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Management of Opioid Addiction

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- Clinical focus: Hospital-based treatment of addiction
- Research focus: Innovations in pharmacologic and behavioral treatments of opioid and alcohol use disorders including GLP-1 and psychedelic therapies

I have the following relevant financial conflicts of interest to disclose:

In-kind support from Braeburn to use medications for NIH-funded clinical trials

I have no other relevant financial disclosures.

Learning objectives

- *Describe the current state of the opioid crisis.*
- *Identify the approaches to treating opioid use disorder*
- *Understand novel buprenorphine initiation strategies*

Status of the opioid crisis in the US

Based on data available for analysis on: April 6, 2025

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

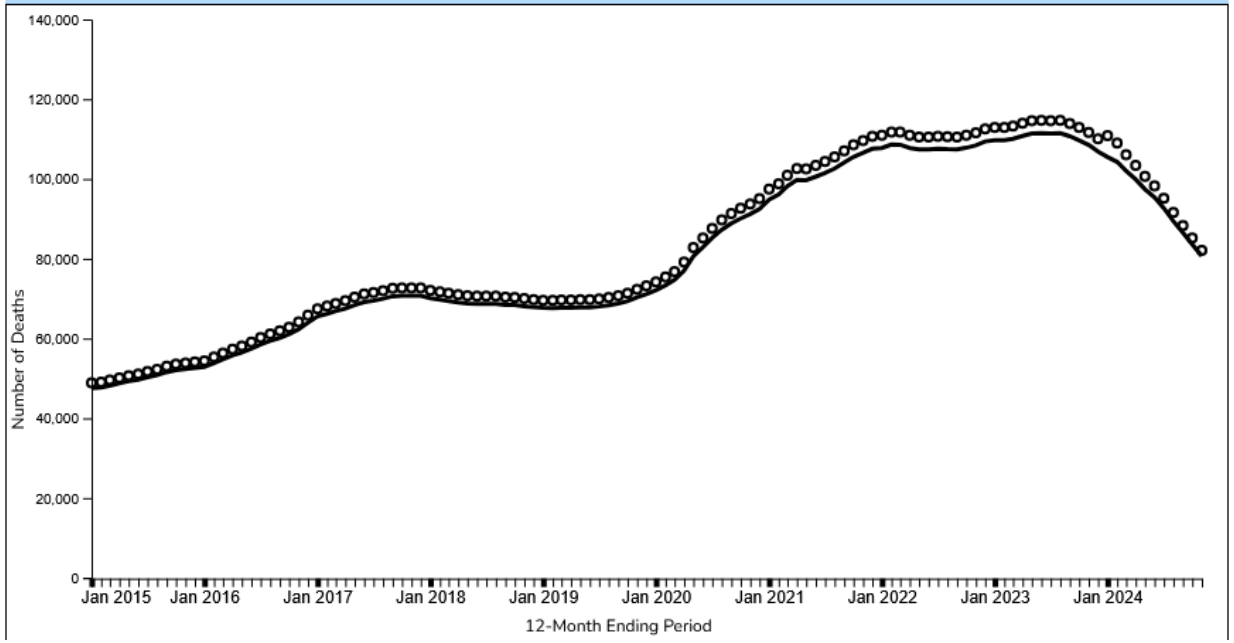
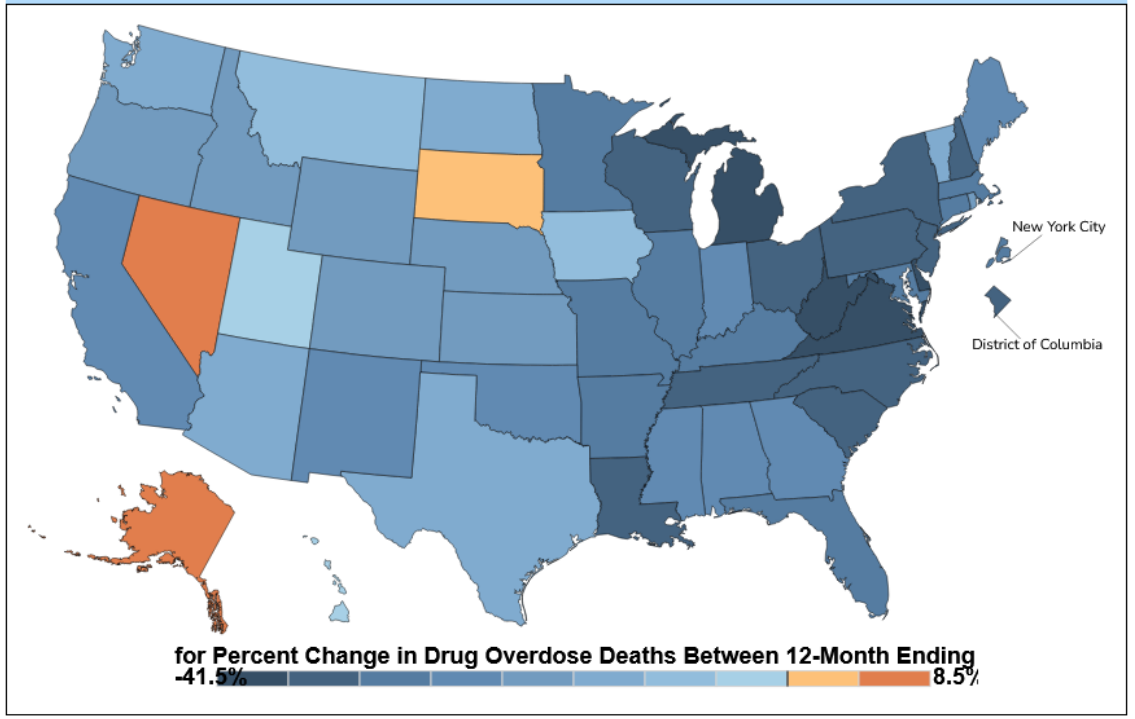
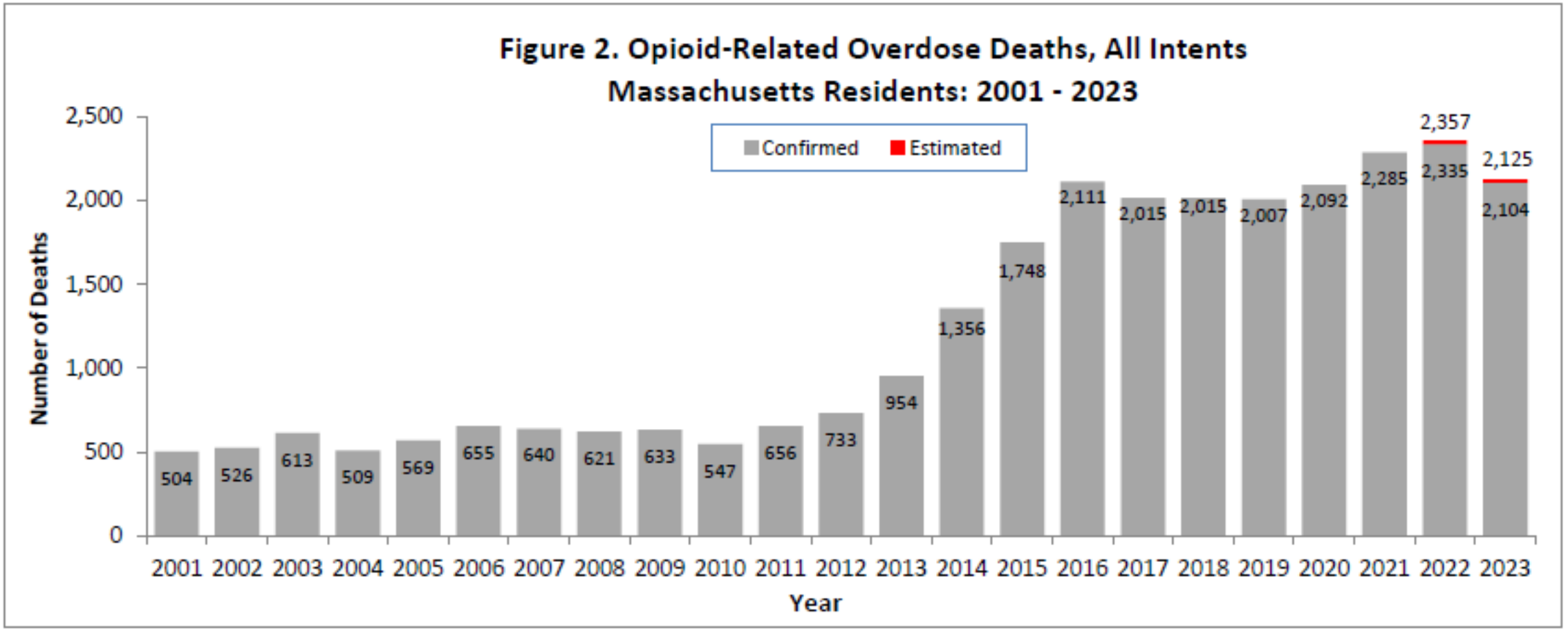


