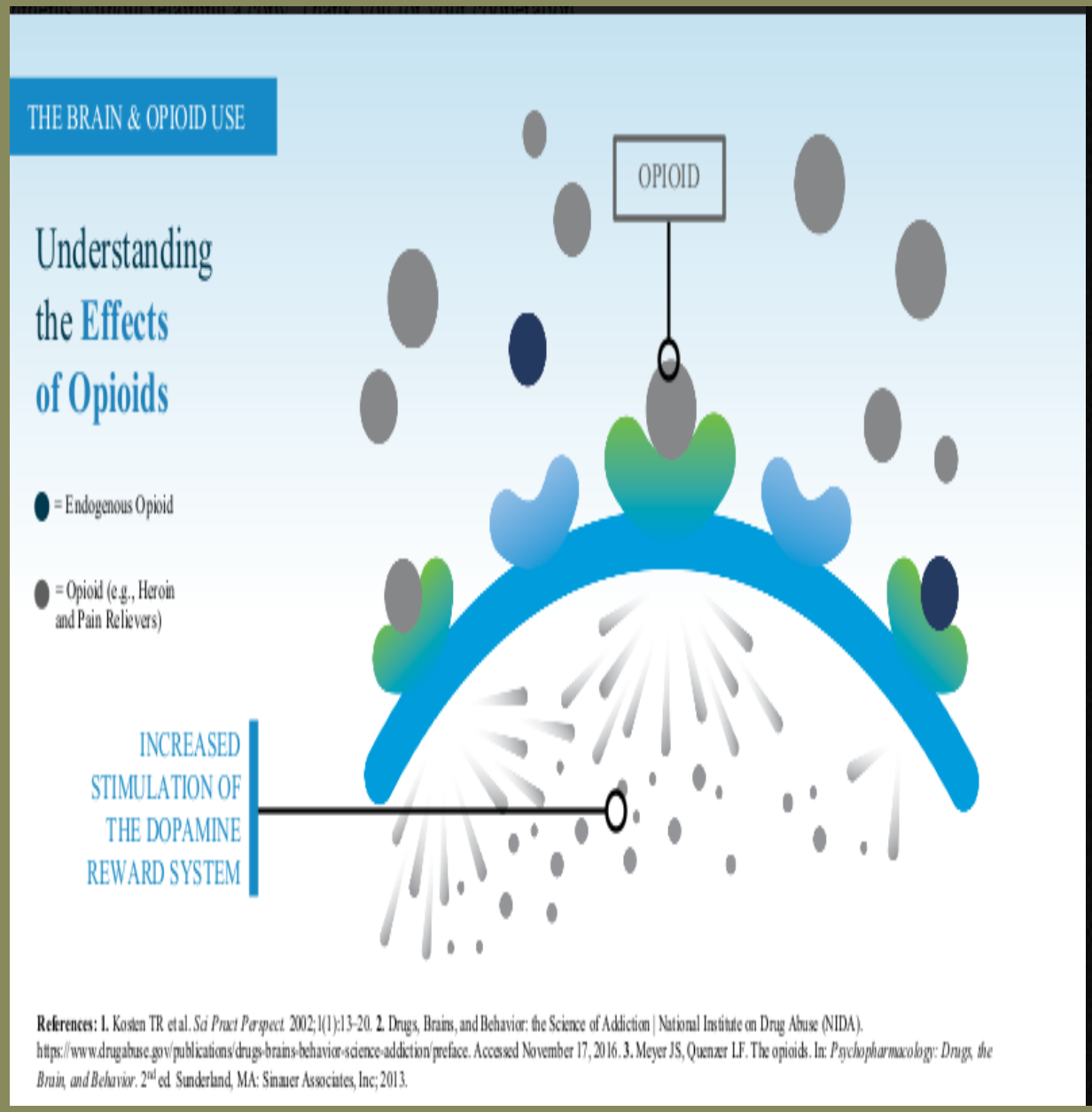
- Treat as the chronic illness that it is
- Understand that like any chronic illness , relapse can be part of the disease
- We continue to treat patients that are obese and sedentary with insulin to treat their diabetes
- We treat patients with lung cancer who still smoke or have smoked for years
- We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

Why should SUD be any different?

