Brigham and Women's Hospital
Founding Member, Mass General Brigham

Management of Opioid Addiction

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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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 in general medical settings

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

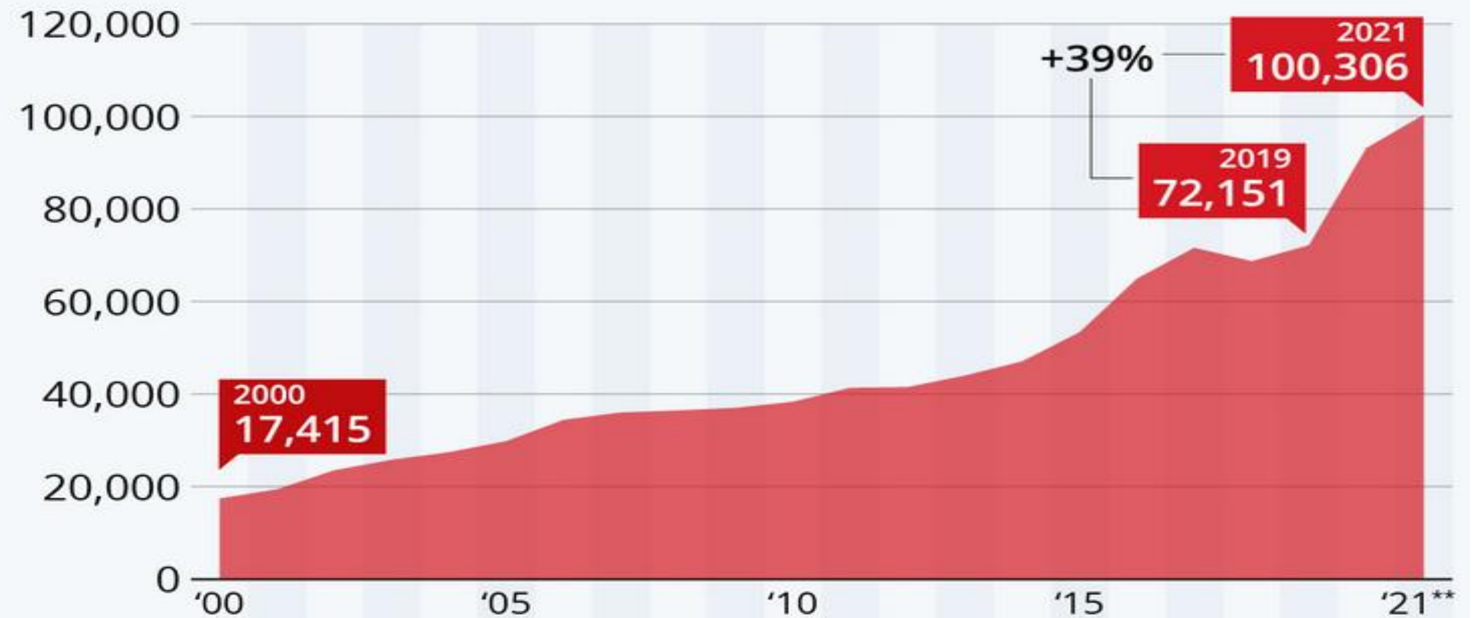
Grant funding from National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism

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*

Current status of the opioid crisis in the US



https://www.statista.com/chart/18744/the-number-of-drug-overdose-deaths-in-the-us/

Current status of the opioid crisis in MA

Figure 2. Opioid-Related Overdose Deaths, All Intents
Massachusetts Residents: 2000 - 2022

Legend: Confirmed, Estimated

Number of Deaths (axis: 0, 500, 1,000, 1,500, 2,000, 2,500)

Year	Confirmed	Confirmed + Estimated
2000	375	
2001	504	
2002	526	
2003	613	
2004	509	
2005	569	
2006	655	
2007	640	
2008	621	
2009	633	
2010	547	
2011	656	
2012	733	
2013	954	
2014	1,356	
2015	1,748	
2016	2,111	
2017	2,013	
2018	2,015	
2019	2,007	
2020	2,092	
2021	2,283	2,299
2022	2,331	2,359

Year

MA DPH 20224

Current status of the opioid crisis in MA

Confirmed Opioid-Related Overdose Death Rates, All Intents, by Race and Hispanic Ethnicity