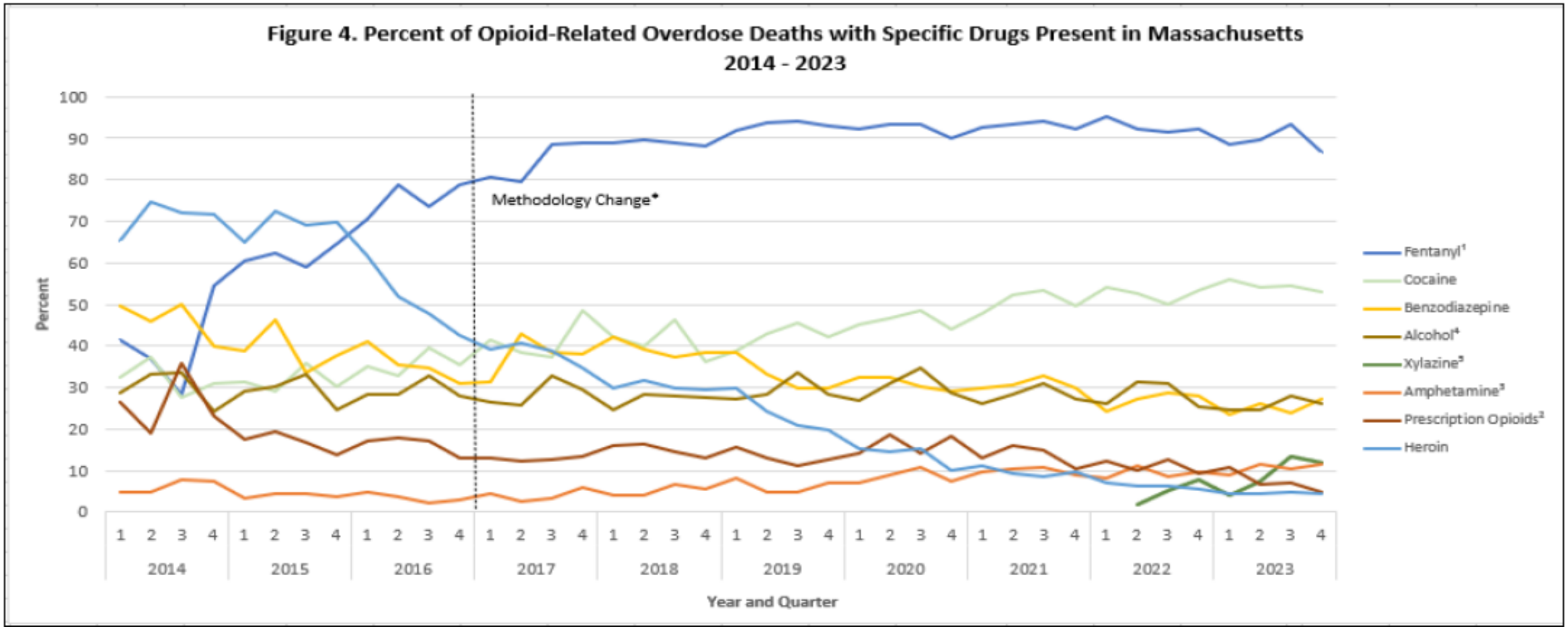
Figure 1b. Percent Change in Predicted 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: November 2023 to November 2024



Status of the opioid crisis in MA



Fentanyl continues to wreak havoc



Adulterants increasingly found in the opioid drug supply

- Street name “Tranq”, “Tranq dope”, “zombie drug”
- Xylazine an veterinary tranquilizer used for sedation or pain relief especially cats, likely being added as a cutting agent, but also adding to the psychoactivity of opioids
- Alpha-2 agonist, analog of clonidine → bradycardia and hypotension
- Can complicate opioid overdose resuscitation efforts because xylazine overdose is not responsive to naloxone
- Associated with disfiguring skin ulcers

Adulterants increasingly found in the opioid drug supply

Xylazine

- Street name “Tranq”, “Tranq dope”, “zombie drug”
- Veterinary sedative
- Alpha-2 agonist, analog of clonidine → bradycardia and hypotension
- Associated with disfiguring skin ulcers

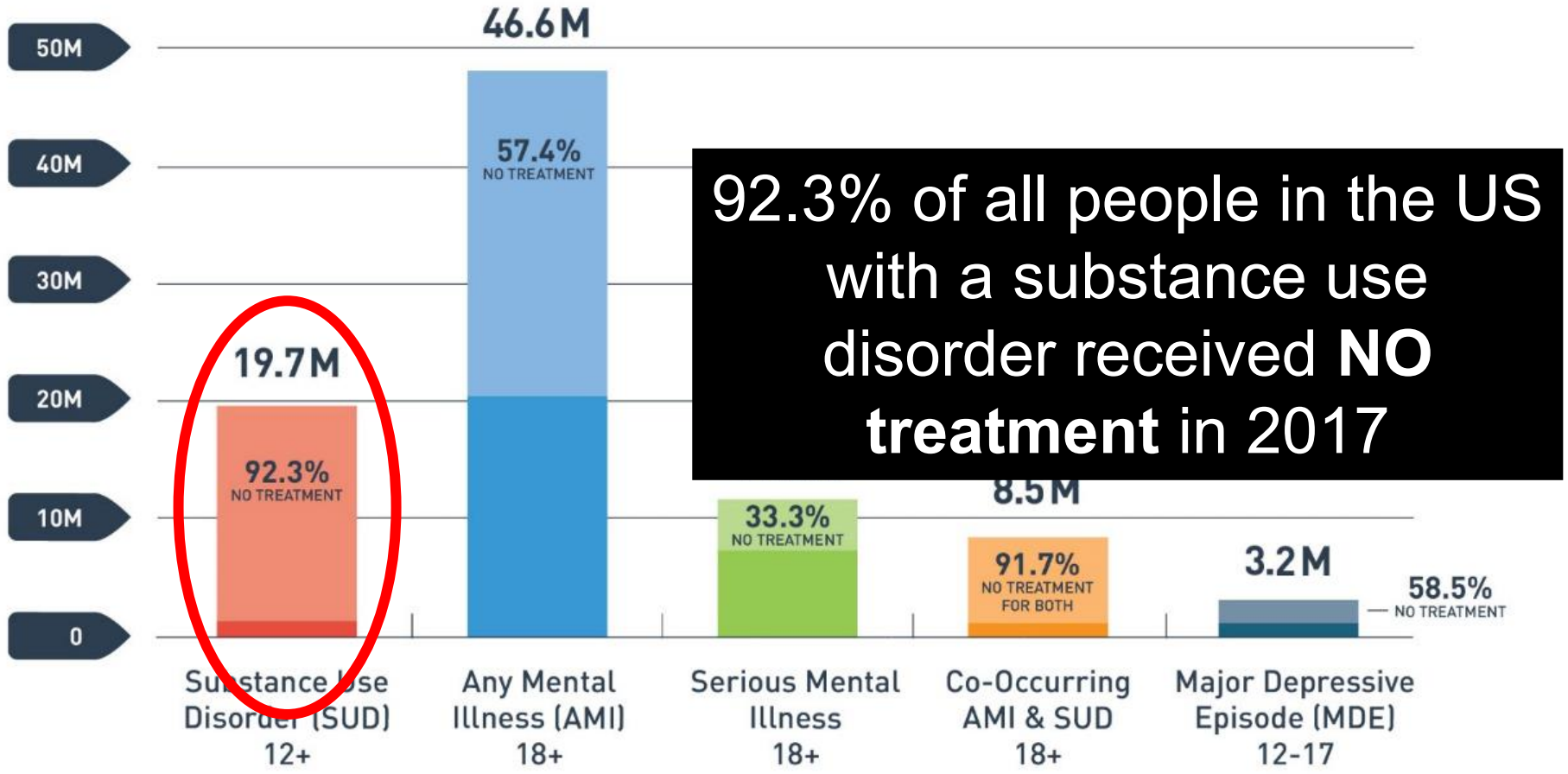
Medetomidine

- Alpha-2 agonist, veterinary sedative like xylazine
- Profound sedation, bradycardia, hypotension
- Severe withdrawal → hypertension, anxiety, vomiting, often requiring ICU

Nitazenes

- Isotonitazene, protonitazene, etc
- Novel opioids of high potency → profounf respiratory depression
- Does not get detected through regular testing

