Mass General Brigham

Updates in Opioid Use Disorder Treatment

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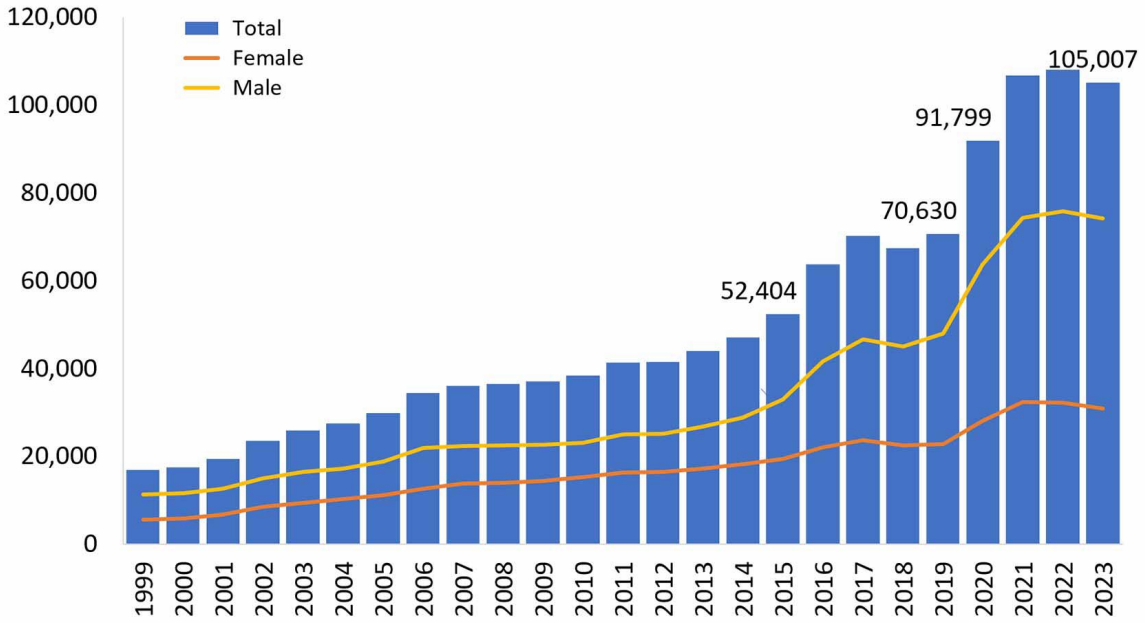
Objectives

Review	Evolution of the overdose crisis and opioid drug supply
Describe	The evidence for opioid use disorder (OUD) treatment
Detail	Innovative approaches for starting medications for OUD

The Overdose Crisis in the United States

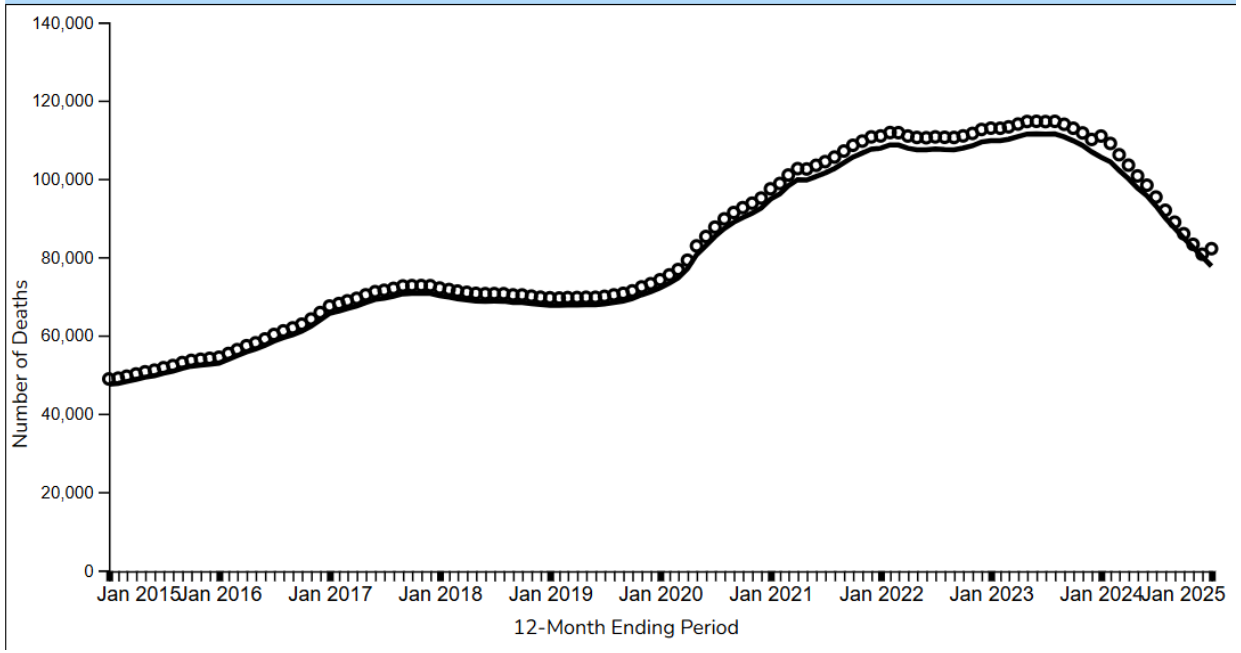
Figure 1. U.S. Overdose Deaths* by Sex, 1999-2023



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2023 on CDC WONDER Online Database, released 1/2025.

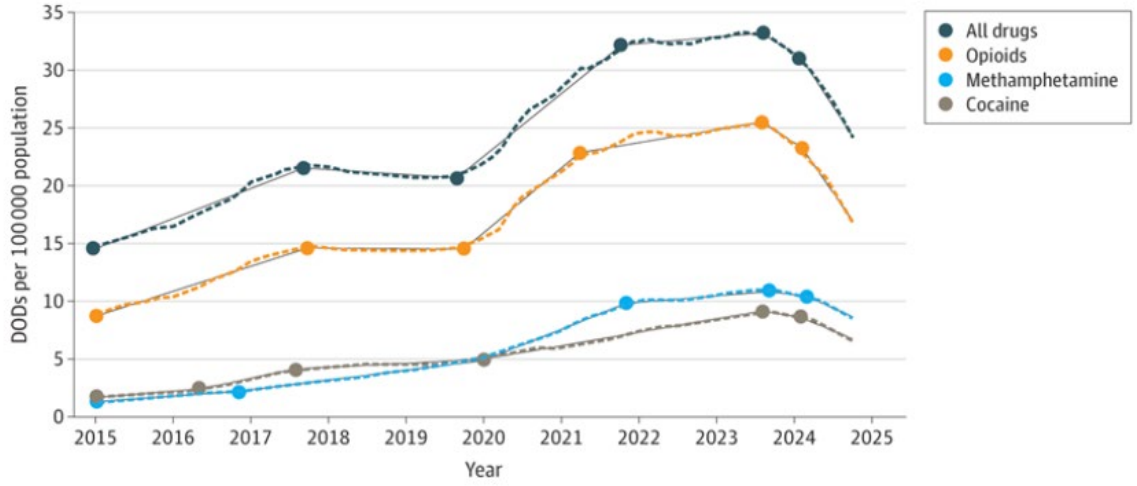
Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



Declining overdose trends

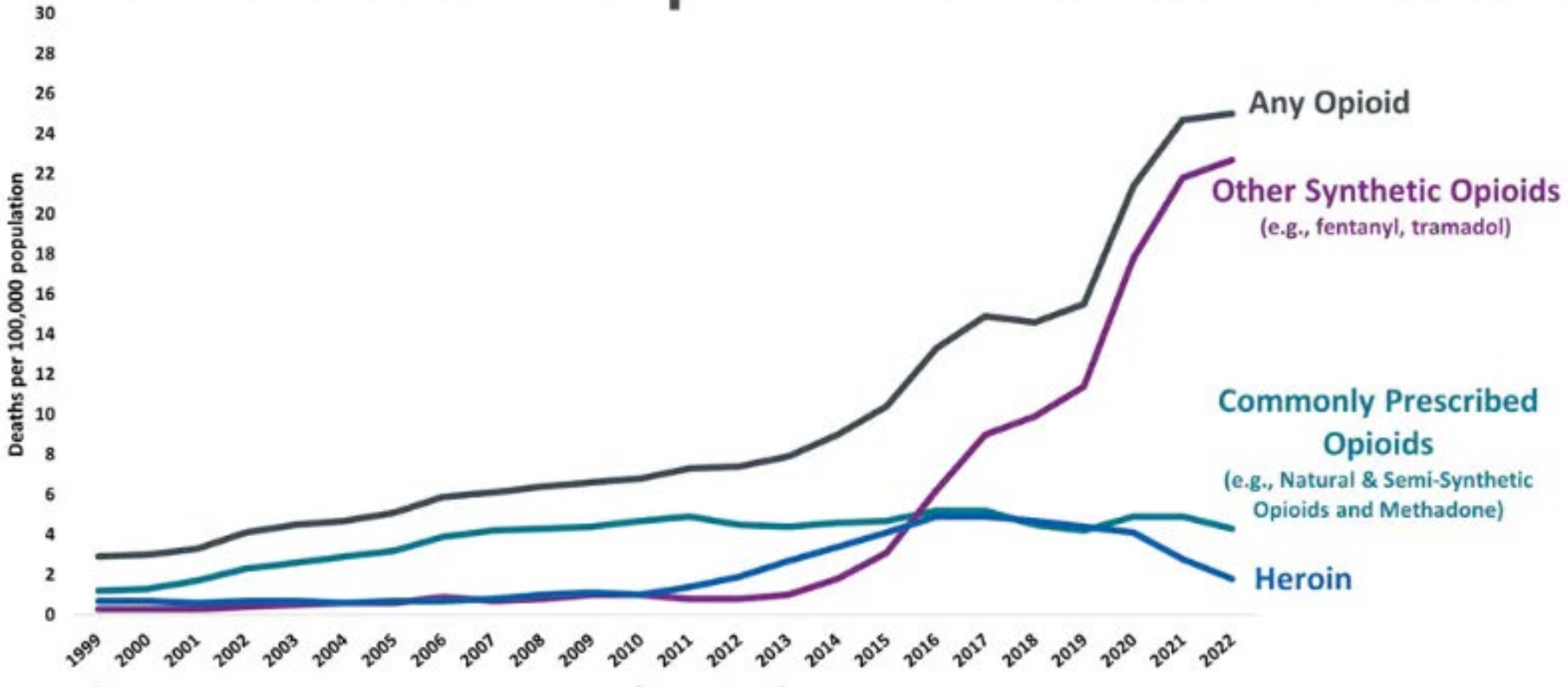
- 800,645 US residents died from drug overdose between 2015-2024
- National drug overdose death rates peaked in August 2023 and began declining thereafter
- However, by late 2023, deaths were continuing to accelerate among older individuals, American Indian/Alaska Native, Black, Latino, and multiracial individuals

Figure 1. Joinpoint Analysis of Drug Overdose Death (DOD) Rates



Post et al. Decline in US drug overdose deaths by region, substance and demographics. JAMA 2025;8;(6):e2514997