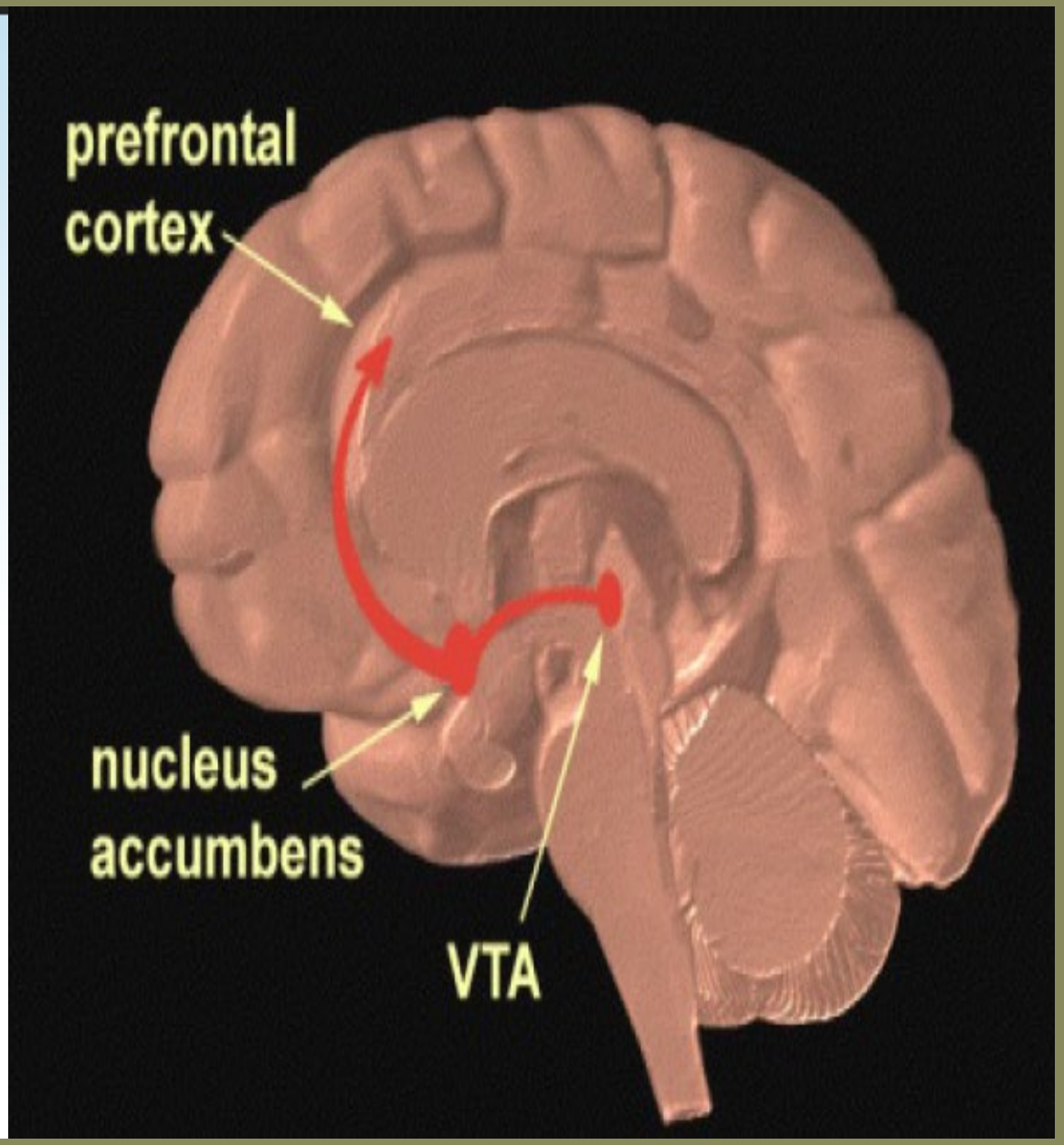
Approach to SUD treatment

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



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.



Buprenorphine initiation

- Standard induction (guidelines based on heroin use not fentanyl)
- Macro-induction- off label but widely used and being studied
- Micro-induction- Operationally difficult but safe May lose some people- off label
- Hybrid inductions

Efficacy and Affinity

Ligand	% Efficacy
Full agonist	E = 100
Partial agonist	0 < E < 100
Antagonist	E = 0
Inverse agonist	E < 0

Ligand	Ki (Affinity) (nmol)
Hydrocodone	41.58
Oxycodone	25.87
Heroin	9.6
Methadone	3.38
Fentanyl	1.35
Morphine	1.14
Naloxone	1.1
Hydromorphone	0.6
Buprenorphine	0.21

Opioid Response Network

Volpe DA. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Reg Toxicol Pharmacol 2011

Drugs that can precipitate withdrawal

- Naloxone (opioid “antidote”)
- Naltrexone (revia/vivitrol)
- Buprenorphine

Naloxone (“Narcan”)

Given to reverse the affects of an opioid overdose

High receptor affinity > most opioids

Displaces the opioid off the receptor which, if the opioid is used chronically, can lead to severe opioid precipitated withdrawal

ED Clinicians often using this opportunity to begin Buprenorphine

Buprenorphine Macrodosing Initiation

Contact ED substance use navigator/hospital to home coordinator if available.

Macrodosing is an alternative approach to initiating buprenorphine for patients who do not meet traditional criteria and for whom delays in treatment pose significant risk. Macrodosing should be reserved for people with high opioid tolerance. Higher initial and total Day 1 doses are off-label but have been shown to be effective in achieving therapeutic levels of buprenorphine.[1]

Indications:

- **Patients in withdrawal from fentanyl use, or**
- **Patients who have had full naloxone reversal of an opioid overdose** (i.e., naloxone-induced withdrawal)

Are any exclusion criteria to buprenorphine macrodosing present?

- Allergy or hypersensitivity to buprenorphine or naloxone
- Reported methadone use in the last 72 hours
- Unable to provide informed consent
- Altered mental status, depressed level of consciousness, or delirium
- Acute intoxication
- Severe medical illness such as sepsis, respiratory distress, severe liver dysfunction
- Concurrent withdrawal from alcohol or benzodiazepines
- Elderly

YES →

Provide supportive care and re-evaluate.

OPTIONS:

- ☐ Consult addiction medicine if available; patient may be a candidate for methadone or SROM
- ☐ Offer RAAM referral/harm reduction resources
- ☐ Provide naloxone kit

NO ↓

Is patient awake with COWS ≥ 13

Has at least 18 hours elapsed since last fentanyl use? (not necessary post-naloxone reversal)

NO →

OPTIONS:

- ☐ Offer home buprenorphine start
- ☐ Offer microinduction buprenorphine start
- ☐ Offer return to ED when in withdrawal for buprenorphine treatment
- ☐ Patient handouts about buprenorphine treatment, home start, microdosing
- ☐ Provide naloxone kit

YES ↓

Explain:

- Goal is to achieve full treatment dose within a matter of hours
- May experience transient worsening of withdrawal symptoms before relief
- For patients in naloxone-induced withdrawal macrodosing should be started as soon as possible