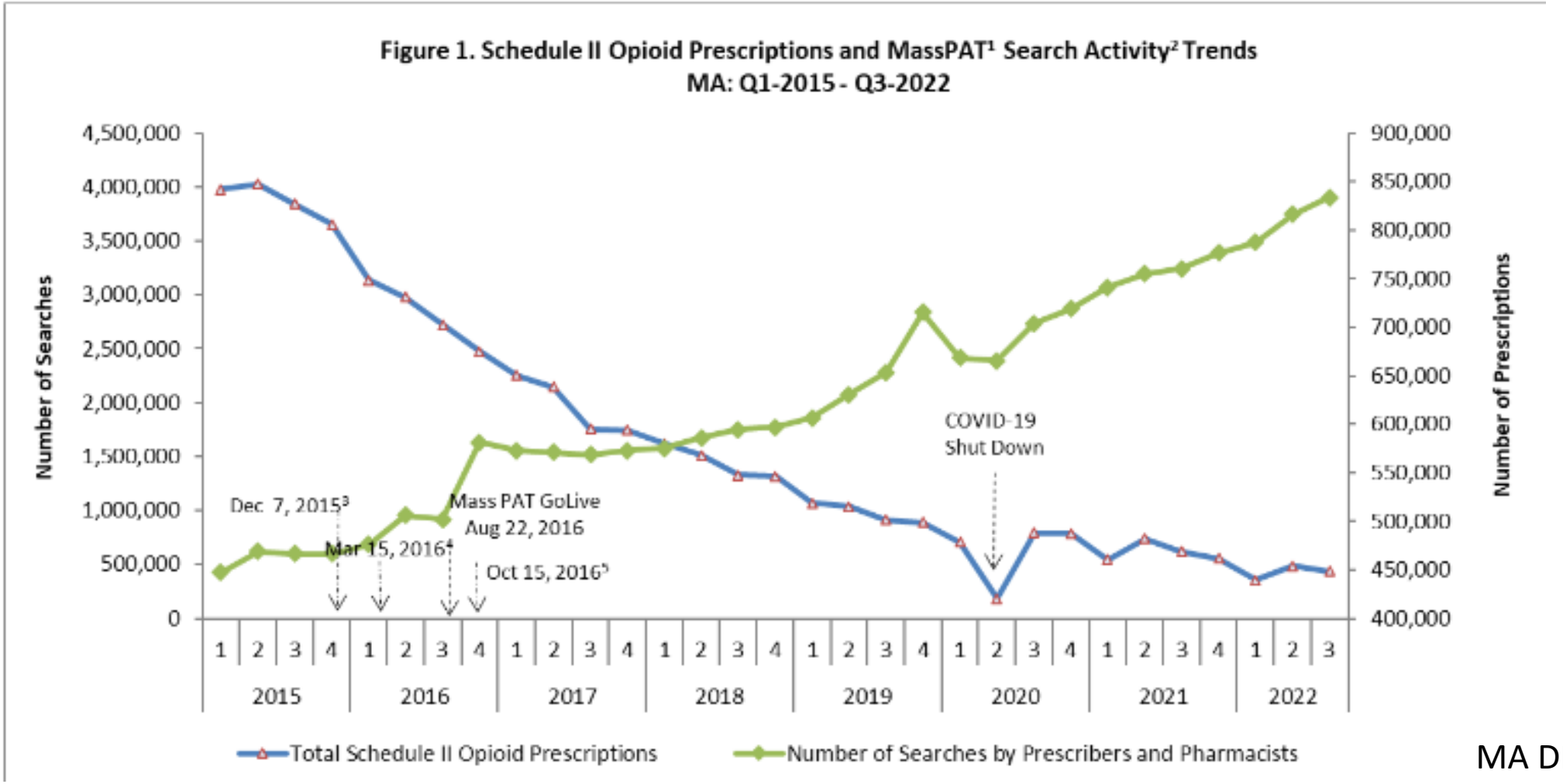
Majority of those with addiction get no treatment whatsoever



92.3% of all people in the US with a substance use disorder received **NO treatment** in 2017

National Survey on Drug Use and Health 2023

Prescribing of opioid analgesics have continues to fall



MA DPH 2022

Addiction (Substance Use Disorder): A chronic relapsing disorder characterized by compulsive use and long-lasting brain changes…

Opioid use disorder

2-3: mild

4-5: moderate

6+: severe

Tolerance
Withdrawal
Using larger amounts than intended
Persistent desire and inability to cut down
Can’t stop despite knowledge of harm
Spending a lot of time using/obtaining/recovering from substance use
Cravings
Using the substance in Dangerous situations
Important social and other activities are given up for drug use
Failed role obligations
Social conflict

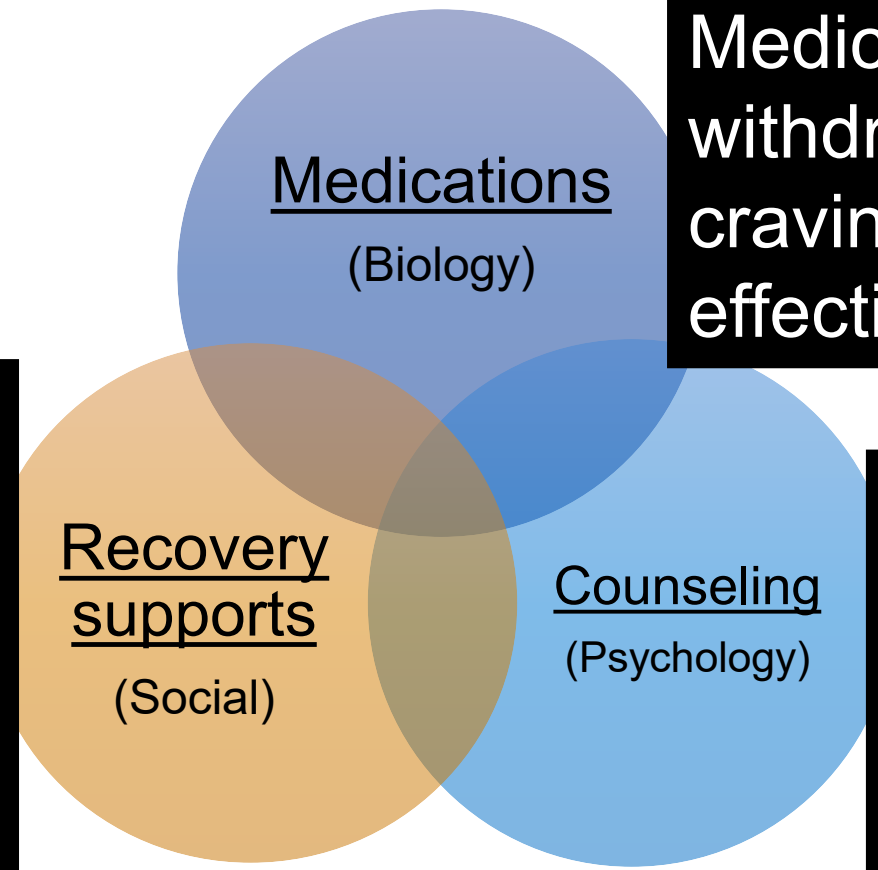
DSM5

…or simply the 3 Cs of addiction

Loss of **C**ontrol	• Inability to stop or reduce use; compulsive use
Cravings	• Strong urges to use
Consequences	• Accumulation of physical, psychological, and social harm

DSM 5

Treatment has 3 legs: Bio-Psycho-Social



Medications treat the withdrawal and cravings very effectively

Recovery means creating a supportive environment, learning from peers, and becoming healthy in relationships and life

Counseling helps patients learn about recovery, relapse prevention, and treatment of co-morbid mental illness.