Age-adjusted Rates per 100,000

	2014	2015	2016	2017	2018	2019	2020
All Races	20.2	26.2	31.3	29.6	29.5	29.4	30.9
White non-Hispanic	23.9	31.1	36.5	33.7	34.3	33.4	33.1
Black non-Hispanic	11.2	15.6	16.4	[illegible]	15.7	22.1	36.0
Hispanic	[illegible]	20.5	32.0	31.5	[illegible]	32.2	36.3
Asian/Pacific Islander non-Hispanic	2.2	1.9	2.9	2.5	3.4	2.6	3.3

MA DPH 2022

Fentanyl continues to wreak havoc

Figure 4. Percent of Opioid-Related Overdose Deaths with Specific Drugs Present in Massachusetts : 2014 - 2023

Methodology Change*

Fentanyl[1]
Cocaine
Alcohol[4]
Benzodiazepine
Prescription Opioids[2]
Amphetamine[3]
Heroin
Xylazine

Percent

Year and Quarter

2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

MA DPH 2024

Xylazine 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

Majority of those with addiction get no treatment whatsoever

50M
40M
30M
20M
10M
0

19.7M
92.3%
NO TREATMENT
Substance Use Disorder (SUD)
12+

46.6M
57.4%
NO TREATMENT
Any Mental Illness (AMI)
18+

11.2M
33.3%
NO TREATMENT
Serious Mental Illness
18+

8.5M
91.7%
NO TREATMENT FOR BOTH
Co-Occurring AMI & SUD
18+

3.2M
58.5%
NO TREATMENT
Major Depressive Episode (MDE)
12-17

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

Figure 1. Schedule II Opioid Prescriptions and MassPAT[1] Search Activity[2] Trends
MA: Q1-2015 - Q3-2022

Number of Searches: 0; 500,000; 1,000,000; 1,500,000; 2,000,000; 2,500,000; 3,000,000; 3,500,000; 4,000,000; 4,500,000

Number of Prescriptions: 400,000; 450,000; 500,000; 550,000; 600,000; 650,000; 700,000; 750,000; 800,000; 850,000; 900,000

Quarters: 1 2 3 4 (2015); 1 2 3 4 (2016); 1 2 3 4 (2017); 1 2 3 4 (2018); 1 2 3 4 (2019); 1 2 3 4 (2020); 1 2 3 4 (2021); 1 2 3 (2022)

Dec 7, 2015[3]

Mar 15, 2016[4]

Mass PAT GoLive
Aug 22, 2016

Oct 15, 2016[5]

COVID-19
Shut Down

Total Schedule II Opioid Prescriptions

Number of Searches by Prescribers and Pharmacists

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 **<u>C</u>**<u>ontrol</u>	• Inability to stop or reduce use; compulsive use
<u>C</u><u>ravings</u>	• Strong urges to use
<u>C</u><u>onsequences</u>	• Accumulation of physical, psychological, and social harm

DSM 5

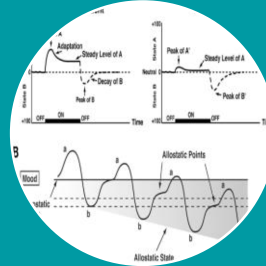
Neurobiologic models of addiction

Habit

- Reflexive behavior
- “Low entropy”

Operant Conditioning

- Positive and negative reinforcement
- “Liking”
- Binge-intoxication stage



Opponent-process

- Reward vs anti-reward
- Withdrawal-negative affect stage

Incentive sensitization

- **“Craving”**
- Pre-occupation and anticipation stage

Impaired cognitive control

- Poor inhibitory control
- Risk taking despite harm

Treatment has 3 legs: Bio-Psycho-Social

Medications (Biology)

Medications treat the withdrawal and cravings very effectively

Recovery supports (Social)

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

Counseling (Psychology)

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

15

There are 3 choices for medications

Buprenorphine

Methadone

IM Naltrexone

Buprenorphine maintenance is effective treatment

Number remaining in treatment

20
15
10
5
0

0 50 100 150 200 250 300 350

Time from randomisation (days)