Three Waves of Opioid Overdose Deaths



Wave 1: Rise in Prescription Opioid Overdose Deaths Started in the 1990s

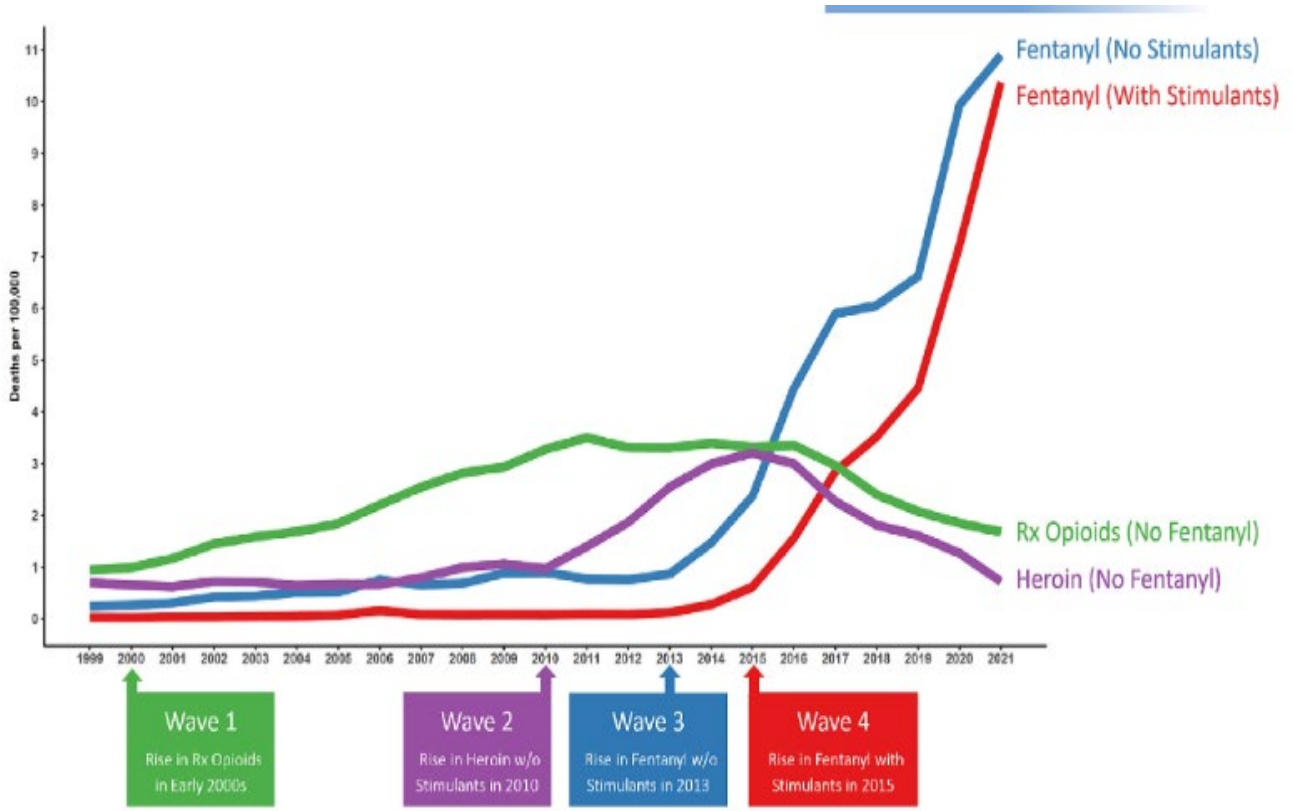
Wave 2: Rise in Heroin Overdose Deaths Started in 2010

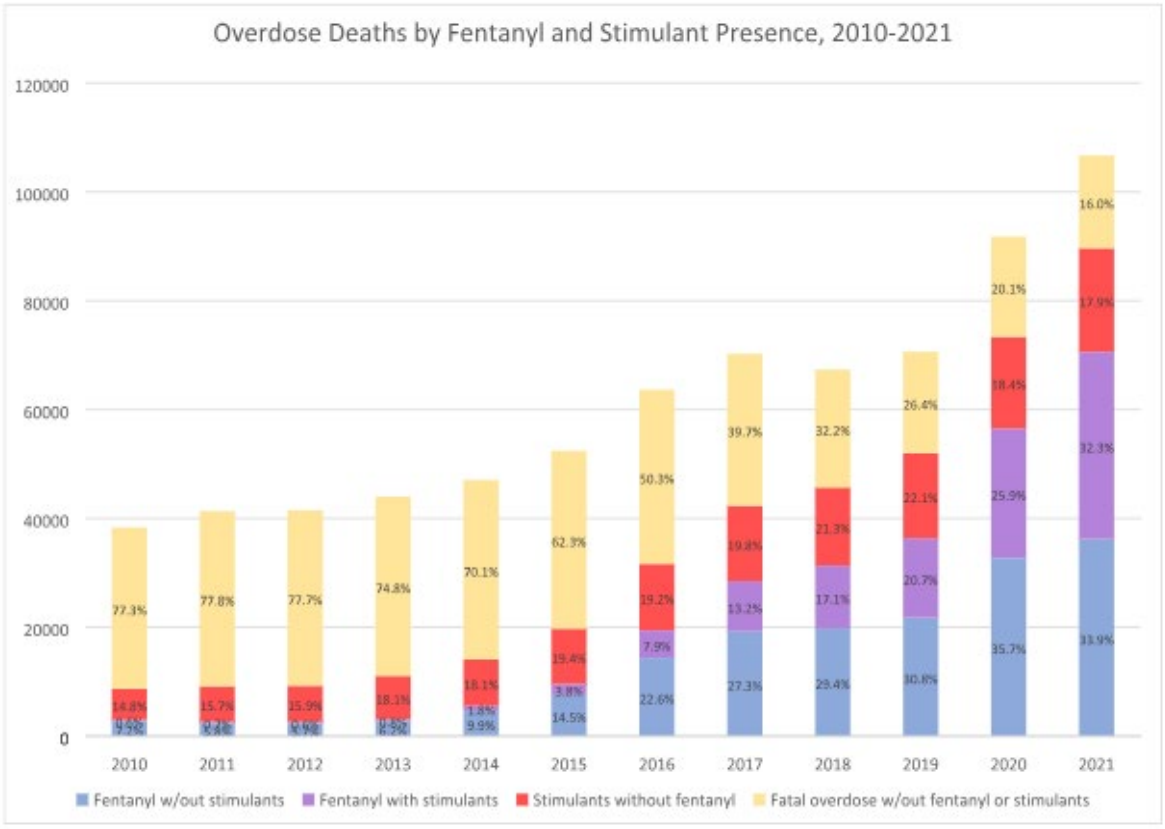
Wave 3: Rise in Synthetic Opioid Overdose Deaths Started in 2013

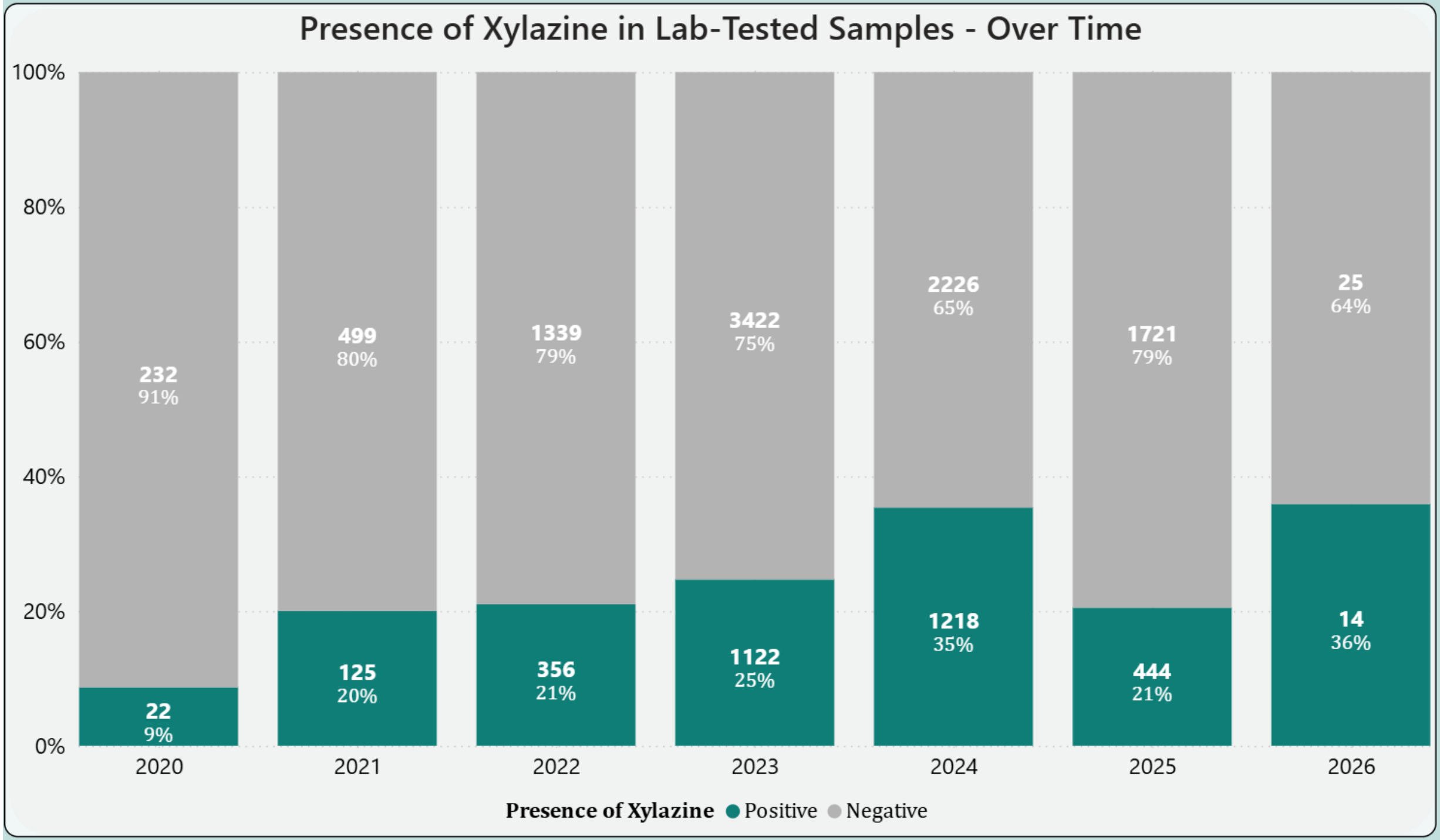
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2024. https://wonder.cdc.gov/.