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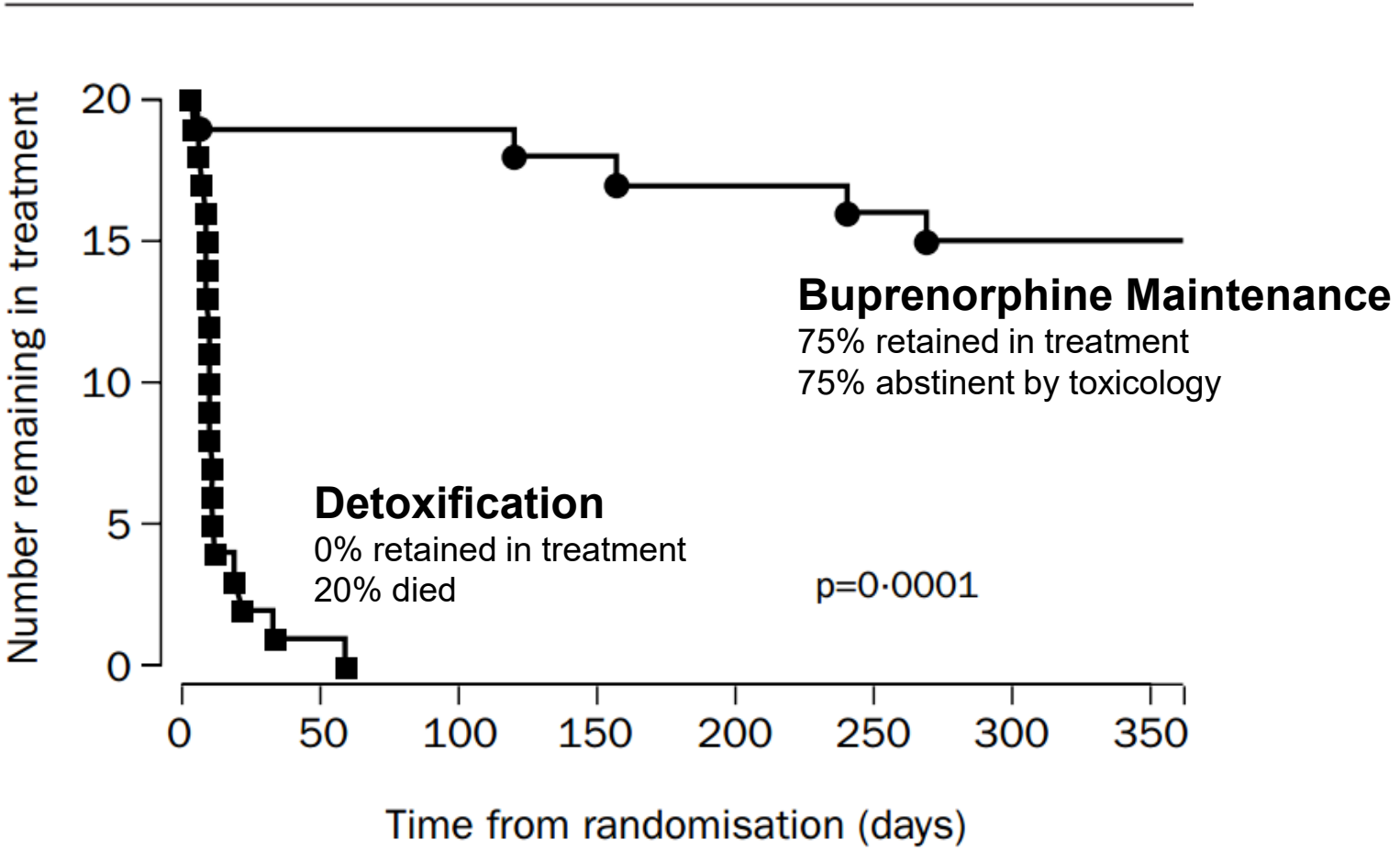
There are 3 choices for medications

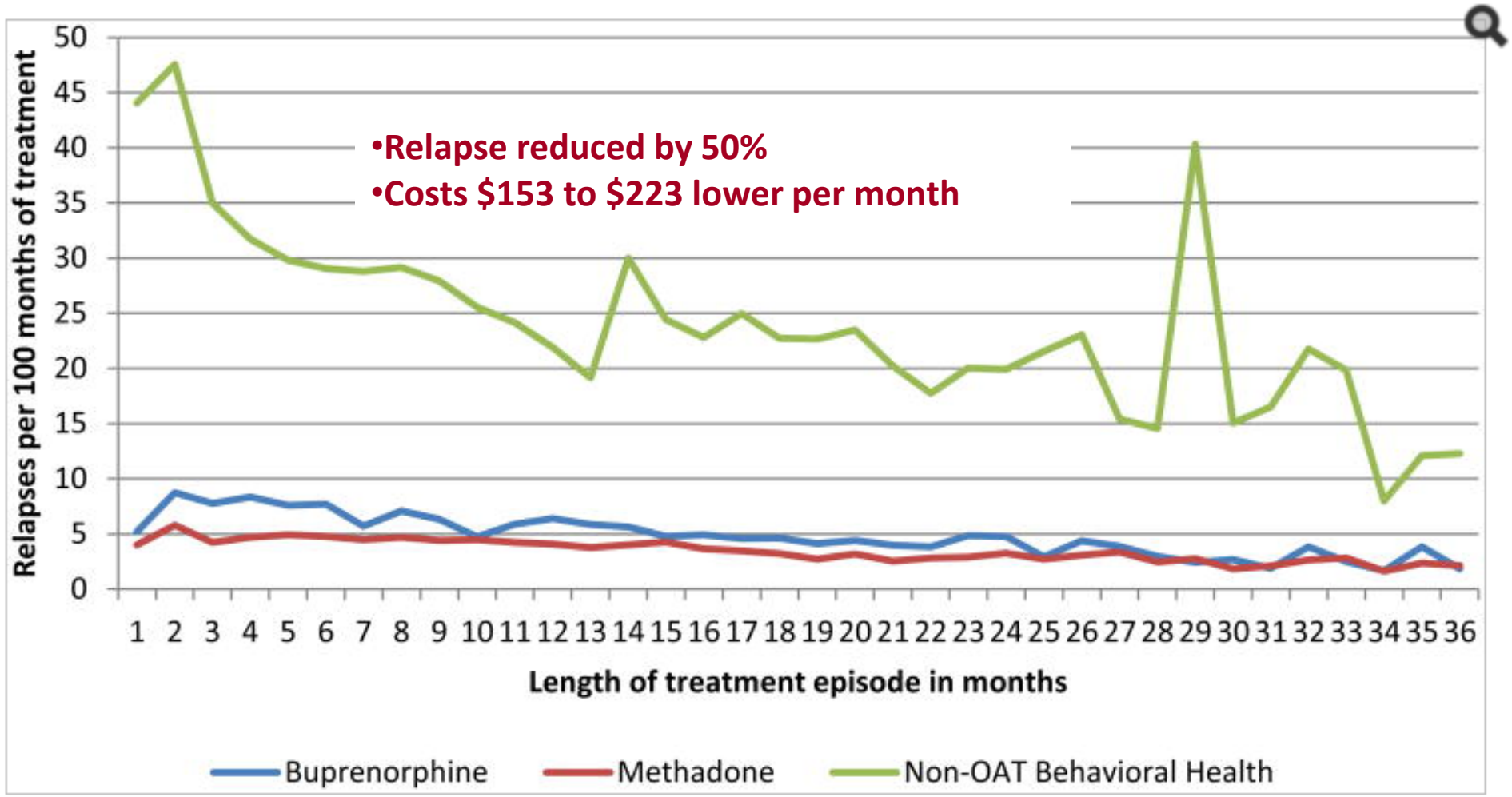
- Buprenorphine
- Methadone
- IM Naltrexone