Buprenorphine Maintenance
75% retained in treatment
75% abstinent by toxicology

Detoxification
0% retained in treatment
20% died

p=0·0001

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

Buprenorphine reduces illicit opioid use and prevent relapse

Relapses per 100 months of treatment

Length of treatment episode in months	1	2	3	...	36

- **Relapse reduced by 50%**
- **Costs $153 to $223 lower per month**

Y-axis: Relapses per 100 months of treatment (0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50)

X-axis: Length of treatment episode in months (1–36)

Legend: Buprenorphine, Methadone, Non-OAT Behavioral Health

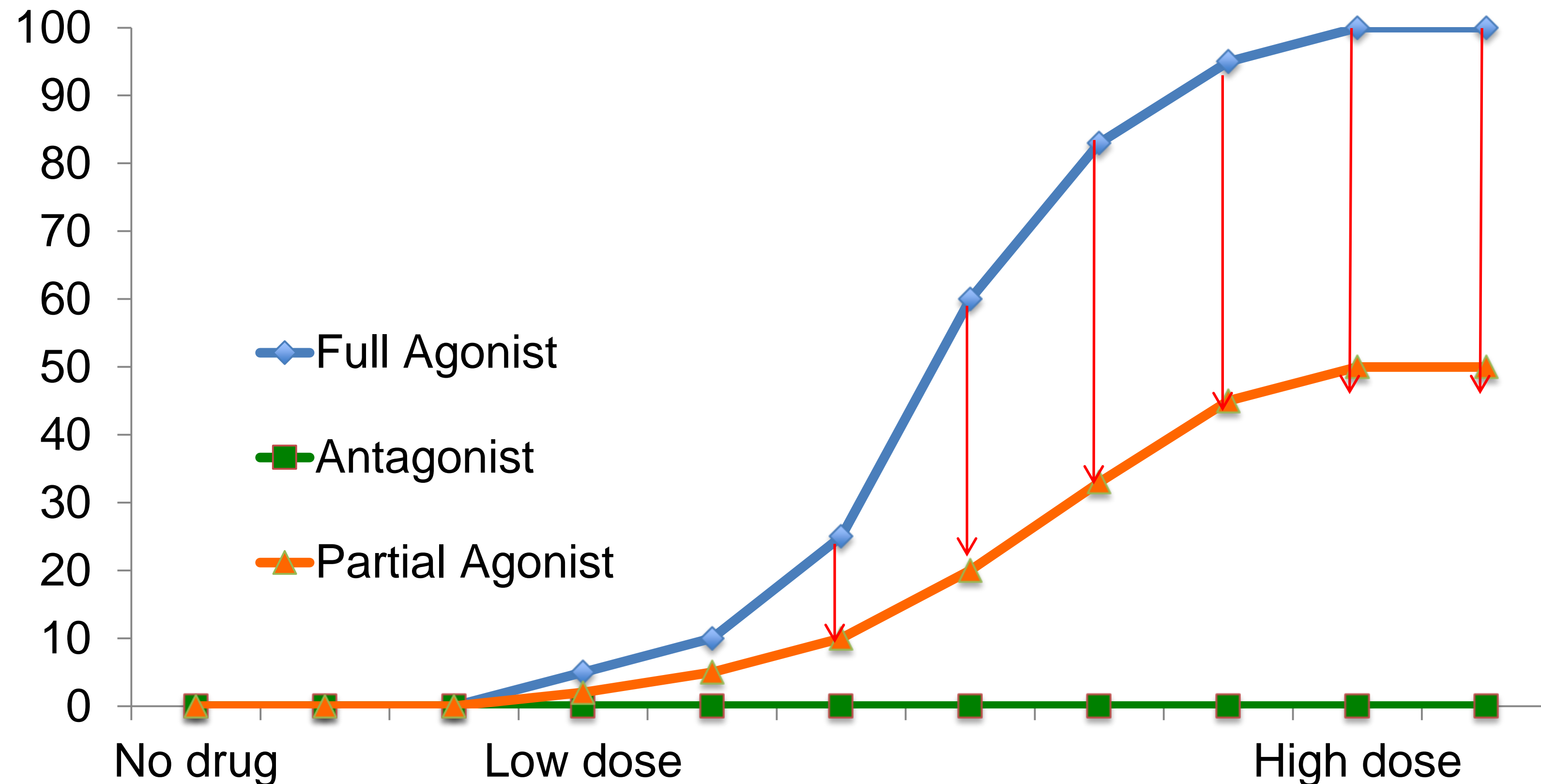
Clark RE et al. J Subst Abuse Treat. 2015 Oct;57:75-80