Provide 16mg buprenorphine SL as 2x8mg tablets → **Reassess in one hour**

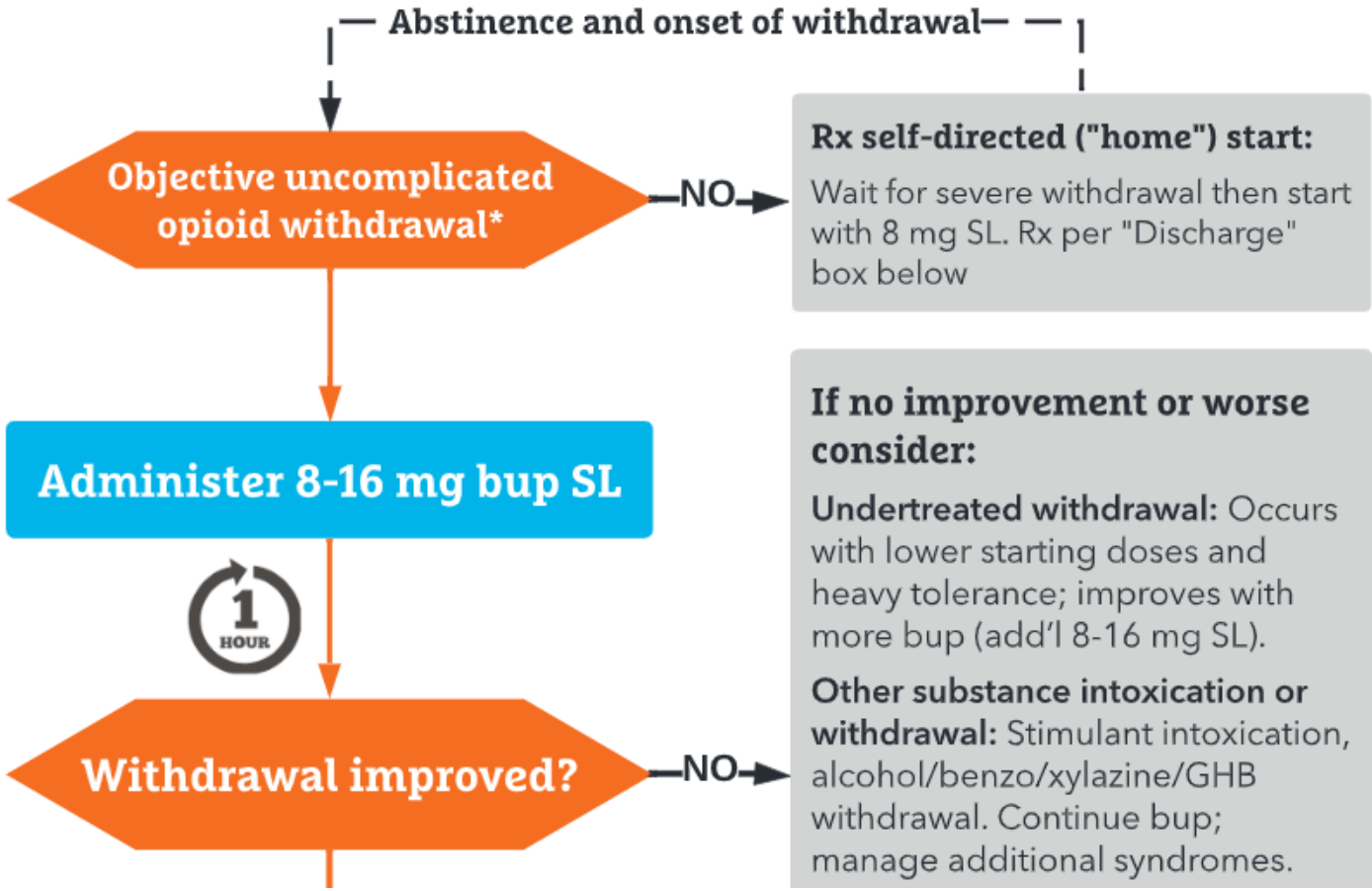
Repeat buprenorphine 8–16mg q1–2h until withdrawal is resolved or sedation (recommended Day 1 maximum is 32mg)

- Discharge with prescription for total dose dispensed in the ED as daily observed dose until planned follow-up (max 7 days)
- Refer to RAAM/community clinic
- Dispense naloxone kit
- Buprenorphine handout
- Harm Reduction Info Sheet

- See High-Dose Buprenorphine Initiation ("Macrodosing") Reference Guide for ED Providers
- See Buprenorphine Reference Guide for further information

[1] https://cabridge.org/resource/starting-buprenorphine-immediately-after-reversal-of-opioid-overdose-with-naloxone/

Buprenorphine (Bup) Emergency Department Quick Start



Rx self-directed ("home") start:

Wait for severe withdrawal then start with 8 mg SL. Rx per "Discharge" box below

If no improvement or worse consider:

Undertreated withdrawal: Occurs with lower starting doses and heavy tolerance; improves with more bup (add'l 8-16 mg SL).

Other substance intoxication or withdrawal: Stimulant intoxication, alcohol/benzo/xylazine/GHB withdrawal. Continue bup; manage additional syndromes.

We encourage shared decision making with patient for dosing.

*** Opioid Withdrawal:**

At least one clear objective sign (prefer ≥ 2): Tachycardia, mydriasis, yawning, rhinorrhea, vomiting, diarrhea, piloerection. **Ask the patient if they are in bad withdrawal** and if they feel ready to start bup. If they feel their withdrawal is mild, it is too soon.

If unsure, use COWS (clinical opioid withdrawal scale). Start if COWS ≥ 8 AND objective signs.

Typical withdrawal onset >12 hours after last short acting opioid use (excluding fentanyl); variable after last use of fentanyl or methadone (may be >72 hours).

Start protocol may vary for complicating factors:

- Altered mental status, delirium, intoxication
- Severe acute pain, trauma, or planned large surgery
- Organ failure or other severe medical illness

YES

Administer 2nd dose
Additional 8-16 mg SL bup for total daily dose of 16-32 mg

Discharge

- **Prescribe sufficient bup/nx until follow-up,** e.g., buprenorphine/naloxone 8/2 mg SL films 2-4 films qday #32-64, 0 refills (may Rx more PRN). Notes to pharmacy: bill Medi-Cal FFS, ICD 10 F11.20.
- **An X-waiver is no longer needed to prescribe bup.**
- **Dispense naloxone** from the ED (not

withdrawal. Continue bup; manage additional syndromes.

Bup side-effects: Nausea, headache, dysphoria. Continue bup, treat side-effects with supportive medications.

Other medical/psychiatric illness: Anxiety, sepsis, influenza, DKA, thyrotoxicosis, etc. Continue bup, manage underlying condition.

If sudden/significant worsening, consider precipitated withdrawal: See box below.

- Severe acute pain, trauma, or planned large surgery
- Organ failure or other severe medical illness (decompensated heart failure, respiratory distress, hemodynamically unstable, etc.)
- Recent methadone use
- Minimal opioid tolerance (consider lower dosing)

Most people who use fentanyl do well with starts following this guide. For fentanyl specific initiation questions, see Fentanyl FAQ.

If patient has already completed withdrawal (no longer symptomatic withdrawal, often >72 hrs from last use of opioids) and wants to start bup: give bup 8 mg SL q6h PRN cravings, usual dose 16-32mg/day. After first day, consolidate dosing to daily.