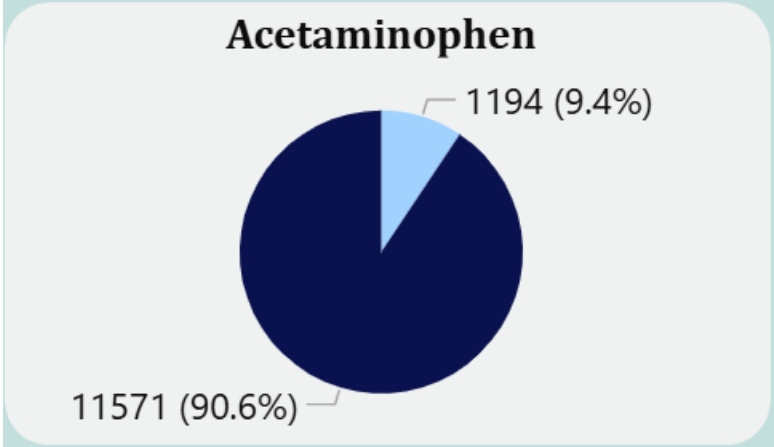
CDC

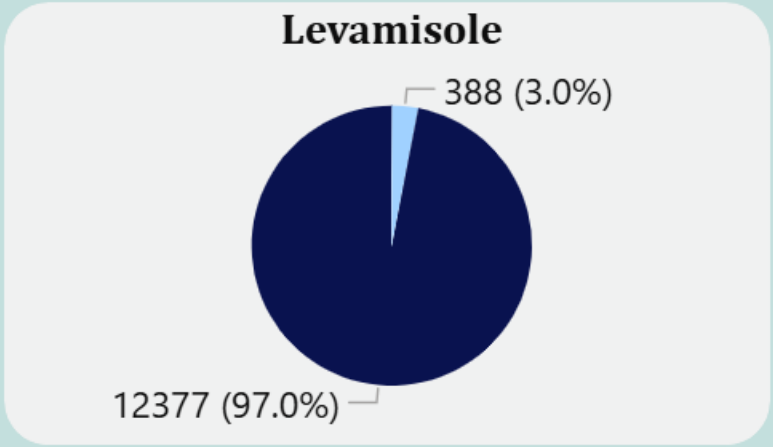
Rising rates of stimulant involved overdose deaths

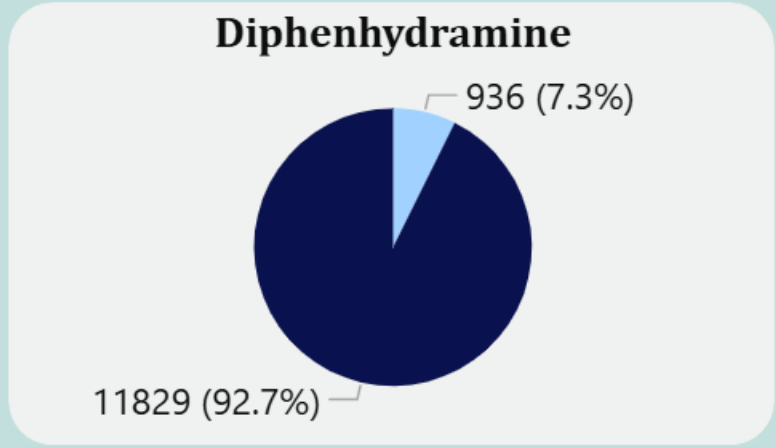


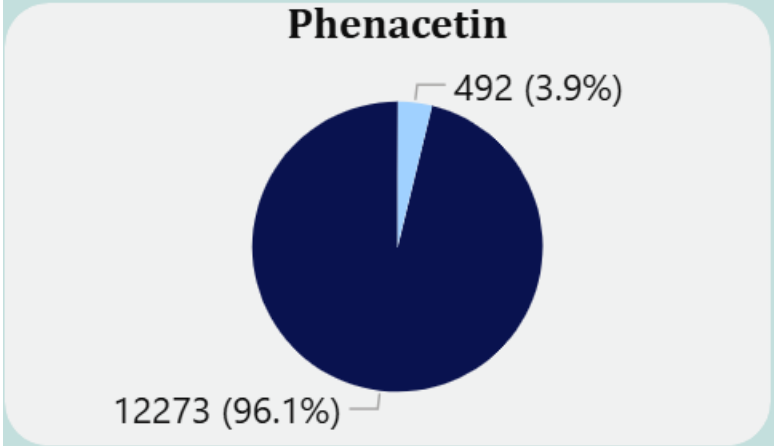


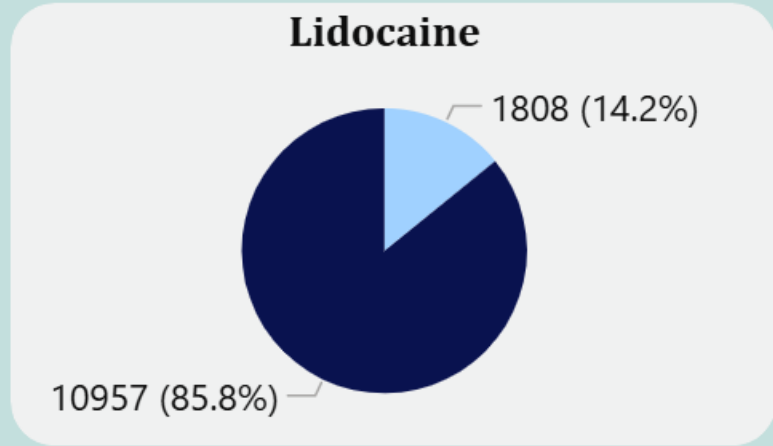

Presence of Xylazine in Lab-Tested Samples - Over Time
100%
80%
60%
40%
20%
0%
232
91%
22
9%
499
80%
125
20%
1339
79%
356
21%
3422
75%
1122
25%
2226
65%
1218
35%
1721
79%
444
21%
25
64%
14
36%
2020
2021
2022
2023
2024
2025
2026
Presence of Xylazine
Positive
Negative

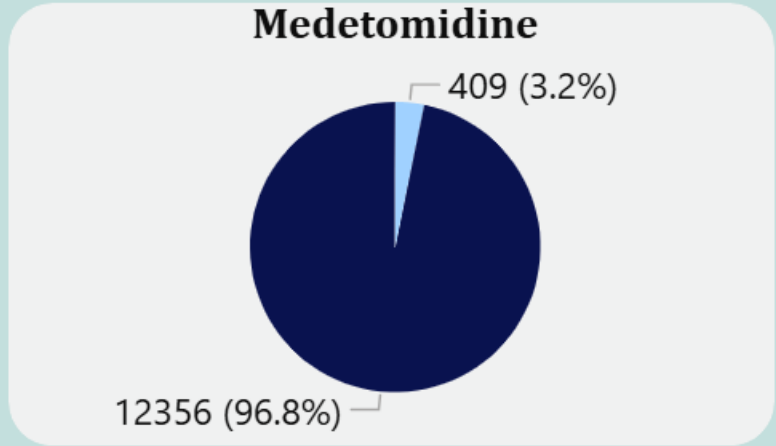

Acetaminophen
1194 (9.4%)
11571 (90.6%)

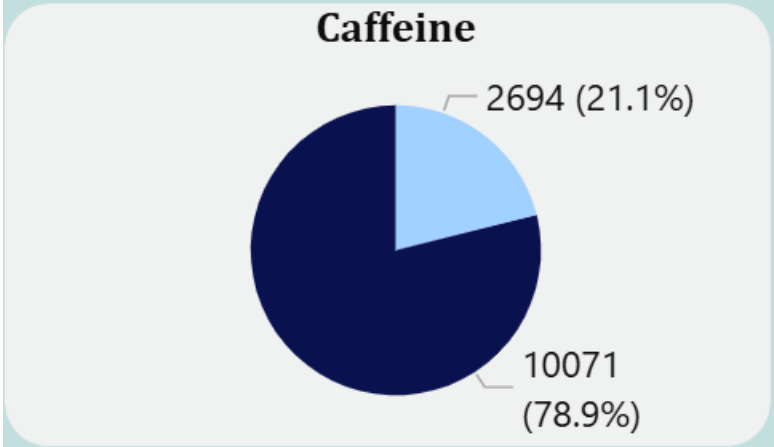

Levamisole
388 (3.0%)
12377 (97.0%)

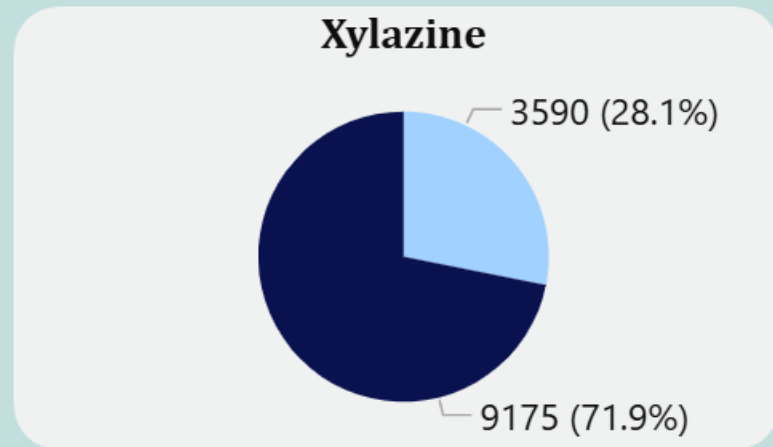

Diphenhydramine
936 (7.3%)
11829 (92.7%)

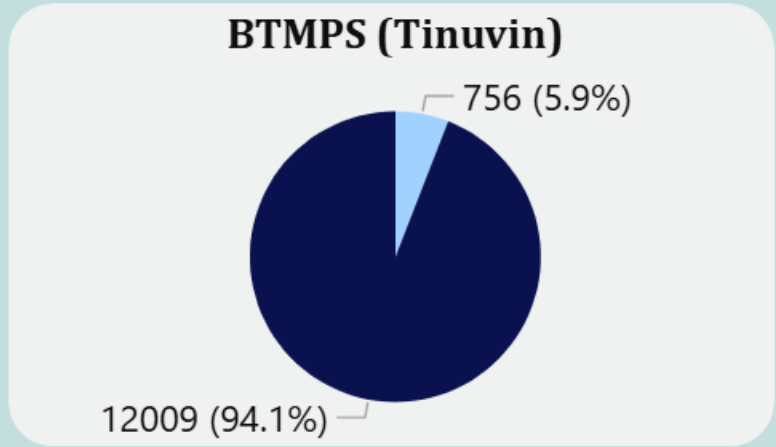

Phenacetin
492 (3.9%)
12273 (96.1%)


Lidocaine
1808 (14.2%)
10957 (85.8%)


Medetomidine
409 (3.2%)
12356 (96.8%)