Buprenorphine maintenance is effective treatment



Kakko et al. Lancet. 2003 Feb 22;361(9358):662-8

Buprenorphine reduces illicit opioid use and prevent relapse

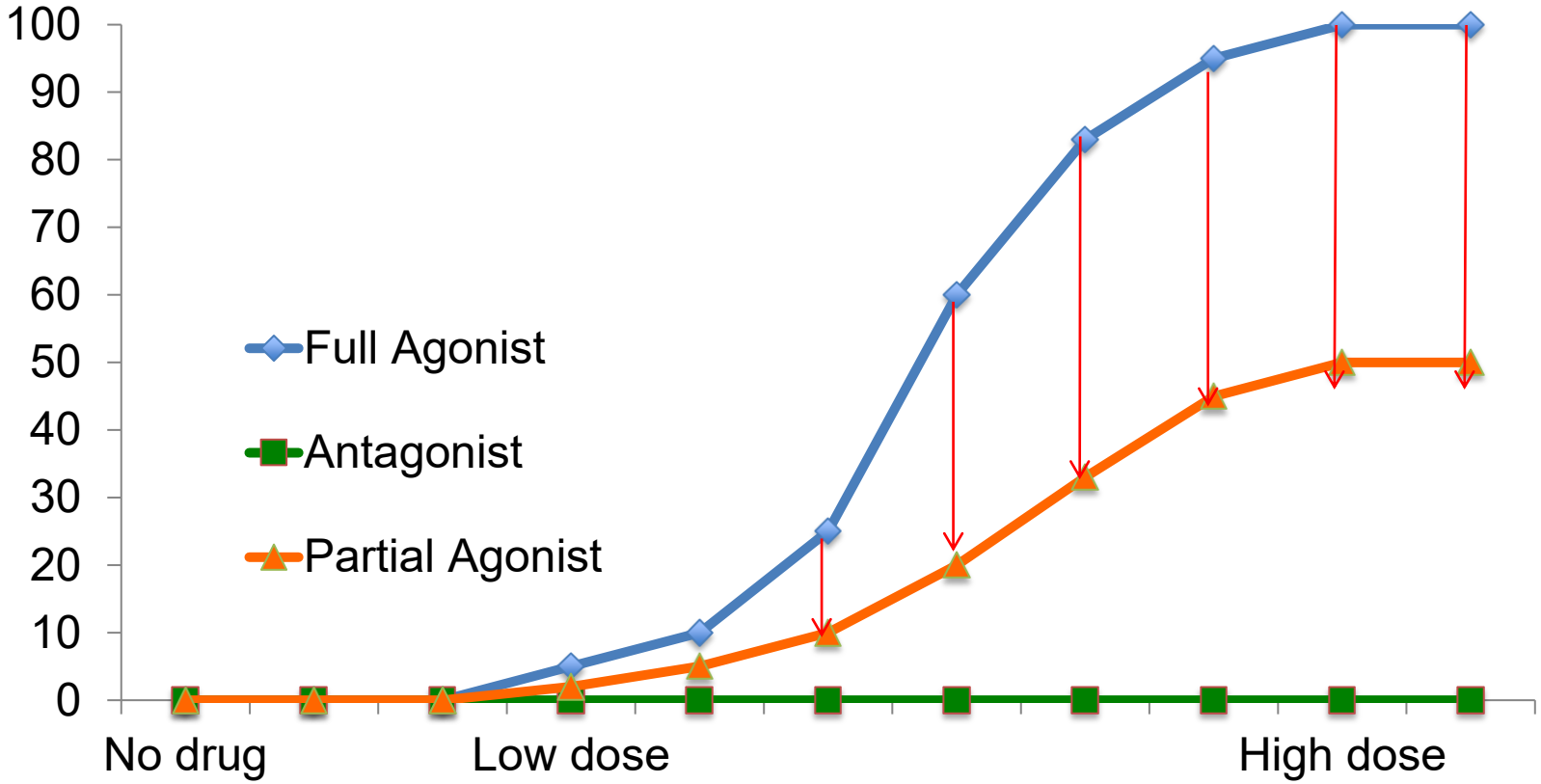


Clark RE et al. J Subst Abuse Treat. 2015 Oct;57:75-80

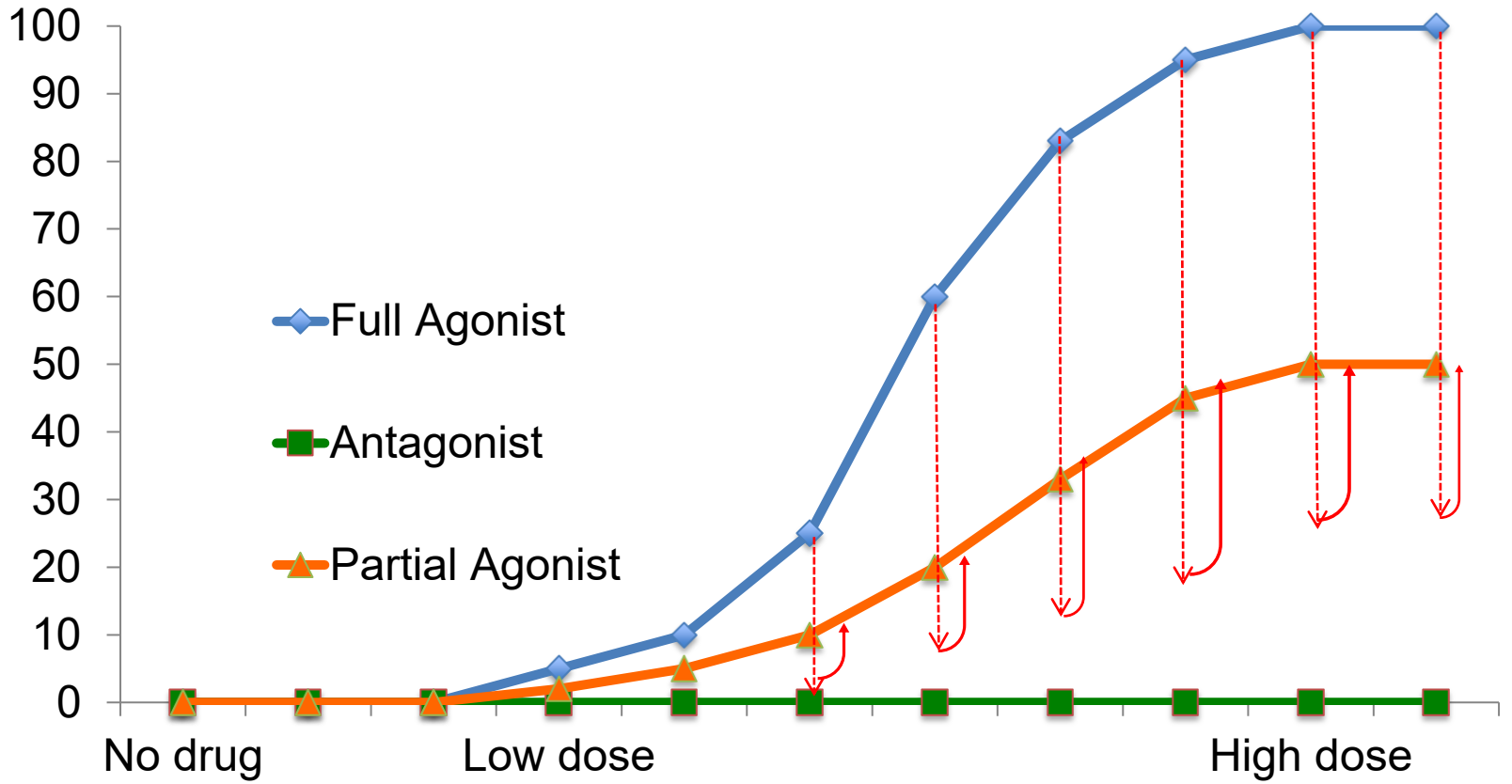
Buprenorphine addresses the 3Cs of addiction

	On heroin / fentanyl	On buprenorphine
Loss of **C**ontrol	• Unable to control illicit opioid use	• Can control the use of buprenorphine
Cravings	• Strong cravings that perpetuate addiction	• Reduced cravings b/c buprenorphine has opioid effects
Consequences	• Harmful consequences	• Positive consequences

Precipitated withdrawal if buprenorphine given while full agonists on-board



Avoidance of precipitated withdrawal by first waiting for full agonist to dissipate



History of buprenorphine inductions

1st wave (2002-2010)

- In-clinic inductions with at least 2 hours of observation as standard
- Multiple visits on week 1
- Some early reports of home-inductions (Lee et al 2009)

2nd wave (2010-2013)

- RCT of home vs in-clinic inductions (Gunderson et al 2010)
- Growing evidence for safety of home inductions (Lee et al 2014)

3rd wave (2013-)

- Growing reports of precipitated w/d despite following standard induction protocols
- 1st case report of micro-dosing (Hammig et al 2016)

When are patients ready?

- Clinical Opioid Withdrawal Scale (COWS) score 8 or greater
- Typically 6-8 hours since last use
- At least 36 hours if transitioning from methadone
- Asking the patient if they feel ready (not suitable for those naïve to buprenorphine)

Home induction has been standard of care

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.

Buprenorphine - Beginning Treatment

Day One: Before taking a buprenorphine tablet you want to feel lousy from your withdrawal symptoms. Very lousy. It should be at least 12 hours since you used heroin or pain pills (oxycontin, vicodin, etc.) and at least 24 hours since you used methadone.

Wait it out as long as you can. The worse you feel when you begin the medication, the better it will make you feel and the more satisfied you will be with the whole experience.

You should have a least 3 of the following feelings: • twitching, tremors or shaking • joint and bone aches • bad chills or sweating • anxious or irritable • goose pimples