Treatment of precipitated withdrawal

Precipitated withdrawal is a sudden, significant worsening of withdrawal after bup or full antagonist (e.g., naloxone).

Administer additional 16 mg SL bup immediately.
Reassess in 30-60 minutes. If continued distress remains: Repeat 8-16 mg bup SL.

If precipitated withdrawal not resolved by bup:

- **An X-waiver is no longer needed to prescribe bup.**
- **Dispense naloxone** from the ED (not just prescribed): e.g., naloxone 4 mg IN spray #2.
- **Document** Opioid Withdrawal and/or Opioid Use Disorder as a diagnosis.

Reassess in 30-60 minutes. If continued distress remains: Repeat 8-16 mg bup SL.

If precipitated withdrawal not resolved by bup:

Consider alpha-2 agonists (clonidine or dexmedetomidine), antipsychotics (e.g., haloperidol), cautious use of benzodiazepines (e.g., 1-2 mg PO lorazepam x 1), high potency opioid (e.g., fentanyl 100-200 mcg IV q30 or infusion), or ketamine (0.3 mg/kg IV slow push q30 minutes or continuous infusion until calm). Once withdrawal is managed, continue daily bup dose.

Bup dosing notes

This guidance is for the ED. We advocate for continuation & initiation of bup in inpatient and outpatient settings. Algorithms vary based on clinical scenario.

- Any prescriber can order bup in the ED/hospital. It can also be prescribed as medication for opioid use disorder (MOUD) by any prescriber with an active Drug Enforcement Agency (DEA) license that includes schedule III medications.
- Either bup or bup/nx (buprenorphine/naloxone) SL films or tab are OK. If chronic pain, may split dose TID-QID.
- Bup monoproduct or bup/nx OK in pregnancy. See **Buprenorphine Quick Start in Pregnancy**.
- Pause opioid pain relievers when starting Bup. OK to introduce opioid pain relievers after bup is started if patient has acute pain.

February 2023

PROVIDER RESOURCES

California Substance Use Line
CA Only (24/7)
1-844-326-2626

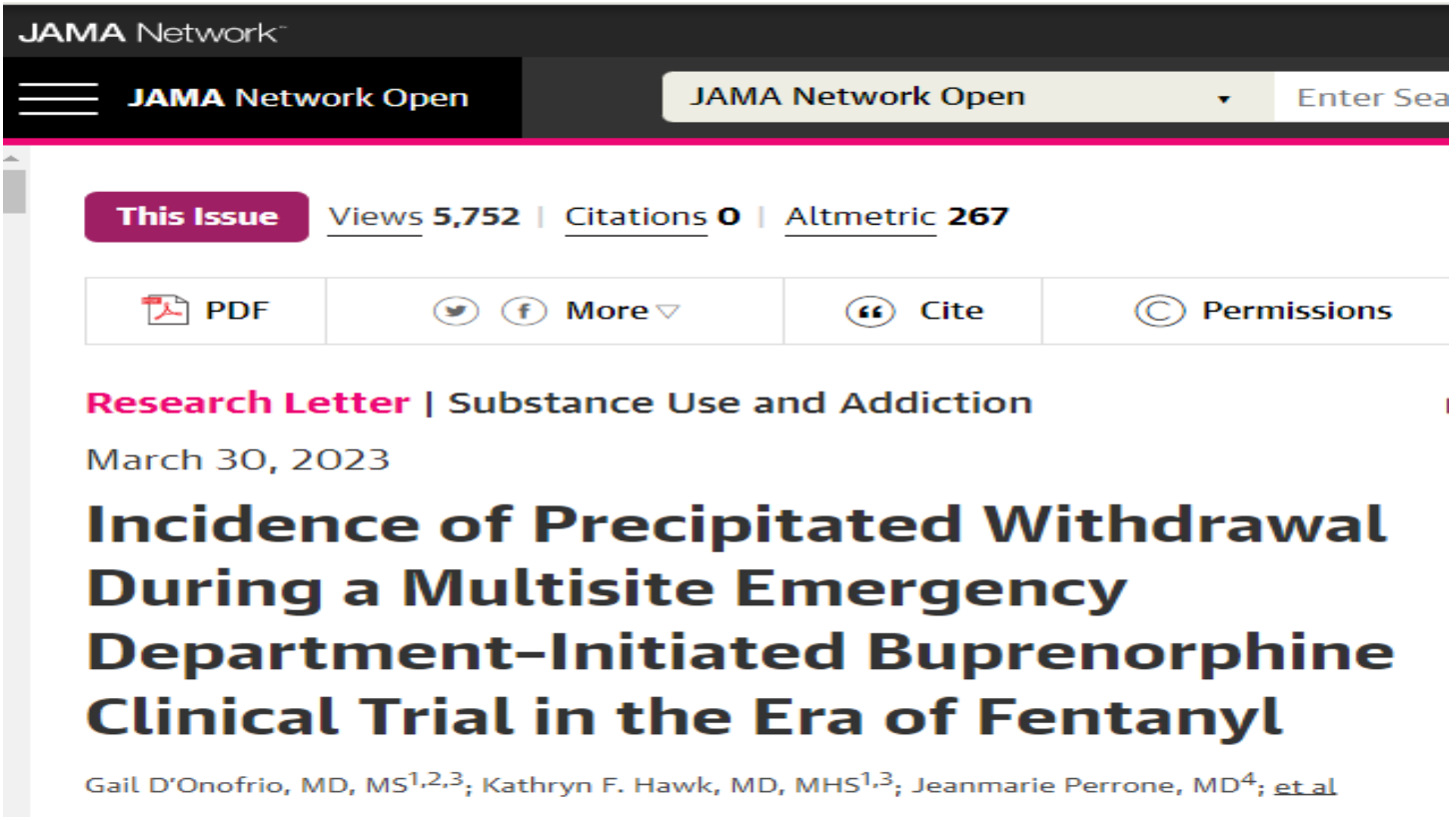
UCSF Substance Use Warmline
National (M-F 6am-5pm; Voicemail 24/7)
1-855-300-3595

Symptoms of Precipitated Withdrawal

- Agitation, restlessness, and anxiety
- Muscle aches
- Insomnia
- Sweating
- Yawning
- Runny nose
- Increased watering of the eyes
- Abdominal cramps
- Diarrhea and nausea
- Dilated pupils
- Goosebumps