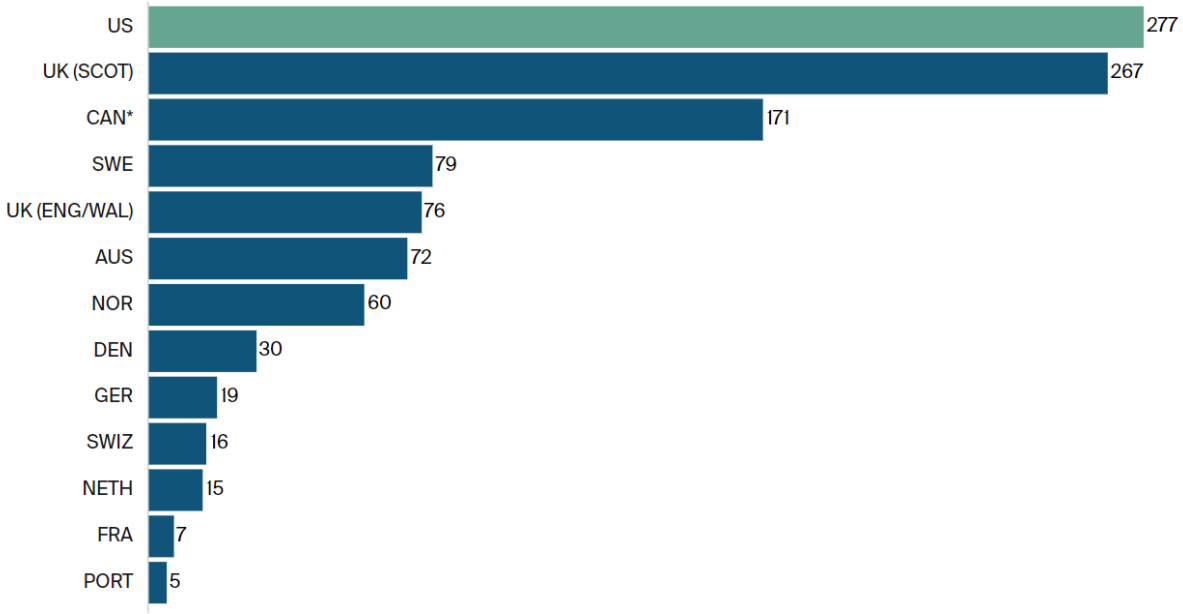

Caffeine
2694 (21.1%)
10071
(78.9%)


Xylazine
3590 (28.1%)
9175 (71.9%)

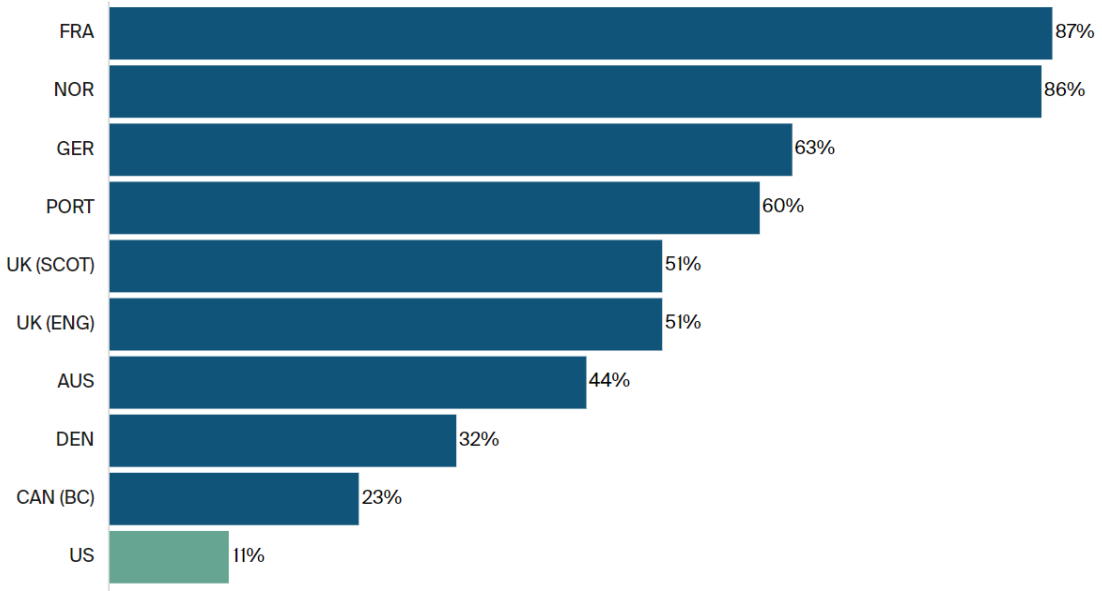

BTMPS (Tinuvin)
756 (5.9%)
12009 (94.1%)

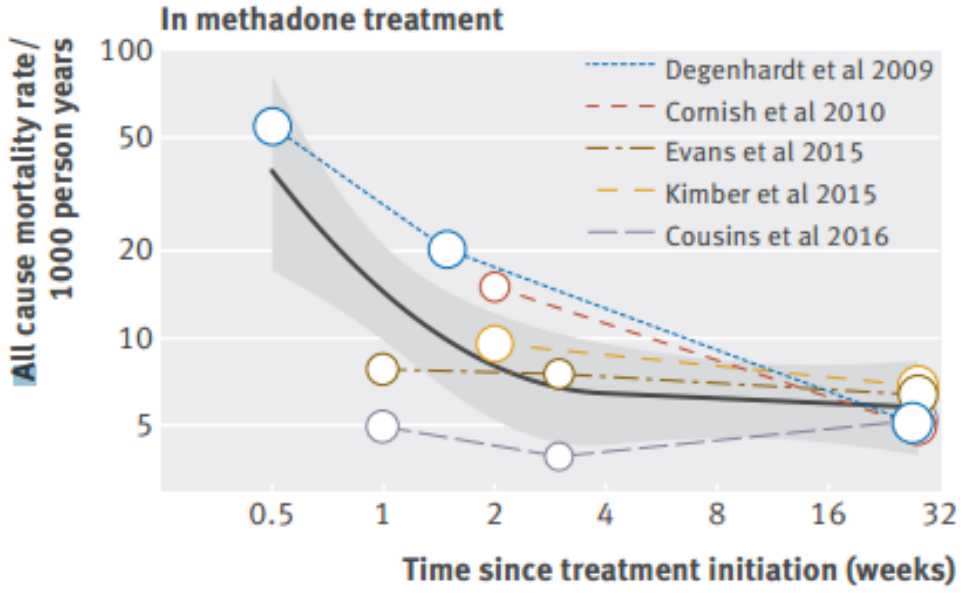
US leads the globe in overdose deaths, yet treatment gaps persist

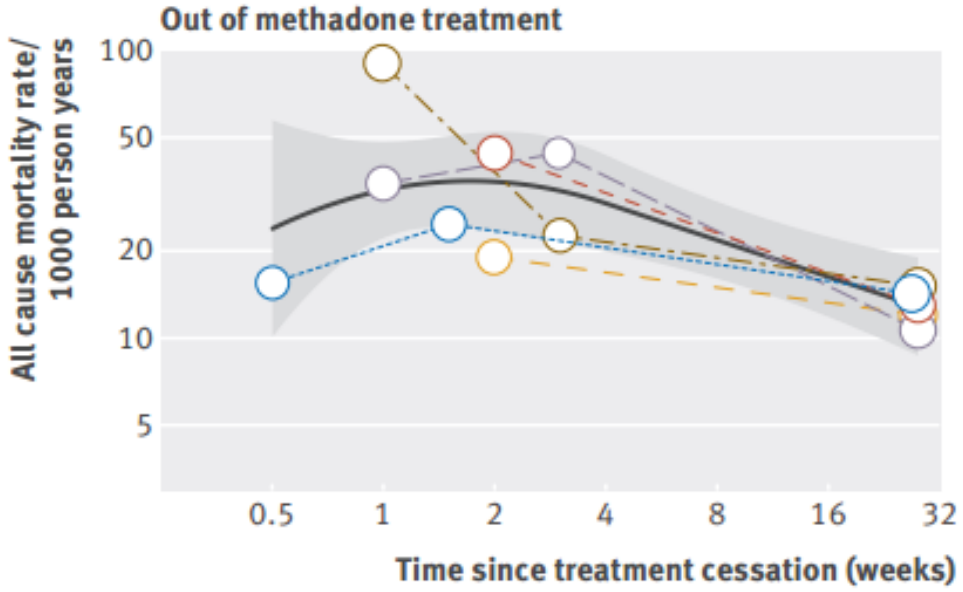
Overdose or drug-related death rate per 1 million population (unadjusted), 2020 or latest year available



Percentage of people with high-risk opioid use or opioid use disorder (OUD) who received opioid-substitution treatment