Buprenorphine addresses the 3Cs of addiction

	On heroin / fentanyl	On buprenorphine
Loss of **Control**	• 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

19

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

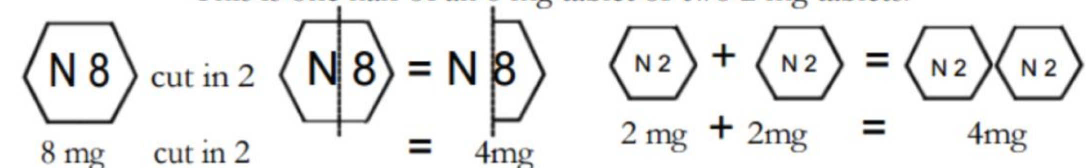
• heavy yawning

• enlarged pupils

• runny nose, tears in eyes

• stomach cramps, nausea, vomiting, or diarrhea

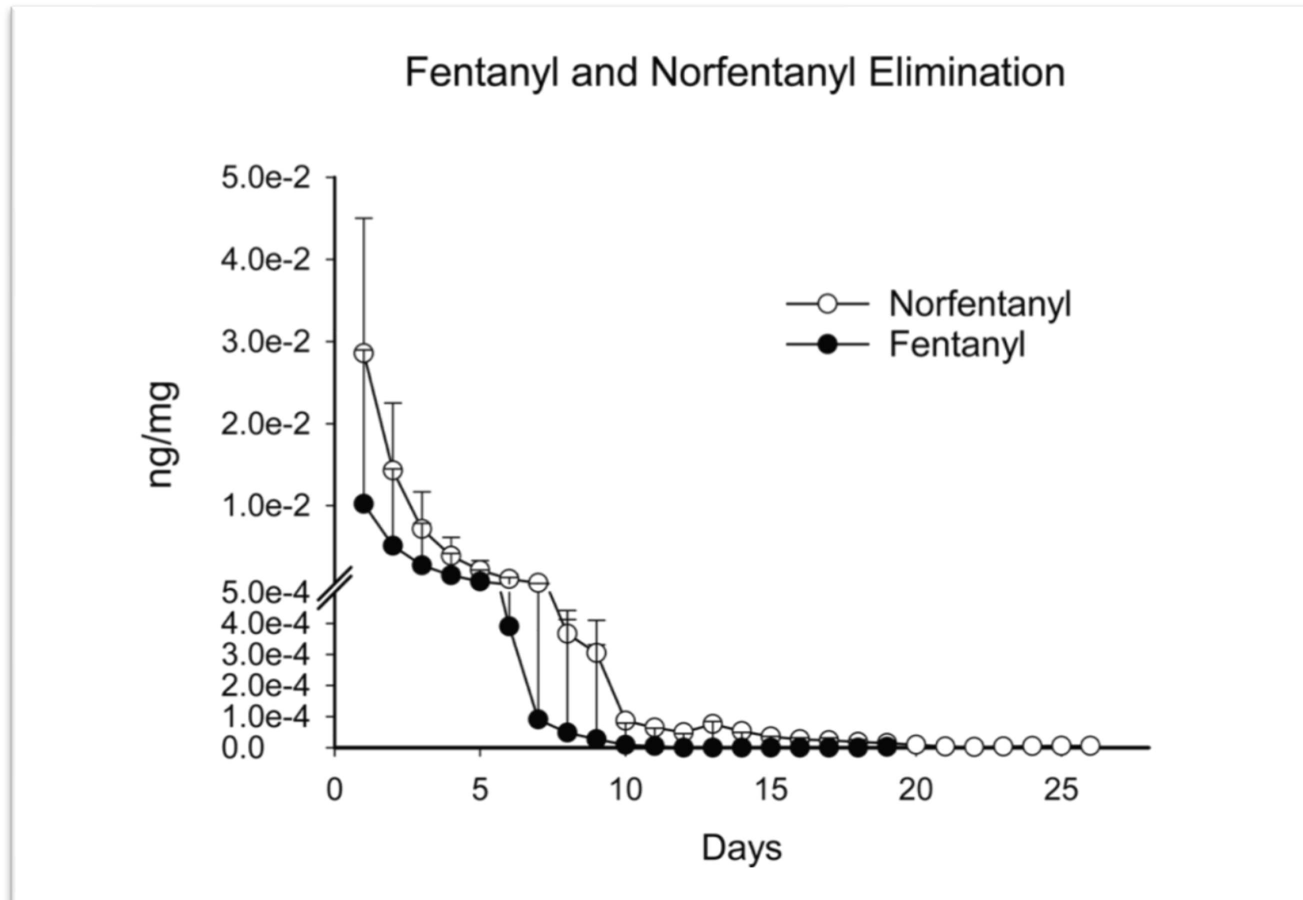
First Dose: 4 mg of Buprenorphine (Bup) under the tongue.
This is one half of an 8 mg tablet or two 2 mg tablets:



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

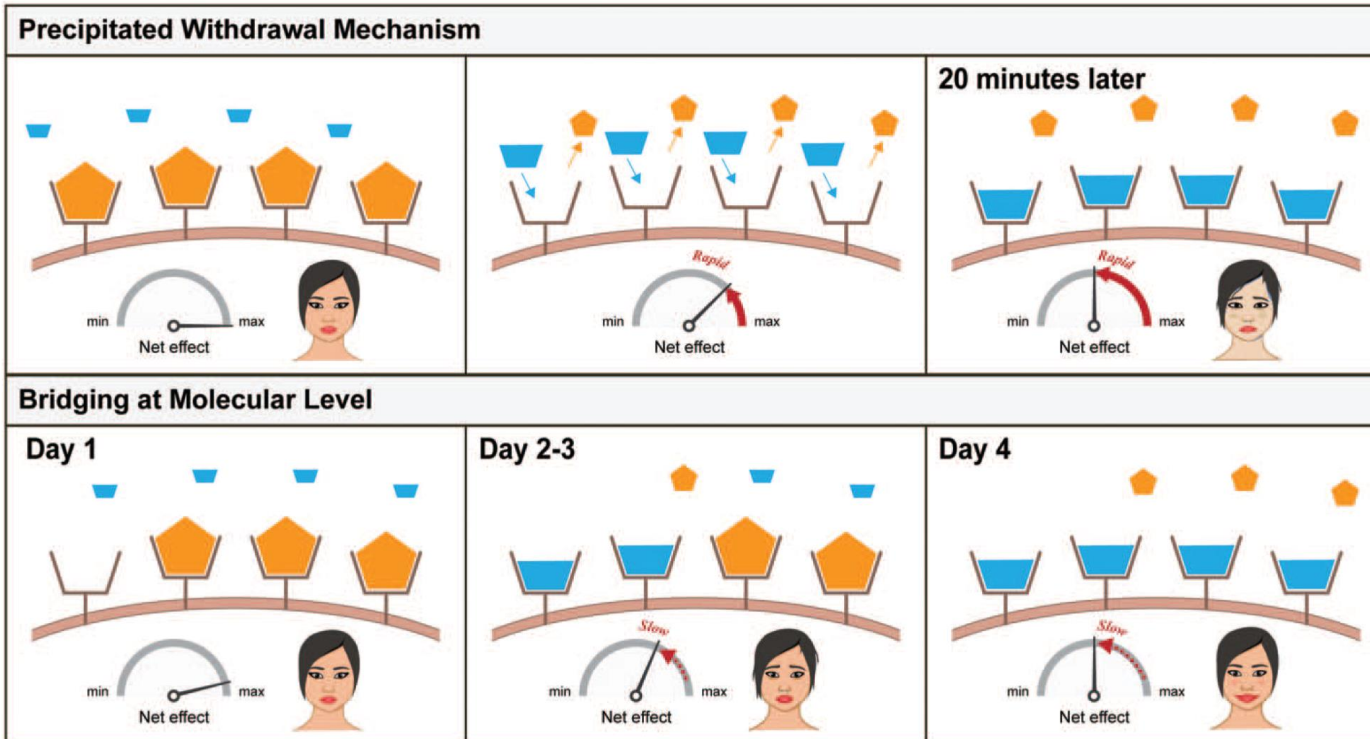


Huhn et al Drug Alc Dep 2020

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)