Objective

To determine the incidence of PW in an ongoing trial of ED-initiated buprenorphine



ED INNOVATION

ED-INitiated BupreNOrphine VAlidaTION Network Trial

Hybrid Type 1 Effectiveness-Implementation Design

Implementation

To use implementation facilitation and training to achieve competence in ED-initiated XR-BUP and SL-BUP inductions in approximately 30 diverse ED sites

Effectiveness

To compare the effectiveness of XR-BUP and SL-BUP induction in approximately 1200 patients with untreated OUD in the ED on the primary outcome of engagement in formal addiction treatment at 7 days

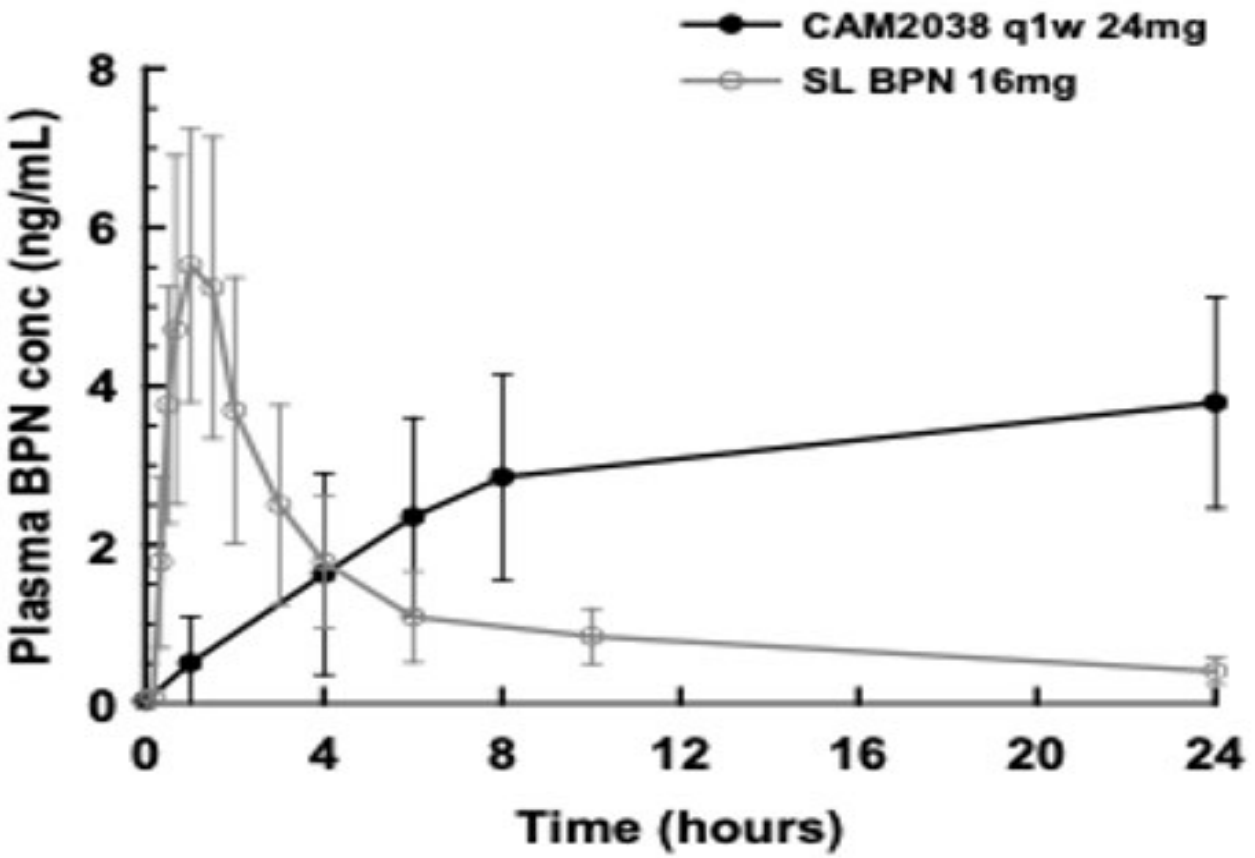
D'Onofrio, Contemporary Clinical Trials, 2021

ED INNOVATION

CAM2038 24mg XR-BUP 7-day injectable vs 16mg SL-BUP per day

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**



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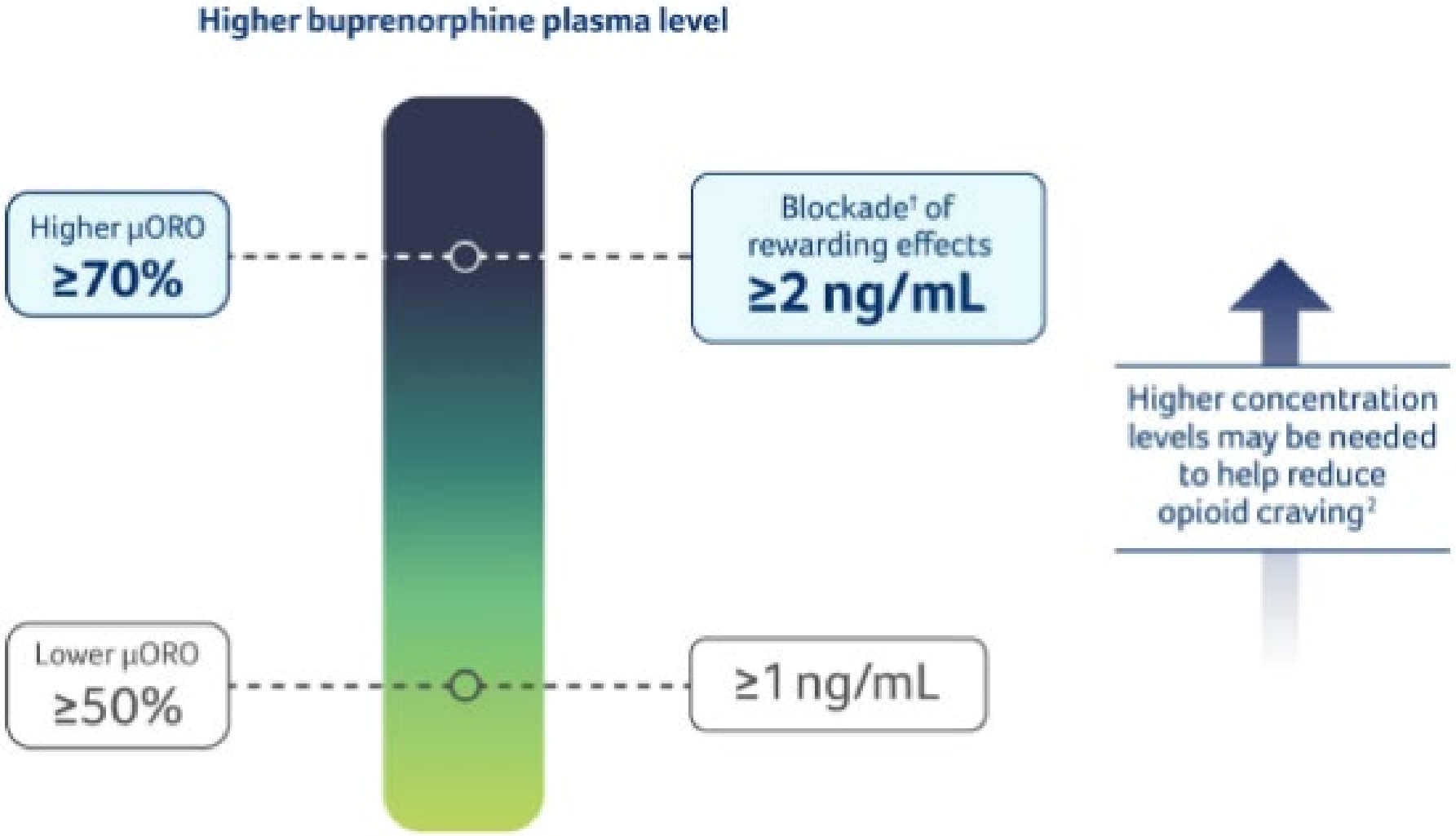