Methadone and buprenorphine reduce mortality

All cause **mortality rates (per 1000 person years):**

- In methadone treatment: 11.3
- Out of methadone treatment: 36.1

- In buprenorphine treatment: 4.3
- Out of buprenorphine treatment: 9.5

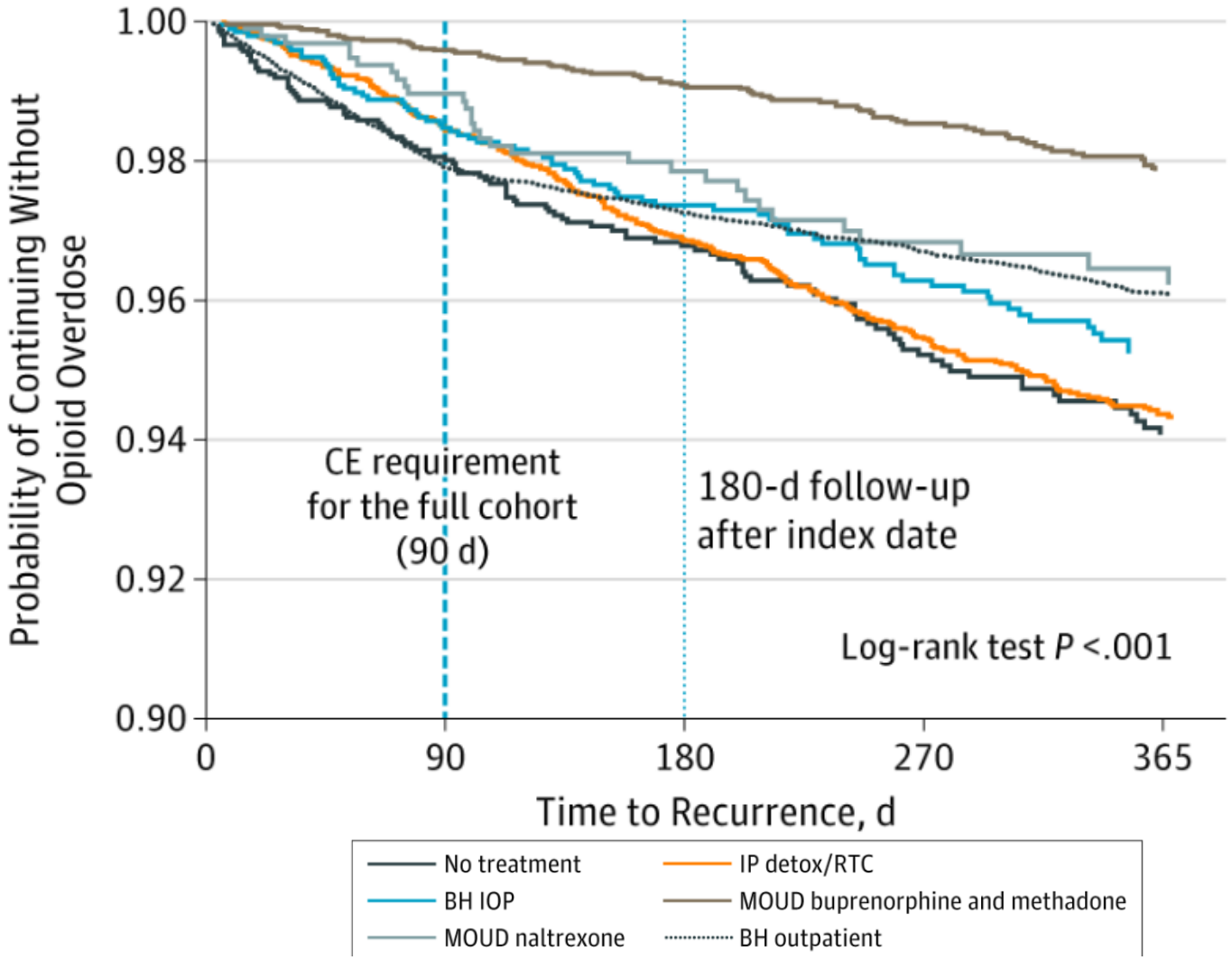
Overdose **mortality rates:**

- In methadone treatment: 2.6
- Out of methadone treatment: 12.7

- In buprenorphine treatment: 1.4
- Out of buprenorphine treatment: 4.6

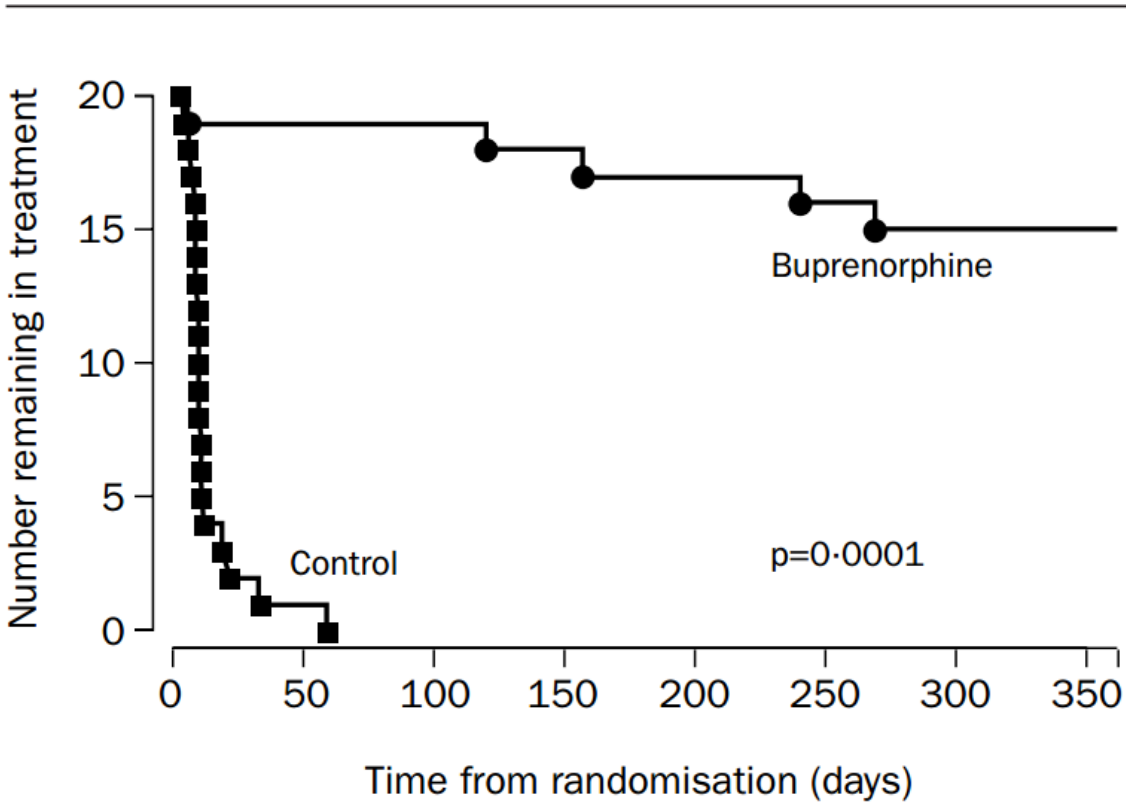
Sordo L, Barrio G, Bravo MJ, et al. *BMJ*. 2017;357:j1550. Published 2017 Apr 26.

Methadone & buprenorphine associated w/ reduced OD



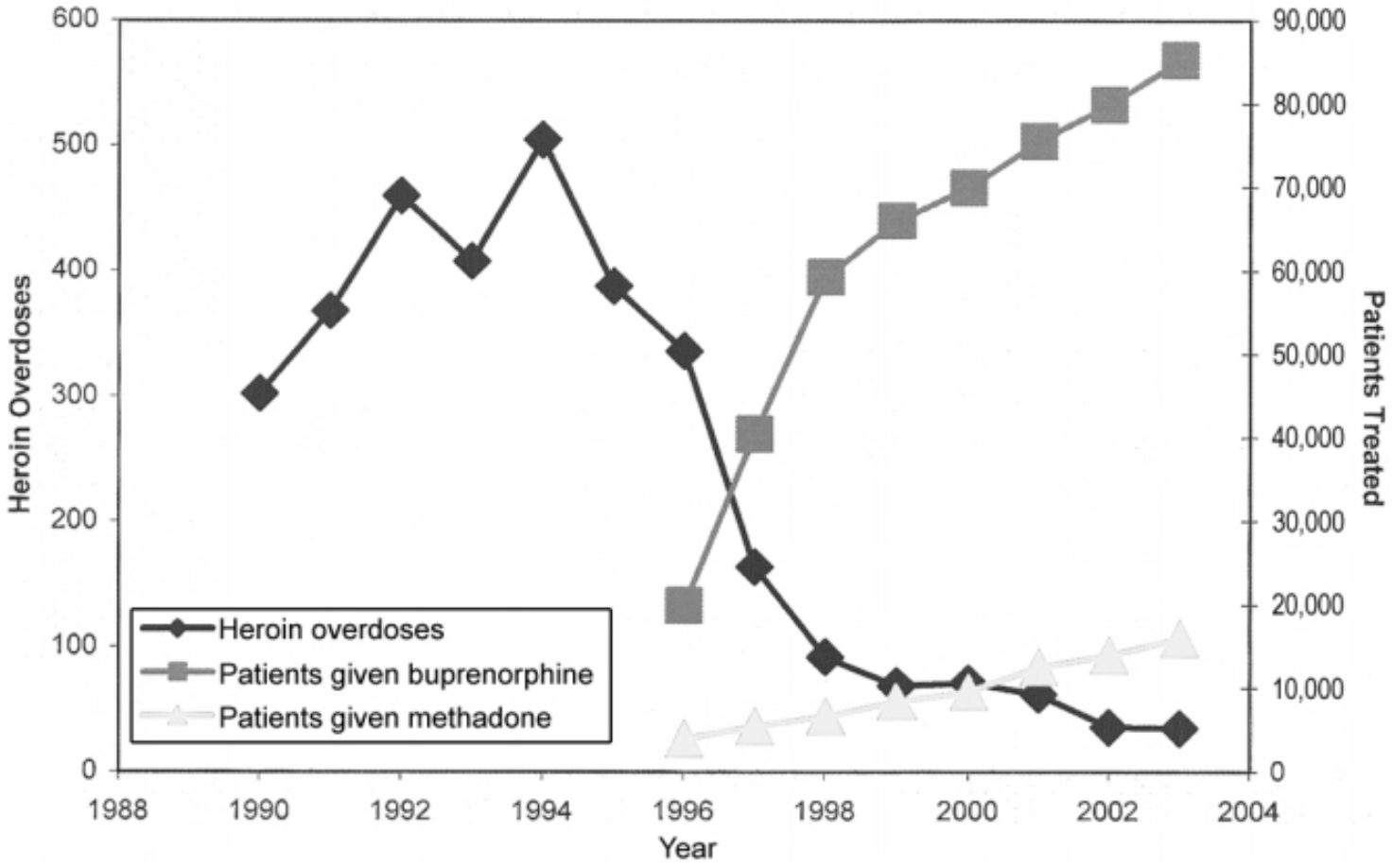
Wakeman SE, Larochelle MR, Ameli O, et al. *JAMA Netw Open.* 2020;3(2):e1920622.

Buprenorphine treatment outcomes superior to withdrawal management plus psychosocial treatment



Kakko et al. The Lancet, Volume 361, Issue 9358, 2003, 662 - 668

Expansion of access to opioid agonist therapy saves lives



- France expanded access to buprenorphine
- No required physician training, no patient limits, no toxicology or counseling requirements
- ~90,000 pts treated w/ buprenorphine, 10,000 w/ methadone
- 5-fold reduction in heroin overdose deaths, 6-fold reduction in active IDU, HIV prevalence among PWID decreased from 40% to 20%

Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. *Clin Infect Dis*. 2006;43 Suppl 4:S197–S215. doi:10.1086/508184

Most treated patients achieve remission over time

Table 2.

Change in clinical characteristics from study entry to follow-up 18, 30, and 42 months later.

Participant characteristics	Month 0[1] (*n* = 338)	Month 18 (*n* = 252)	Month 30 (*n* = 312)	Month 42 (*n* = 306)
Substance use, past month				
Current opioid dependence[2], %**	100	16.3[a]	11.5	7.8[b]
Abstinent from illicit opioids[3], %***	0	51.2[a]	63.5[b]	61.4[b]
Opioid agonist treatment, %	0	31.8	38.1	36.9

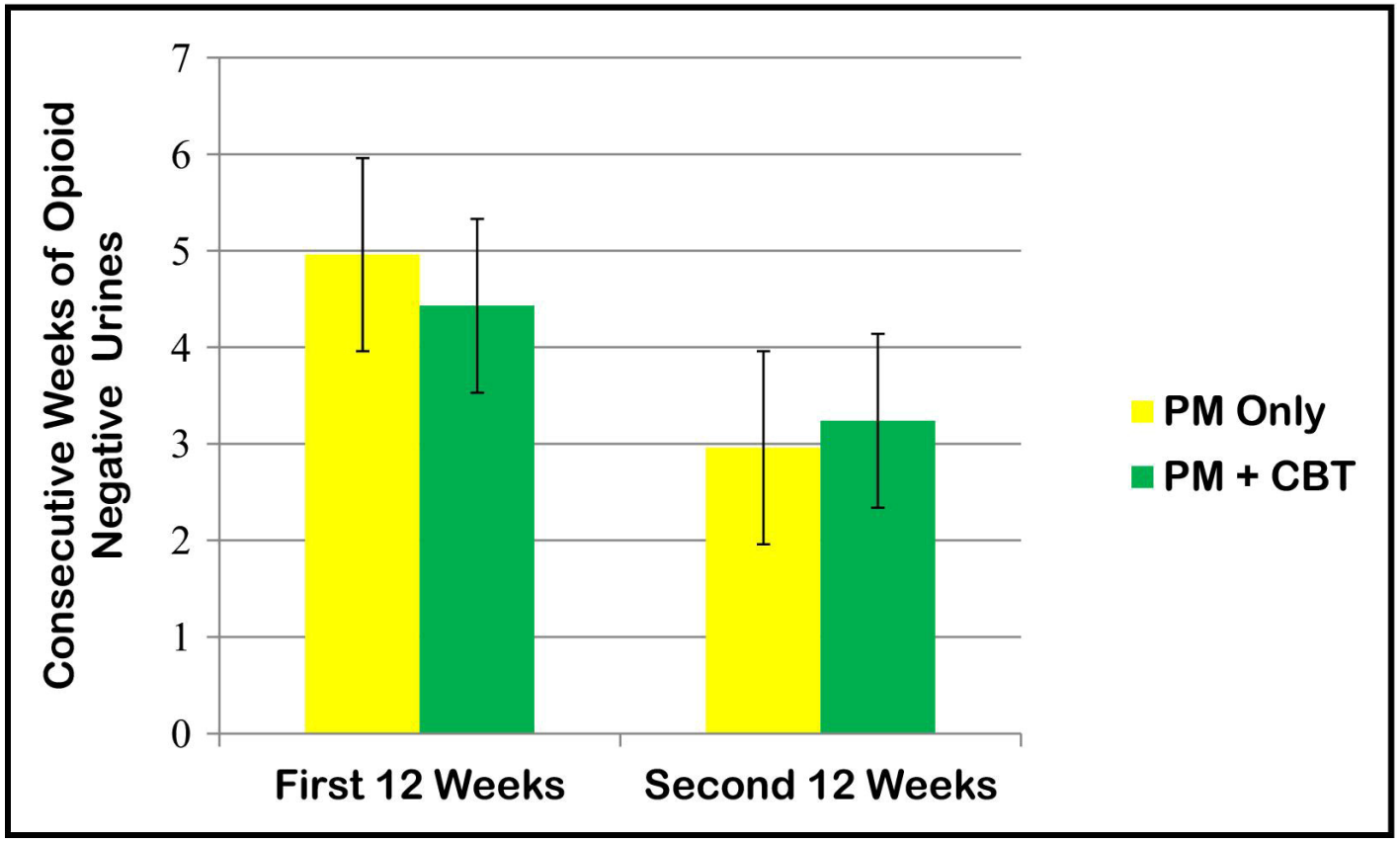
Weiss et al. Drug Alc Depend. 2015;150:112-9.