• very restless, can't sit still

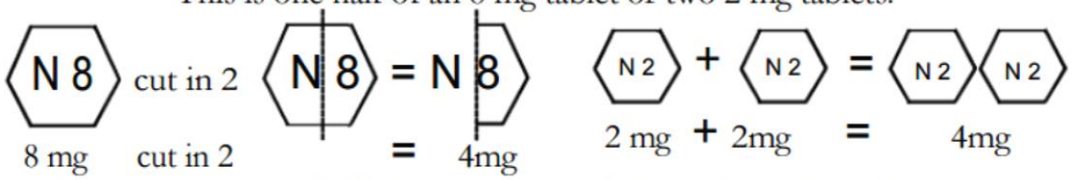

• heavy yawning


• enlarged pupils


• runny nose, tears in eyes


• stomach cramps, nausea, vomiting, or diarrhea

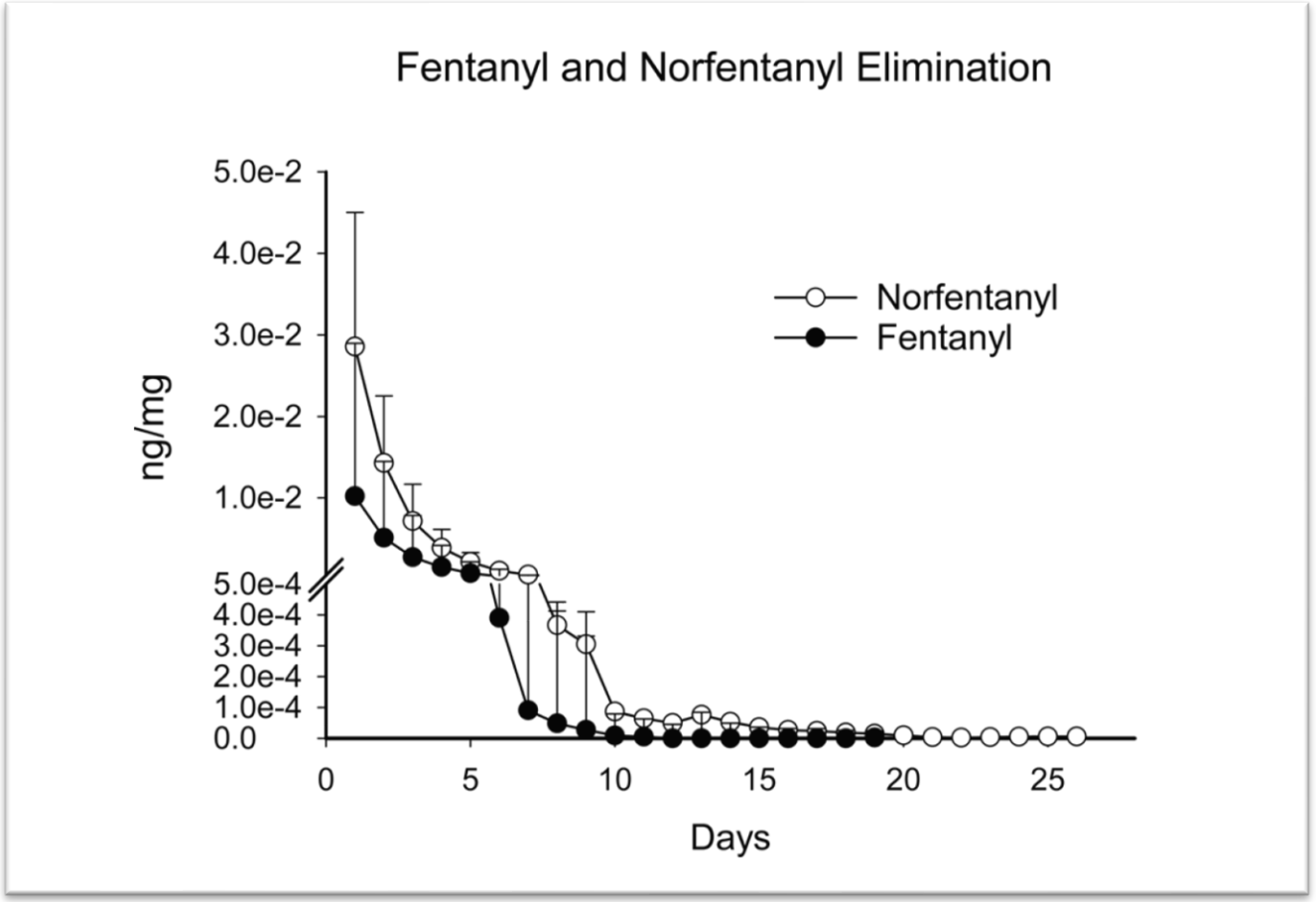
First Dose: 4 mg of Buprenorphine (Bup) under the tongue.
This is one half of an 8 mg tablet or two 2 mg tablets:



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2628995/bin/11606_2008_866_MOESM1_ESM.pdf

ASAM 2020; Lee et al 2014

Delayed clearance of fentanyl creating difficult inductions for some patients

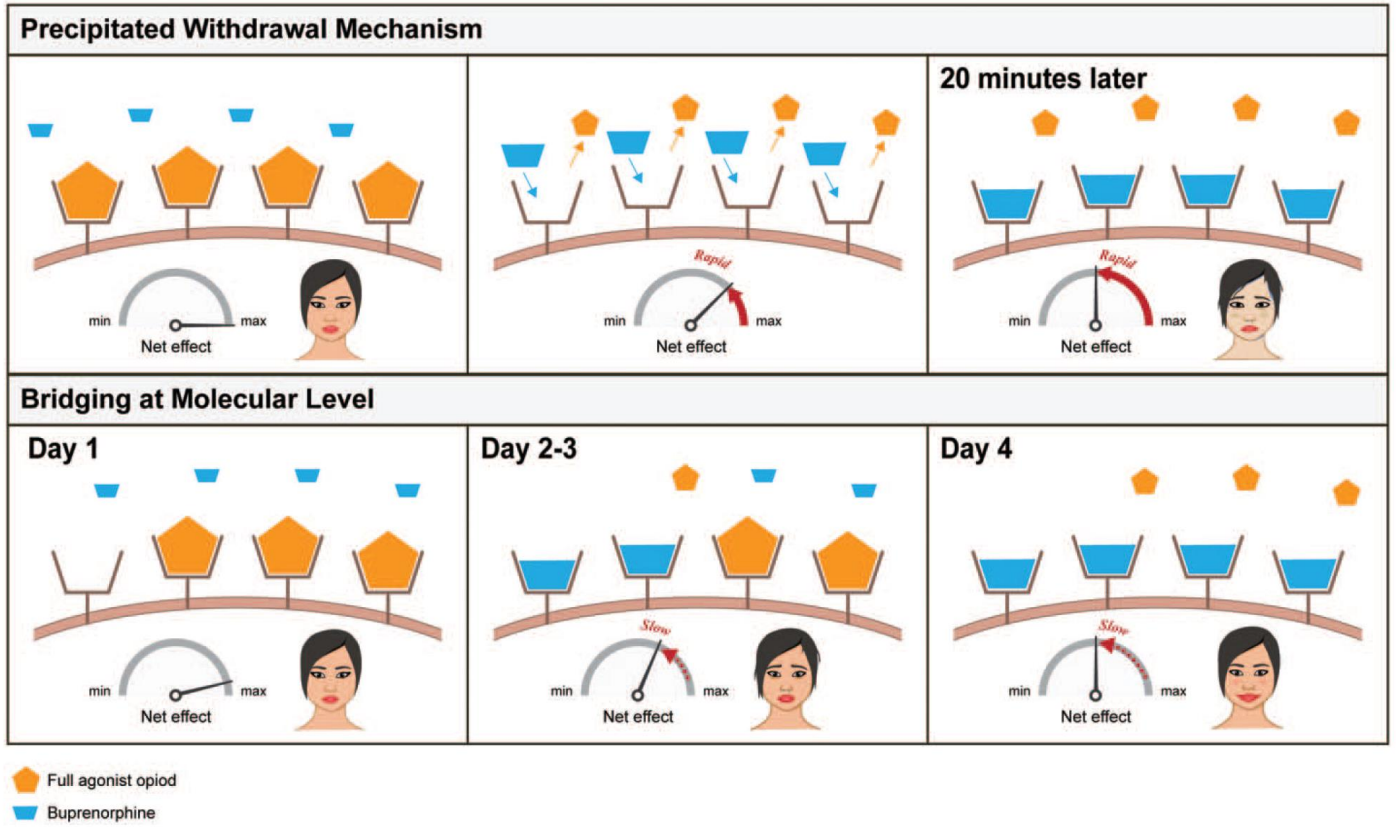


Huhn et al Drug Alc Dep 2020

What is a low-dose induction (aka “micro-dosing”)?

- Starting SL buprenorphine **without waiting for withdrawal**
  - Using smaller starting dose of SL (i.e. <0.5mg for SL)
  - Or use transdermal/buccal/IV buprenorphine before starting SL dose
- Either stop the opioid or gradually reduce (cross-taper)
- Duration of induction 3-7+ days
- Likely see some worsening withdrawal but mild