Higher buprenorphine plasma level
Higher μORO
≥70%
Blockade[1] of rewarding effects
≥2 ng/mL
Higher concentration levels may be needed to help reduce opioid craving[2]
Lower μORO
≥50%
≥1 ng/mL

Patient Eligibility

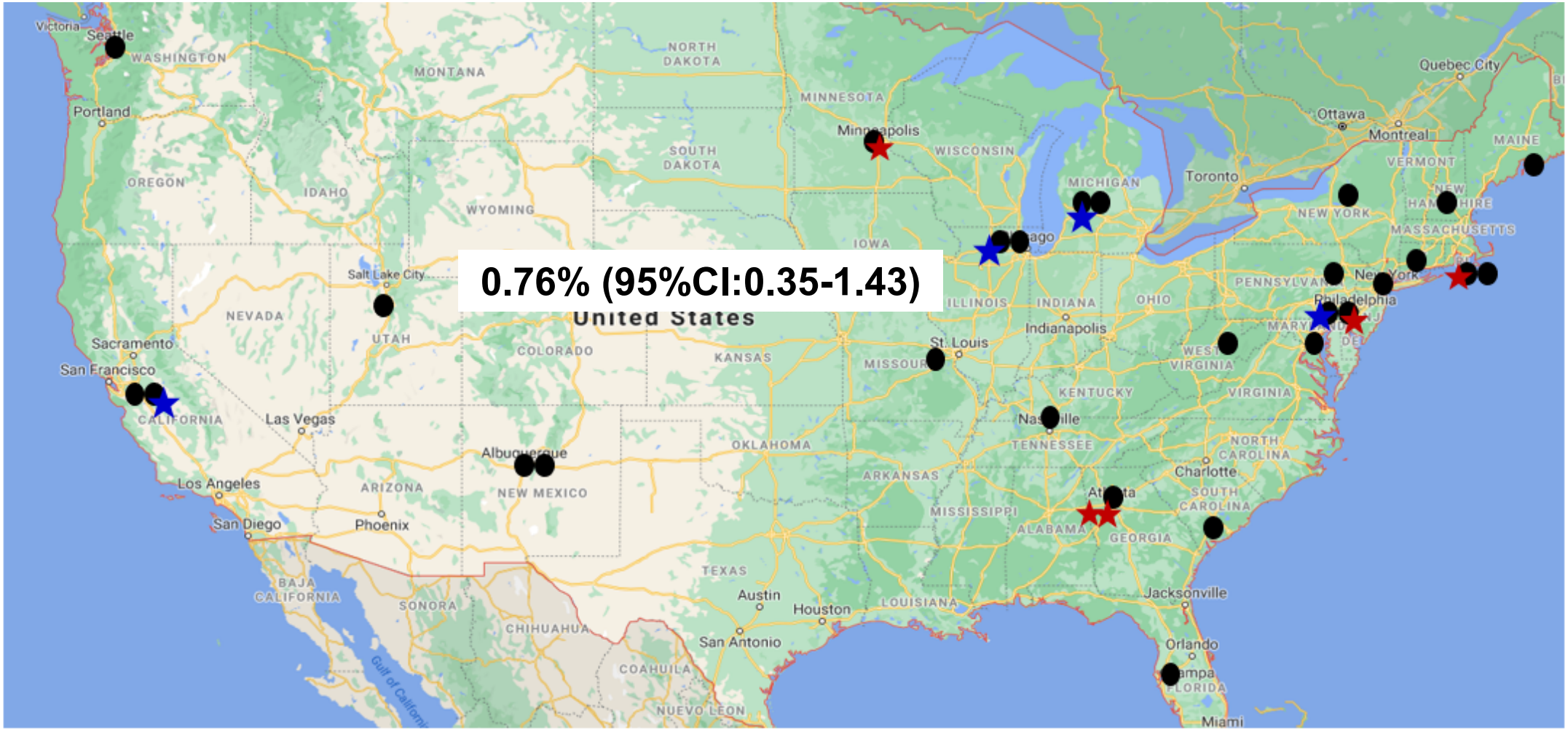
Inclusion

- 18 years or older
- Meet DSM-5 diagnostic criteria for moderate to severe OUD
- Have a COWS score of $\geq$ 4
- Have a urine toxicology test that is positive for opioids (opiates, oxycodone, buprenorphine, fentanyl)
- Able to speak English sufficiently