Using healthcare touchpoints as reachable moments

- Initiating methadone in hospital:
  - 82% present for follow-up addiction care
- Initiating buprenorphine in hospital vs withdrawal management alone:
  - Buprenorphine: 72.2% enter treatment after discharge
  - Withdrawal management : 11.9% enter treatment after discharge
- Initiating buprenorphine in ED vs referral to treatment
  - 78% vs 37% engaged in buprenorphine treatment at 30 days
  - Fewer days of opioid use w/ buprenorphine tx

J Gen Intern Med. Aug 2010; 25(8): 803–808; JAMA Intern Med 2014 Aug;174(8):1369-76.); D'Onofrio et al. JAMA 2015 Apr 28;313(16):1636-44

Treatment effective in primary care

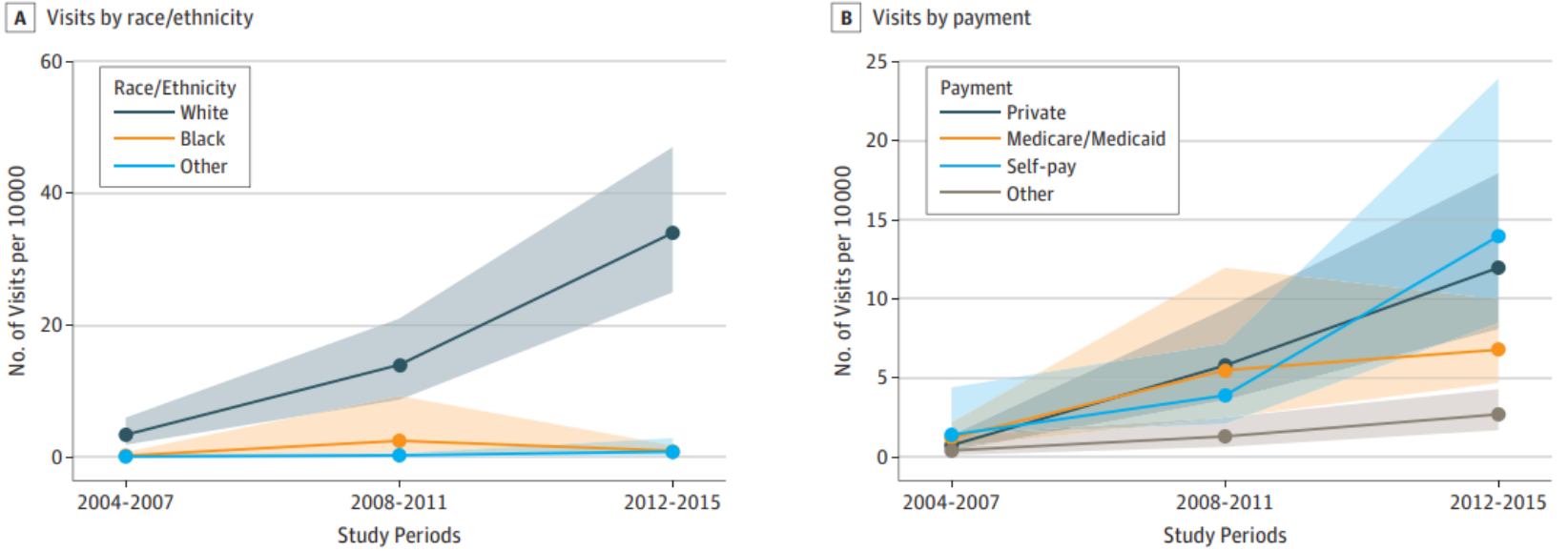


No difference in opioid use, study completion, or cocaine use between the 2 groups

Fiellin DA et al. Am J Med 126:1 2013

Inequities in MOUD treatment access

Figure. Buprenorphine Visits by Race/Ethnicity and Payment Type, 2004-2015



Buprenorphine visits (n = 1369) and 95% CIs per 10 000 visits (shaded areas), grouped by year and stratified by race/ethnicity and payment type. Estimates account for complex survey design elements and are nationally representative.

NASEM Consensus Report

Conclusion 6:
Medication-based treatment is effective across all treatment settings studied to date. Withholding or failing to have available all classes of U.S. Food and Drug Administration–approved medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment.

Treatment with FDA-approved medications is clearly effective in a broader range of care settings (e.g., office-based care settings, acute care, and criminal justice settings) than is currently the norm. There is no scientific evidence that justifies withholding medications from OUD patients in any setting or denying social services (e.g., housing, income supports) to individuals on medication for OUD. Therefore, to withhold treatment or deny services under these circumstances is unethical.

Any DEA-registered Practitioner Can Prescribe!

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Substance Abuse and Mental Health Services Administration

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Medications for Substance Use Disorders

Removal of DATA Waiver Requirement

Medications, Counseling, and Related Conditions

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Provider Support Services

Pharmacist Verification of

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. SAMHSA and DEA are actively working on implementation of a separate provision of the Omnibus related to training requirements for DEA registration that becomes effective in June 2023. Please continue to check this webpage for further updates and guidance.

What does the care cascade look like?

Identify patients through screening or acute presentation

Make a diagnosis

Initiate treatment without delay

Retain patients in treatment

Similar to Management of Diabetes or HIV

- Goal to prevent acute and chronic complications
- Patient-centered and directed treatment plans and goals
- Treatment includes:
  - Medication
  - Behavioral support
  - Lifestyle changes
  - Regular monitoring

Goal of medication for OUD: buprenorphine& methadone

- Relieve: withdrawal symptoms
- Block: effects of other opioids
- Reduce: cravings
- Prevent: overdose

Details of Treatment

Agonist treatment: daily methadone, daily or XR buprenorphine

- Stable level of opioid effect experienced as feeling normal
- Anyone can prescribe buprenorphine
- Ongoing methadone treatment must be dispensed by opioid treatment program, can be initiated under 72 hour rule

The aims of agonist treatment include:

- Stop using or reduce opioids and associated risks
- Improvement in health, quality of life, functional status

Antagonist treatment consists of once monthly injection

- Anyone can prescribe naltrexone

Choice of medication

Patient preference and prior experience crucial

- Most effective medication is the one they will take!

Structure of OTPs can facilitate engagement for some patients and serve as a barrier for others

- *"I think I'd probably do better with methadone…If you were to give me a choice, if I could have outpatient methadone, that would be ideal. I just don't want to go there every single day to that place. I don't think it would actually work with my schedule…my job should be at the top of my list of importance."*

Naltrexone: Less effective than opioid agonist therapy for OUD for all comers.

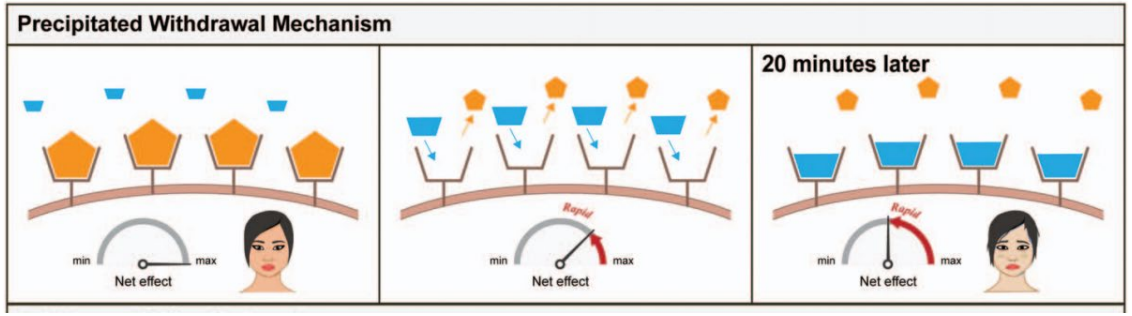
- For sub-group of patients able to complete withdrawal and start naltrexone, seems to be non-inferior

Special circumstances:

- Severe co-occurring pain: Possibly methadone, but growing experience with bupe for pain
- Pregnancy: bupe assoc w/ better neonatal outcomes, methadone better retention for mom
- Prolonged QTc: Buprenorphine

Understanding Buprenorphine

- Partial opioid agonist, ceiling effect for respiratory depression
- High affinity for opioid receptor, can displace full agonist opioids resulting in precipitated withdrawal
- Higher retention in treatment and abstinence rates seen w/ doses >16 mg
- At higher doses, likely as effective as methadone

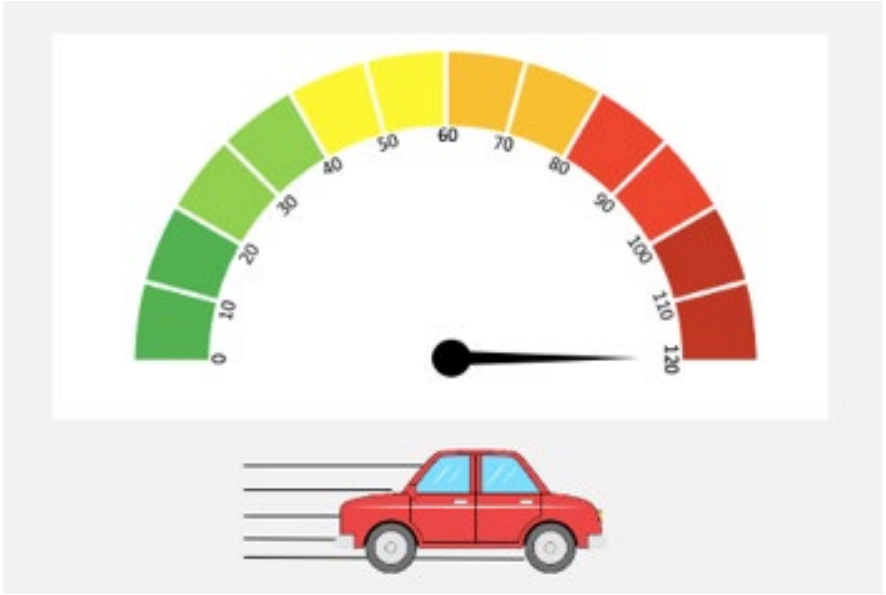


Buprenorphine initiation dosing for a patient in moderate withdrawal

- Day 1: Buprenorphine 8-16 mg Q 1H x 2 doses to a maximum of 32 mg on day 1
- Day 2: Buprenorphine 16-24 mg daily
- Counseling critical– must be objectively in withdrawal and not just anxious; signs not symptoms of withdrawal
- Low dose initiation or XR-bupe (DTI) are alternative approaches