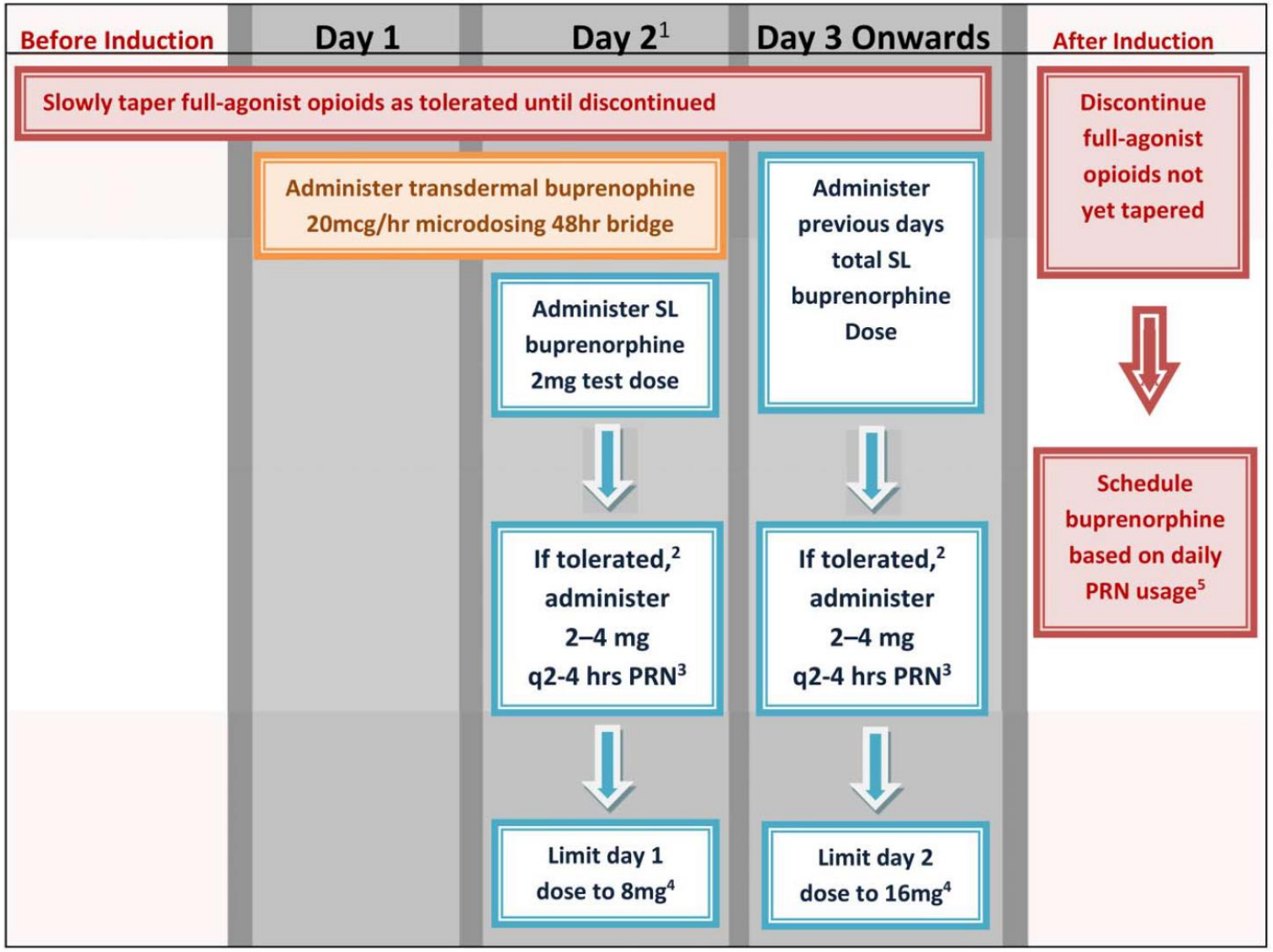
Pharmacology of low-dose buprenorphine induction (LDBI)



1) Initial dose must be sufficiently low
2) Continue the full agonist
3) Gradually increase SL buprenorphine

Ghosh et al Can J Addiction 2020

Example transdermal protocol (Stanford)



Raheemullah and Lembke 2019

Example buccal protocol (Yale)

TABLE 2. Buccal Buprenorphine Induction Strategy

Day	Buccal Buprenorphine Film Dose	SL Buprenorphine/Naloxone Film Dose	Full Opioid Agonist Dose
1	225 mcg PO once (75 mcg film + 150 mcg film)		Full dose
2	225 mcg PO twice daily (75 mcg film + 150 mcg film)		Full dose
3	450 mcg PO twice daily		Full dose
4		2 mg SL BID	Full dose
5		4 mg SL BID	Full dose
6		4 mg SL TID	Full dose
7		4 mg SL TID – 8 mg SL BID	Stop

BID, twice daily; PO, per oral; SL, sublingual; TID, 3 times daily.

Weimer et al 2021

Summary of buprenorphine formulations for low-dose inductions

	Initial dose	Advantage	Disadvantage
Sublingual	0.5-0.1mg	• Readily available • Clinicians very familiar • Most commonly used ROI • Can be used outpatient	• Many hospitals restrict splitting
Buccal	225mcg	• Reach peak effect rapidly • Option if cannot split	• Costly option • May not be on inpatient formulary • Cannot be used outpatient
Transdermal	10-20µg/hr	• Second most reported ROI • Option if cannot split • Ensures slow onset	• Most costly option • May not be on inpatient formulary • Cannot be used outpatient
Intravenous	0.1-0.15mg	• Quickest to reach peak effect • Option if cannot split	• May not be on formulary • Require IV access • Cannot be used outpatient • Theoretically more reinforcing

What is a high-dose induction (aka “macro-dosing”)?

- Starting SL buprenorphine **more rapidly**
  - Wait for withdrawal to emerge (COWS≥8)
  - Then give 8-16mg SL right away
  - Wait 1 hour
  - If persistent withdrawal, the give additional 8-16mg SL
- Incidence of precipitated withdrawal appears to be low with this method
- Facilitates initiation of buprenorphine in ED or outpatient setting

Can buprenorphine be given at higher doses more quickly?

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

Background

- Examine the safety and tolerability of high-dose (>12mg) buprenorphine induction for ED patients

Methods

- Retrospective chart review of patients undergoing a rapid high-dose protocol for induction.
- ED clinicians trained on the High-dose protocol
- When COWS≥8, then 4-8mg SL, then after 30-60mins, 8-24mg given, for total of ≤32mg

Primary outcome

- Precipitated withdrawal, vitals, oxygen, AEs, LOS, hospitalization

Herring et al JAMA 2021

Results

391 unique patients

22.5% homeless, 41.2% with co-morbid psychiatric dx

High-dose protocol given by 54 clinicians during 366 encounters.

No cases of respiratory depression

5 (0.8%) cases of precipitated withdrawal

3 Serious AEs, unrelated to buprenorphine

Conclusion

High-dose protocol in the ED appears safe and well-tolerated

Confirming the low incidence of BPOW with macro-dosing!

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

Background

- Ongoing NIDA-CTN trial (ED-INNOVATION)
- Randomized clinical trial in 30 EDs across the US

Methods

- Comparing SL buprenorphine macro-dosing with initiating XR-BUP
- Interim analysis of the trial with n=1200

Primary outcome

- Precipitated withdrawal (PW), defined as >5 increase in COWS

Results

Among 1200 enrollees, total of 9 (0.76%) cases of PW

5 received SL, 4 on XR-BUP

All had fentanyl positive urines

Time since last use varied from 8 to >24 hours

All eventually resolved PW and discharged, 1 AMA/PDD

No clear predictor of PW

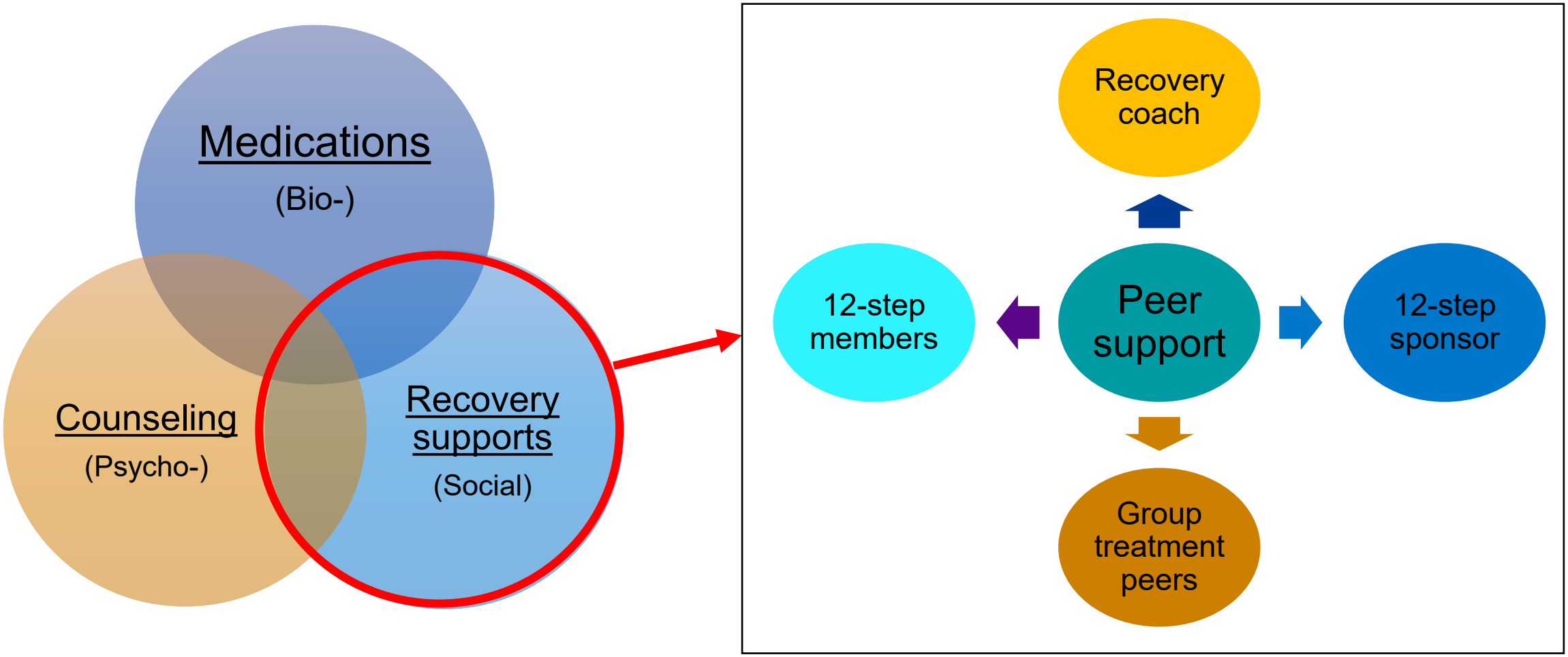
Conclusion

Macro-dose and XR-BUP in the ED appear safe and well-tolerated

Unclear why incidence if low despite high prevalence of fentanyl

D'Onofrio et al JAMA 2023

Peer support is an important element of addiction treatment



Who are peer recovery coaches?