Exclusion

- Urine toxicology positive for methadone
- Pregnancy
- Medical/psychiatric condition that requires hospitalization or opioid administration at the index ED visit, **prior to randomization**
- Actively suicidal or severely cognitively impaired
- Require continued prescription opioids for pain
- A prisoner or in police custody at the time of index ED visit
- Enrolled in formal addiction treatment (**anytime within the past 14 days**) including by court order. **Patients enrolled in formal addiction who are not receiving MOUD are eligible**

Location of all Enrolling Sites and Precipitated Withdrawal



Key

- ● Location of enrolling sites (28)
- ★ Location of SL-BUP precipitated withdrawal (5)
- ★ Location of XR-BUP precipitated withdrawal (4)

Enrollment by sites that experienced withdrawal

Site Location	# PW	Total enrolled	%
Northeast (10 sites)	3	313	0.95
West (6 sites)	1	423	0.24
Midwest (6 sites)	3	207	1.44
South (6 sites)	2	257	0.78
Totals	**9**	**1200**	**0.76**

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

Characteristics of Patients with Precipitated Withdrawal

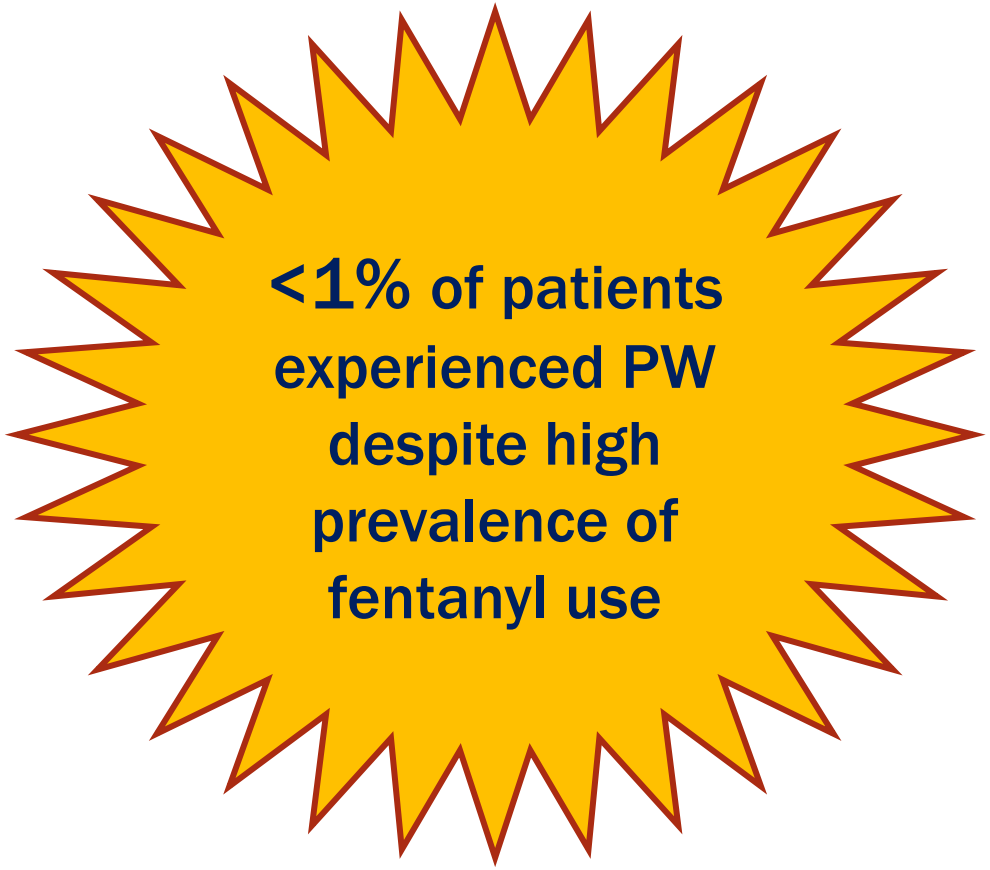
Enrollment Date	Location	Age	Race	Gender	Severity of Use Days/wk	Last Use (hours)	Route	Baseline COWS	Urine Drug Testing	BUP SL vs XR	Disposition	ED LOS (hours/min)
12/20	Northeast	50	Black	Woman	7	16	IV	13	OPI FEN	SL	Discharged	6.40
01/21	West	29	White	Woman	7	8	smoking	15	FEN	XR	Discharged	2.50
02/21	Northeast	47	White	Man	7	8	nasal	12	FEN	XR	Observation[a] Discharged	7.50
04/21	Midwest	61	Black	Woman	7	24	nasal	8	COC, OPI, THC, FEN	XR	AMA	1.41
05/21	Northeast	30	Muti-racial	Man	6	>24	IV	17	COC, THC, FEN	SL	Discharged	7.24
8/21	South	32	Multi-racial	Man	6	24	smoking	16	COC, FEN	SL	Observation[a] Discharged	22.39
9/21	Midwest	49	Black	Man	7	12	nasal	13	COC, THC, FEN	XR	Discharged	8.50
11/21	Midwest	22	AI/AN	Man	7	16	smoking	10	COC, THC, FEN	SL	Discharged	8.43
12/21	South	25	black	Man	7	15	IV	29	COC, FEN	SL	Observation[a] Discharged	20.00

Lessons Learned: Treatment of PW

- ***More Buprenorphine 24-32 mg***

- **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**

Conclusion



There are NO consistent similarities among the individuals experiencing Precipitated Withdrawal!