Low dose Initiation

- Some patients using fentanyl seem to experience precipitated withdrawal even after protracted wait times
- May be due to lipophilicity and range of fentanyl analogs
- Actual rates in clinical trials quite low
- If person not able to wait to be in objective withdrawal, currently taking full agonist opioids and unable to stop, transitioning from methadone, or using fentanyl with a history of precipitated withdrawal, may consider low dose initiation
- Uses small doses (~0.5 mg) to gradually saturate receptor
- Can be done rapidly q3H or over days
- **Fear of precipitated withdrawal should not keep us from starting buprenorphine!**



Initiating buprenorphine

Initiation for patients in withdrawal or able to tolerate objective withdrawal

Day 1: buprenorphine 8-16mg Q1H x 2 up to max dose of 32 mg

Prescribe Buprenorphine/naloxone 8mg/2mg TID x 3-7 days and follow-up in primary care or refer to Bridge Clinic

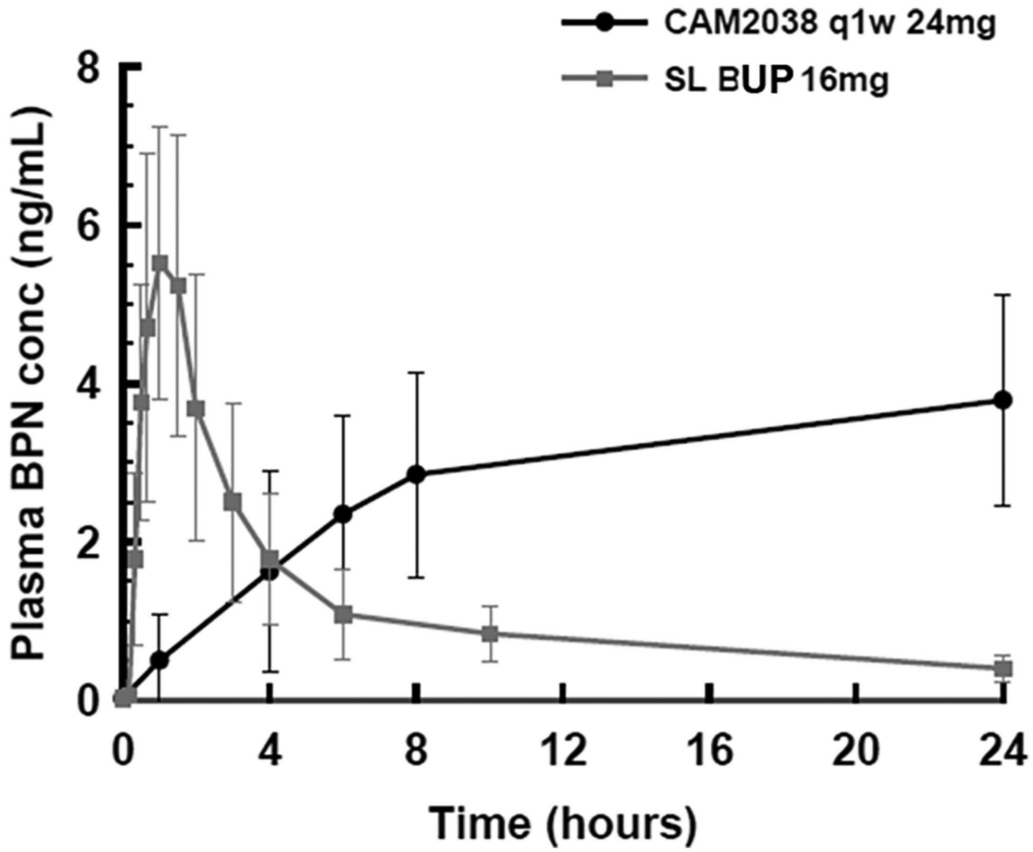
Initiation for patients not able to tolerate withdrawal or currently continuing full opioid

Start buprenorphine at 0.5 mg and increase dose as quickly as QID, or slower based on patient preference

Continue full agonist until patient gets to TDD of 8mg

What about direct to inject (DTI)? Understanding pharmacokinetics of weekly XRB

- SL buprenorphine has rapid absorption, but low oral bioavailability; reaches peak in 60 min
- After 24 mg weekly SC injection, plasma concentrations are therapeutic between 6-8 hours, peak usually within 20 hours.
- Terminal half-life is between 70 and 107 hours
- Slower rise in blood plasma level with weekly formulation makes it a possible agent for low-dose initiation (as opposed to monthly)



D'Onofrio G, Perrone J, Hawk KF, Cowan E, McCormack R, Coupet E Jr, Owens PH, Martel SH, Huntley K, Walsh SL, Lofwall MR, Herring A; ED-INNOVATION Investigators. Early emergency department experience with 7-day extended-release injectable buprenorphine for opioid use disorder. Acad Emerg Med. 2023 Dec;30(12):1264-1271. doi: 10.1111/acem.14782. Epub 2023 Aug 22. PMID: 37501652; PMCID: PMC10822018.

Initiating weekly XRB in the ED

- Multisite study aiming to rapidly expand access to ED-initiated BUP across 28 diverse EDs in the US (mix of geography, urban/suburban, and academic/community)
- Patients with COWS 4+ given 24 mg SC injection, observed for 2 H, and discharged (no rescue doses or supplemental SL) w/ follow-up in 7 days
- Very low rates (>0.5%) of precipitated withdrawal
- Subsequent trial started 24 mg SC in patients with COWS scores ranging from 0-7 and found that 93% of patients tolerated initiation without precipitated withdrawal and 73% were engaged in OUD treatment after 7 days.
- The rate of precipitated withdrawal was lowest among people with a COWS score of 4-7 (3.2%). The rate of precipitated withdrawal was 13.5% for people who had a COWS of 0-3.

D'Onofrio et al.. Acad Emerg Med. 2023 Dec;30(12):1264-1271. .
D'Onofrio et al. JAMA Netw Open. 2024;7;(7):e2420702.

DTI in a low threshold setting

Table 1. Summary of the Injectable-Only Overlapping Buprenorphine Starting Protocol[a]

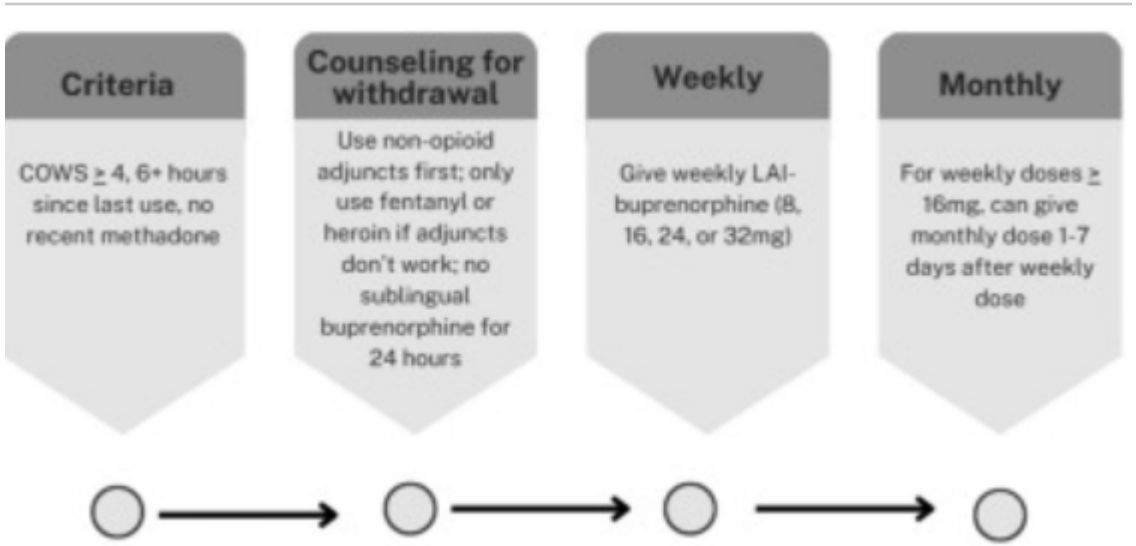
Day	Long-acting injectable buprenorphine administered	Guidance for delayed buprenorphine injections[b]
1	Weekly 8-mg injection	NA
2	Weekly 16-mg injection	Offer the weekly 16-mg injection up to 2 d after the initial 8-mg injection before restarting.
3	Monthly 128-mg or 300-mg injection	Offer the monthly injection up to 3 d after the 16-mg injection before repeating a 16-mg injection. Consider restarting the full protocol if 7 d have passed since the 16-mg injection.

- Recent retrospective evaluation of protocol for overlapping injectable-only buprenorphine initiation among 95 patients
- 75% completed the protocol and 64% received a second monthly long-acting injectable buprenorphine dose

Waters et al. JAMA Netw Open. 2025;8;(8):e2527016.