- “Lived experience” of sustained recovery
- Training to be certified coaches
- Provide non-clinical assistance and mentorship
- Support all pathways to recovery
- Aligns with core principle of trauma-informed care

SAMHSA 2014; Eddie et al Frontiers in Psychology 2019

Evidence for peer supports in improving SUD outcomes is emerging but mixed

Lived Experience in New Models of Care for Substance Use Disorder: A Systematic Review of Peer Recovery Support Services and Recovery Coaching

David Eddie[1], Lauren Hoffman[1], Corrie Vilsaint[1], Alexandra Abry[1], Brandon Bergman[1], Bettina Hoeppner[1], Charles Weinstein[2] and John F. Kelly[1]*

[1] Recovery Research Institute, Center for Addiction Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Design: Systematic review of evidence

Method: Review of RCTs, quasi-experimental studies, and prospective and retrospective studies

Eddie et al Frontiers in Psychology 2019

Results: 24 reports (23 original studies), including 6,544 participants

- 7 RCTs
- 4 quasi-experimental studies
- 8 single- or multi-group prospective/retrospective studies

- Overall, very heterogenous studies, roles, and outcomes
- Often poorly defined and non-manualized procedures
- Positive effects noted but **small to moderate in magnitude**

Conclusions:

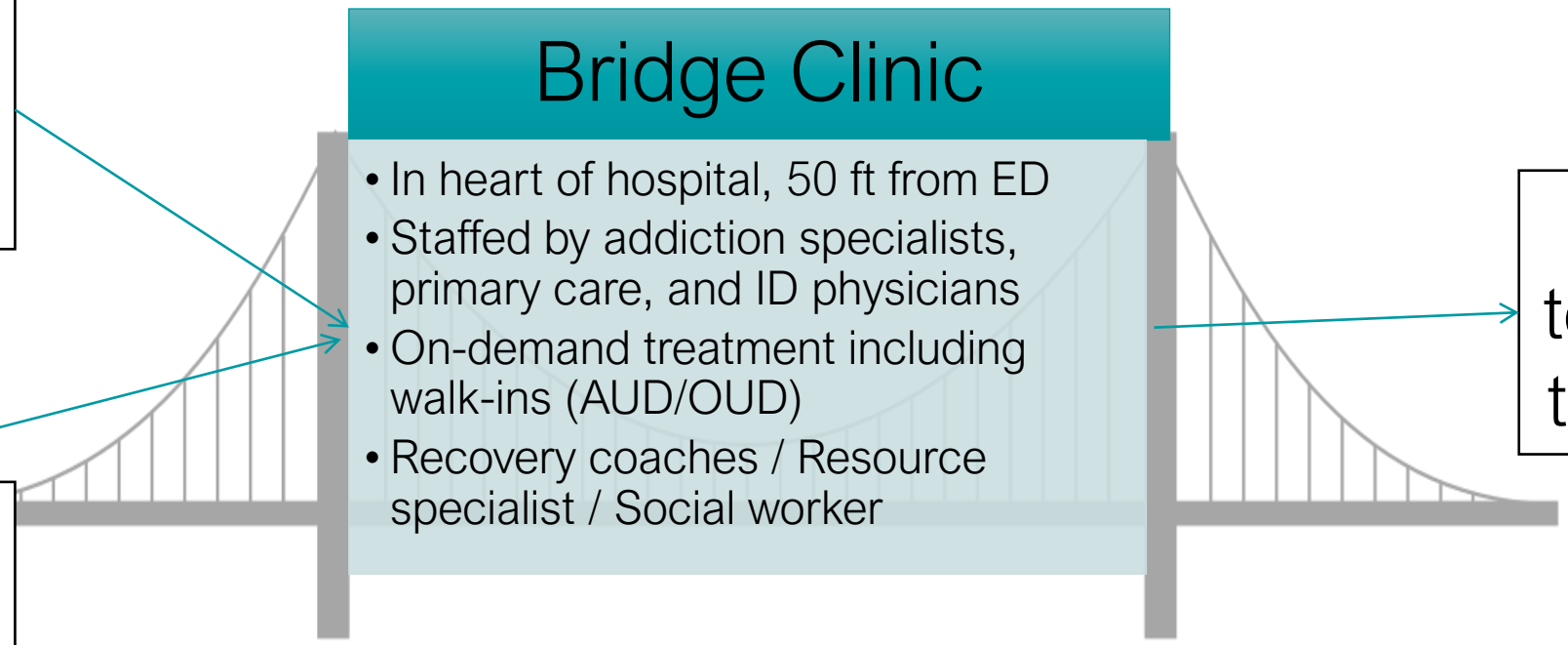
- A lot of **limitations** with available evidence
- Promising, but **far more research needed** to understand:
  - Training → how much, on what, supervision?
  - Setting → clinical, community, hospital?
  - Intensity → how frequent, remote vs in-person?
  - Role → manualized, SUD vs psychiatry?

The Bridge Clinic model (low barrier, low threshold)

Objective: Allow on-demand, rapid-access to outpatient treatment for patients with SUDs and connect them to long-term, community-based treatment & resources

Hospital inpatients needing timely SUD care after discharge

ED patients who presented seeking care or had non-fatal overdose



Longer-term SUD treatment

Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs

Nora D. Volkow, M.D., Carlos Blanco, M.D., Ph.D.

TABLE 1. Treatment development research gaps for opioid use disorder and overdoses[a]

Research Gap	Goal
Need for extended-release MOUD treatments; greatest need is for methadone, for which no extended-release formulations are available	Increase treatment retention, prevent diversion
Development of clinically meaningful alternative end points for clinical trials in OUD, including patient-reported outcomes	Facilitate FDA approval of medications
Medications with targets other than MORs (e.g., other opioid receptors, dopamine D_3 receptors, mGlu receptors, CRF receptors)	Expand treatment options for OUD
Repurposing of medications (e.g., orexin receptor antagonists such as suvorexant; glucagon-like peptide agonists)	Accelerate availability of expanded treatment options
Research on psychedelics, such as psylocibin, ketamine, ibogaine	Expand treatment options for OUD and other substance use disorders
Immunotherapies: vaccines and monoclonal antibodies	Counter effects of ingested or injected opioids by trapping them with antibodies
Neuromodulation (transcranial magnetic stimulation, direct current stimulation, low-intensity focused ultrasound, deep brain stimulation, peripheral nerve stimulation)	Restore the balance of neuronal networks disrupted in OUD
Fast, high-affinity opioid antagonists with longer duration	Reversal of overdoses from fentanyl and other high-potency opioids
Respiratory stimulant drugs	Increase breathing to help reverse polysubstance-related overdoses

[a] CRF=corticotropin-releasing factor; mGlu=metabotropic glutamate receptor; MOR=mu-opioid receptor; MOUD=medication for opioid use disorder; OUD=opioid use disorder.

Research Gap	**Goal**
Repurposing of medications (e.g. orexin receptor antagonists; glucagon-like peptide agonists)	Accelerate availability of expanded treatment options
Research on psychedelics, such as psilocybin, ketamine, ibogaine	Expand treatment options for OUD and other SUD

Volkow and Blanco 2023 Am J Psychiatry

Completed, ongoing, and planned trials of GLP-1 for OUD

Liraglutide (PI: Grigson)

- Completed
- DBPC, RCT (n=25)
- 25 enrolled, 9 completed (liraglutide =1, placebo =8)
- Results not published

Semaglutide (PI: Grigson)

- Recruiting
- Multi-site, 12-week, DBPC, RCT (n=200) of individuals on MOUD
- Dose up to 1.0mg

Semaglutide (PI: Suzuki)

- Recruiting
- Single-site, 12-week, DBPC, RCT (n=40) of individuals on MOUD
- Dose up to 1.0mg

Tirzepatide (PI: Winhusen)

- Recruiting
- Multi-site, NIDA CTN, DBPC, RCT (n=310) of individuals on SL buprenorphine

Brenipatide (Eli Lilly)

- Not yet recruiting
- Multi-site, international, DBPC, RCT (n=465) of individuals on SL buprenorphine

Summary

- Opioid epidemic continues to be a public health crisis, made worse by the adulterants in the drug supply
- Buprenorphine is highly effective in preventing overdoses, and improving lives
- Novel induction strategies are needed in the “fentanyl-era”
- Recommendations to further study the role of psychedelics and GLP-1RAs in the treatment of OUD

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