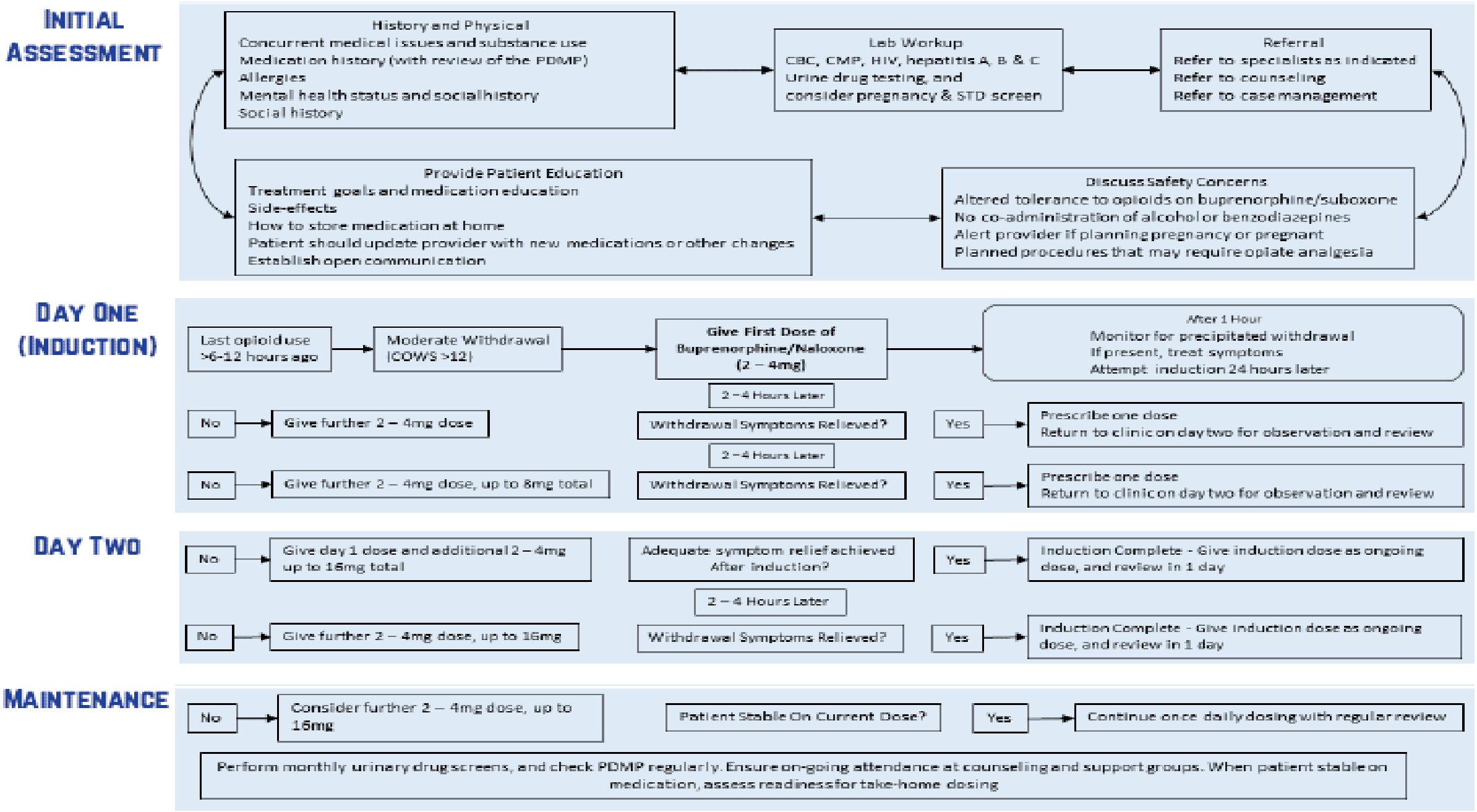
Naltrexone

- FDA approved to treat OUD and AUD
- Oral and long-acting injection
- Should be off opioids for 7-14 days prior to starting naltrexone. Give test dose orally prior to Vivitrol injection
- Can treat similar to Naloxone

Buprenorphine

- Partial agonist used to treat OUD
- Standard induction techniques based on heroin.
- Methadone can be difficult to induce due to its long half life
- Fentanyl behaves like methadone when used chronically (stored in the adipocytes with chronic use)

Standard induction SAMHSA quick start



Management of precipitated opioid withdrawal

- Buprenorphine 8mg x 2 (16mg) preferably without naloxone, repeat x 1 or 2
- Lorazepam 2mg po or IM
- Reassurance—You can and will take care of the patient
- Symptom management:
  - Vomiting: ondansetron, metoclopramide, prochlorperazine
  - Agitation: droperidol, olanzapine, ketamine
  - Diarrhea: loperamide
  - Sympathomimetic sx and agitation: clonidine (BP monitor)

TABLE 1. ADJUNCTIVE THERAPY - *Consider if symptoms persist after maximum dose of buprenorphine given*	
General withdrawal symptoms	Clonidine 0.1 mg PO Q4H PRN (hold for SBP < 90 mmHg) (Max total dose=0.3 mg)
Nausea and vomiting	Ondansetron 4 mg ODT/IV Q4H PRN
Diarrhea	Loperamide 4 mg PO, then 2 mg PO Q2H PRN (max total dose = 8 mg)
Myalgias and arthralgias	Ibuprofen 600 mg PO Q6H PRN

Buprenorphine Microdosing – Bernese Method

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

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

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

Table 3. Protocol Use in Patient 2

Protocol day	Buprenorphine total daily dose, mg	Methadone total daily dose, mg	Maximum pain score, 0–10
0	0	100	7
1	1.0	100	8
2	1.5	100	6
3	3	100	8
4	6	100	7
5	8	100	8
6	8	100	8
7	12	100	6
8	16	0	6
9	16	0	8
10	20	0	8
11	24	0	6

Terasaki, et al. *Pharmacotherapy*. 2019 Oct;39(10):1023-29.
Randhawa, et al. *CMAJ*. 2020 Jan 20;192(3):E73.

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Summary

- Overdose rates continue to rise in spite of MOUD and Naloxone
- Fentanyl is being mixed with many other drugs and has almost completely replaced heroin
- Buprenorphine is a safe and effective drug with a ceiling effect on respiratory depression and the euphoric effects.
- There are three drugs known to precipitate withdrawal . They include Naloxone, Naltrexone and Buprenorphine
- Many ED's now begin buprenorphine treatment while in the ER and use a macro dosing technique with success.
- Significant precipitated withdrawal with buprenorphine only happens in < 1% of patients in spite of chronic fentanyl use.
- Treatment of precipitated withdrawal often involves ***using more buprenorphine or waiting 24 hours and reattempt induction*** . Clonidine, an antiemetic, APAP, Benzo, Lomotil etc., can also be used.

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Please feel free to reach out !! Anytime

THANK YOU
for your
ATTENTION!

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. SAMHSA quick start guide
2. ED INNOVATION TRIAL_JAMA