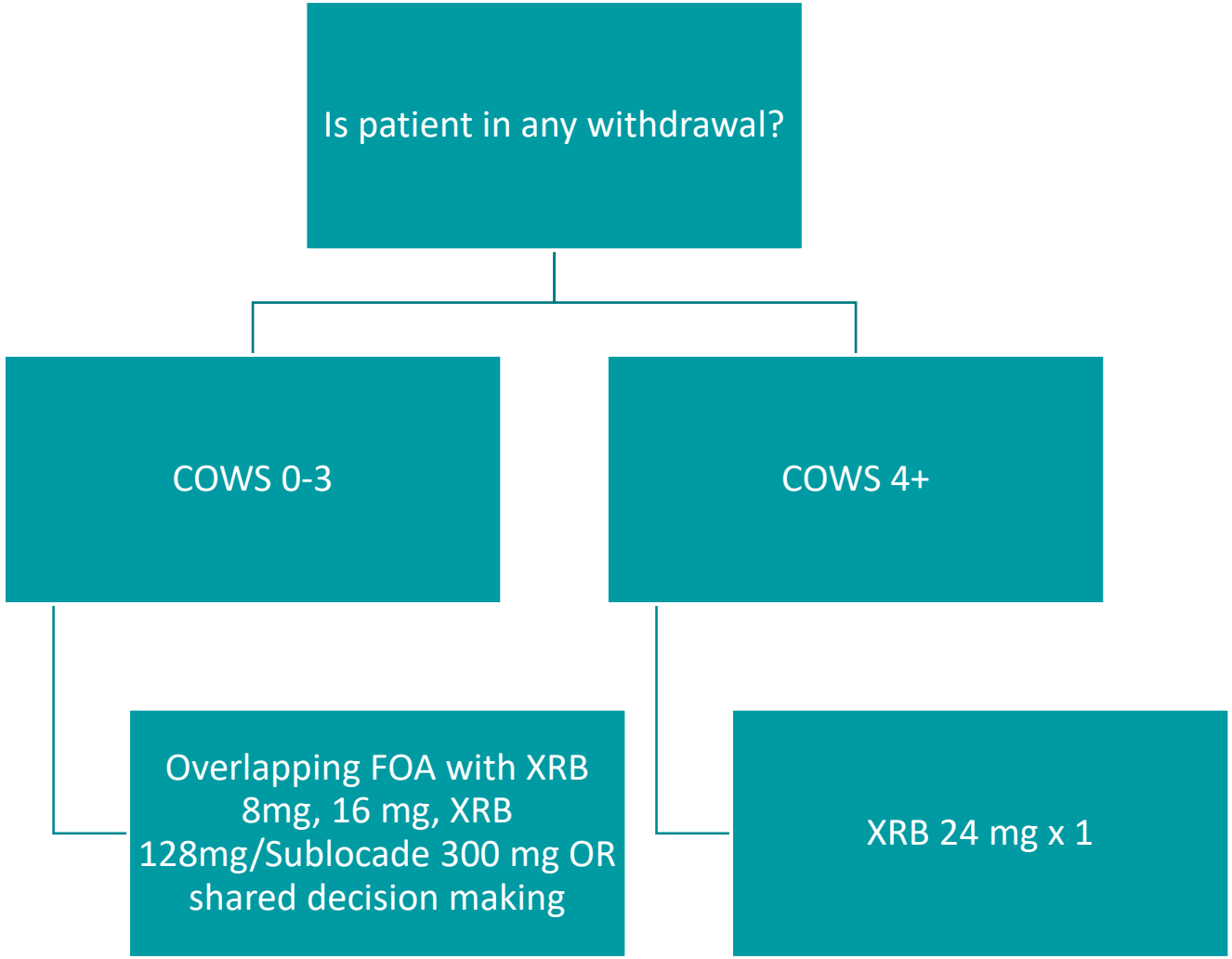
Outpatient initiation of DTI

- 131 DTI initiations among 114 patients
- 22 % received < 4 mg sublingual buprenorphine or transdermal buprenorphine patches
- 69 % at 7 days, 68 % at 30 days, 43 % at 90 days of DTI initiations resulted in continuous buprenorphine retention
- 68% experienced no or minimal withdrawal
- 11% experienced severe withdrawal defined as significant physical symptoms (including diarrhea or vomiting) or functional impairment requiring medical intervention
- 80 % of patients with “severe withdrawal” returned for a subsequent injection



Rosenwohl-Mack S, et al. Drug Alcohol Depend. 2026 Jan 1;278:113011..

Considerations for DTI



Innovations in methadone initiation: more rapid inpatient initiation and titration

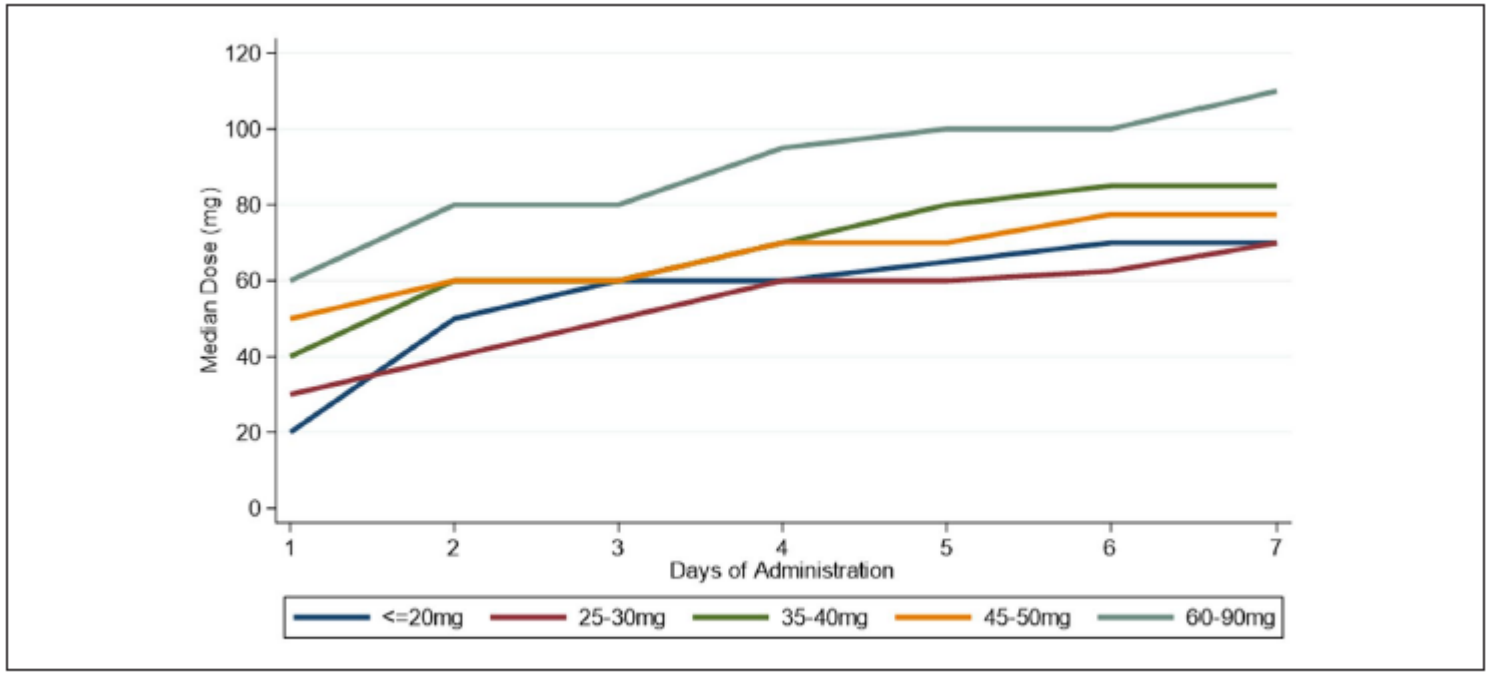
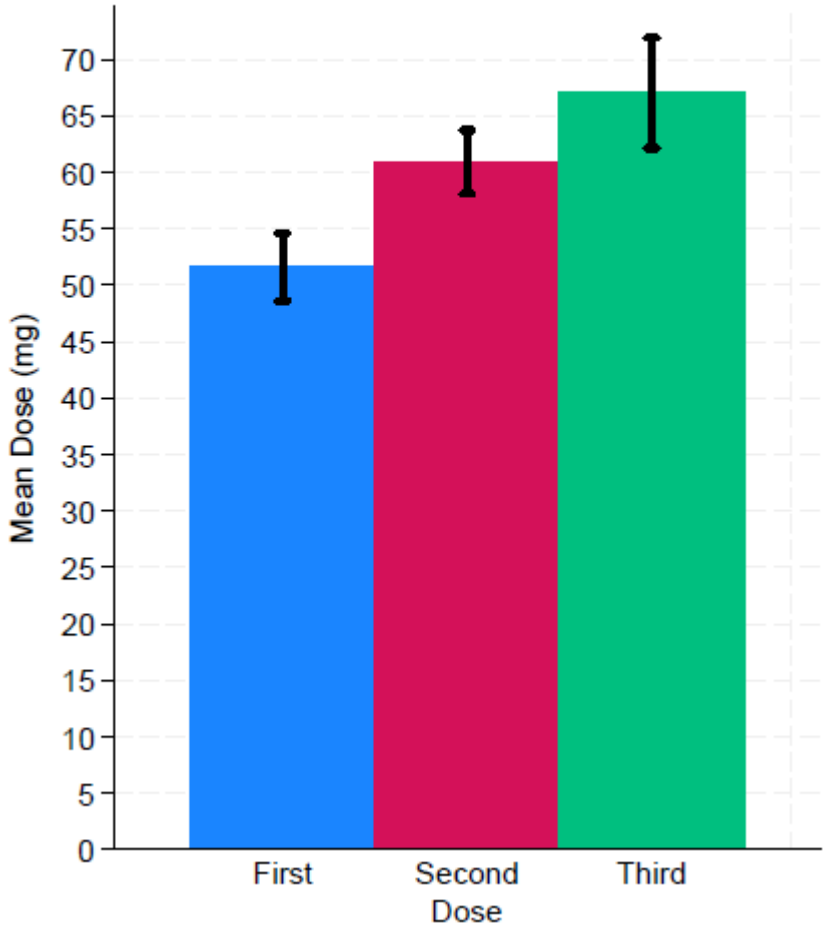


Figure 1. Rate of methadone increase on average with starting dose categories.

Rate of increase on average by starting dose range

72-hour methadone initiation in Bridge Clinics

Figure 1. Mean methadone dose administered



What about methadone sample protocols

ED/Inpatient

- Generally, start at 40-50 mg x 1 and then additional 10 mg PRN for ongoing signs of opioid withdrawal up to max of 90 mg
- Consolidate TDD next day, uptitrate by ~10 mg for ongoing cravings/withdrawal
- EKG prior to starting only if prolonged QTc or risk factors; check EKG again at 100 mg and for dose increases beyond 100 mg

Bridge Clinic/outpatient settings (72 hour)

- Generally, start at 50 mg unless low tolerance and increase by 10-20 mg per day for up to max of 3 days of dosing (and max final dose 80-90 mg without consultation from medical director)
- So example dosing regimen might be 50 mg day 1, 70 mg day 2, 80 mg day 3

Ongoing management of patients

Check in visits, frequently at first, space out as stabilize

Like any chronic care management:

- evaluate symptoms (cravings, withdrawal, use)
- benefits or challenges with medication
- need for additional support
- focus on patient identified goals

Patients don't fail treatment, but treatment can fail patients

If person not doing well, modify treatment

- Increase dose
- Increase supports
- If persistent challenges, explore changing meds
- Incorporate harm reduction

Structure & delivery of care crucial for retention

Patients fall out of care when they are not welcomed back:

- "You could only miss 14 days in a row…to stay on it. And I came back like the 15th day. So, they told me I was no longer eligible."

Patients report staff who "worked with" them and were "nice," "caring," & "respectful" offered support and encouragement were important factors in sticking with treatment:

- "They showed me that there's a light at the end of that tunnel. There's hope. You hear that? There's hope!"

Teruya C. J Psychoactive Drugs. 2014 Nov-Dec;46(5):412-26.

High threshold vs low threshold care

People with substance use disorder face numerous barriers to engage in services

Low-threshold care aims to reduce barriers ('thresholds') through less stringent eligibility criteria to broaden potential reach

Thresholds:

- 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

Bridge Clinics as an Example of Low Threshold Tx

"They [staff] treat you like you're a person, and trying to make your life better, and encourage that. And I [patient] think that's an awesome thing instead of not believing that you can even do it."

"…no one's [staff] going to judge you or give you a hard time. You'll [patients] find that everyone is really understanding. It's hard for me [patient] to open up, honestly…I keep everything to myself…but it's easy here…it's just nice to be able to talk about things."

"…it's nice to be able to just walk in somewhere [immediately post incarceration], and they [staff] are understanding, and accepting, and willing to help still."

"…and coming here [clinic], there was something redeeming about it. I [patient] felt safe. I felt warm. In fact, I felt nurtured, I think would be the best word."

Thank you!