Before Induction	Day 1	Day 2[1]	Day 3 Onwards	After Induction

Slowly taper full-agonist opioids as tolerated until discontinued

Day 1 – Day 2: Administer transdermal buprenophine 20mcg/hr microdosing 48hr bridge

Day 2:

Administer SL buprenophine 2mg test dose

↓

If tolerated,[2] administer 2–4 mg q2-4 hrs PRN[3]

↓

Limit day 1 dose to 8mg[4]

Day 3 Onwards:

Administer previous days total SL buprenorphine Dose

↓

If tolerated,[2] administer 2–4 mg q2-4 hrs PRN[3]

↓

Limit day 2 dose to 16mg[4]

After Induction:

Discontinue full-agonist opioids not yet tapered

↓

Schedule buprenorphine based on daily PRN usage[5]

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

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

Herring et al JAMA 2021

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

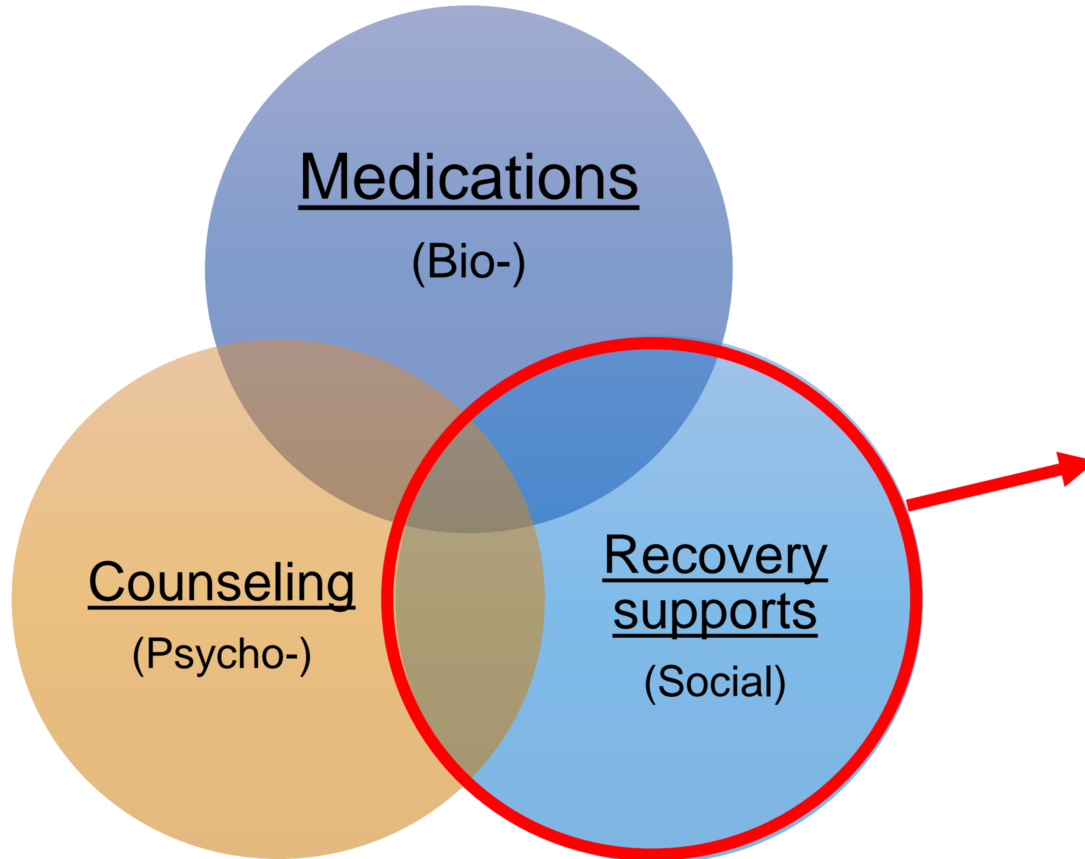
Conclusion

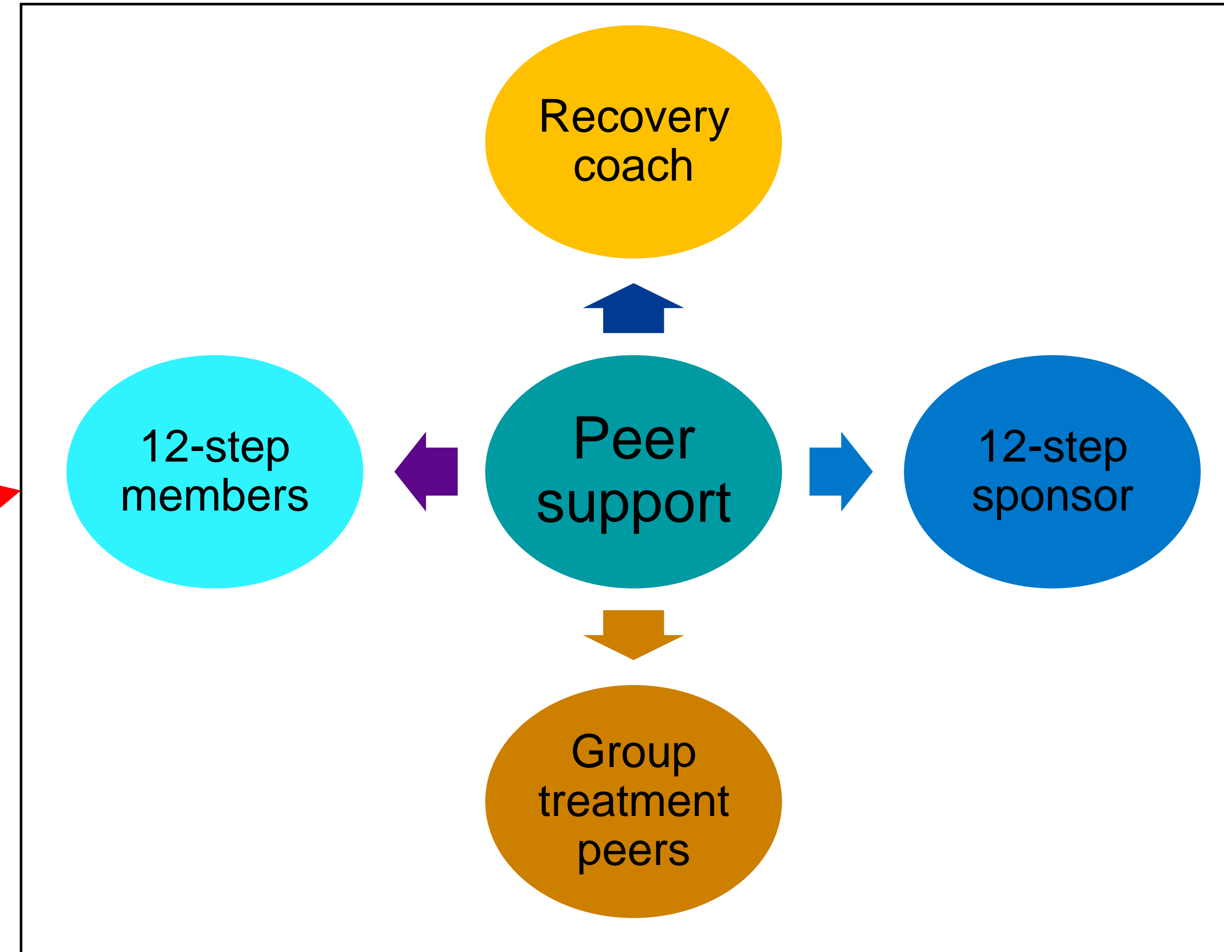
Macro-dose and XR-BUP in the ED appear safe and well-tolerated

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?

Linkage to treatment after buprenorphine initiation in the hospital

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

Typical outpatient treatment
Yale ED bup RCT
MGH consult
BWH consult
BMC bup RCT
OHSU consult
BMC consult

Linked | 30 days | 60 days | 90 days | 120 days | 150 days | 180 days

Suzuki et al AJA 2014; Liebschutz et al JAMA 2016; Trowbridge et al JGIM 2016; Wakeman et al JGIM 2017; D'Onofrio et al JAMA 2015; Suzuki et al Subst Abuse 2015;Englander et al JGIM 2019

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

Bridge Clinic

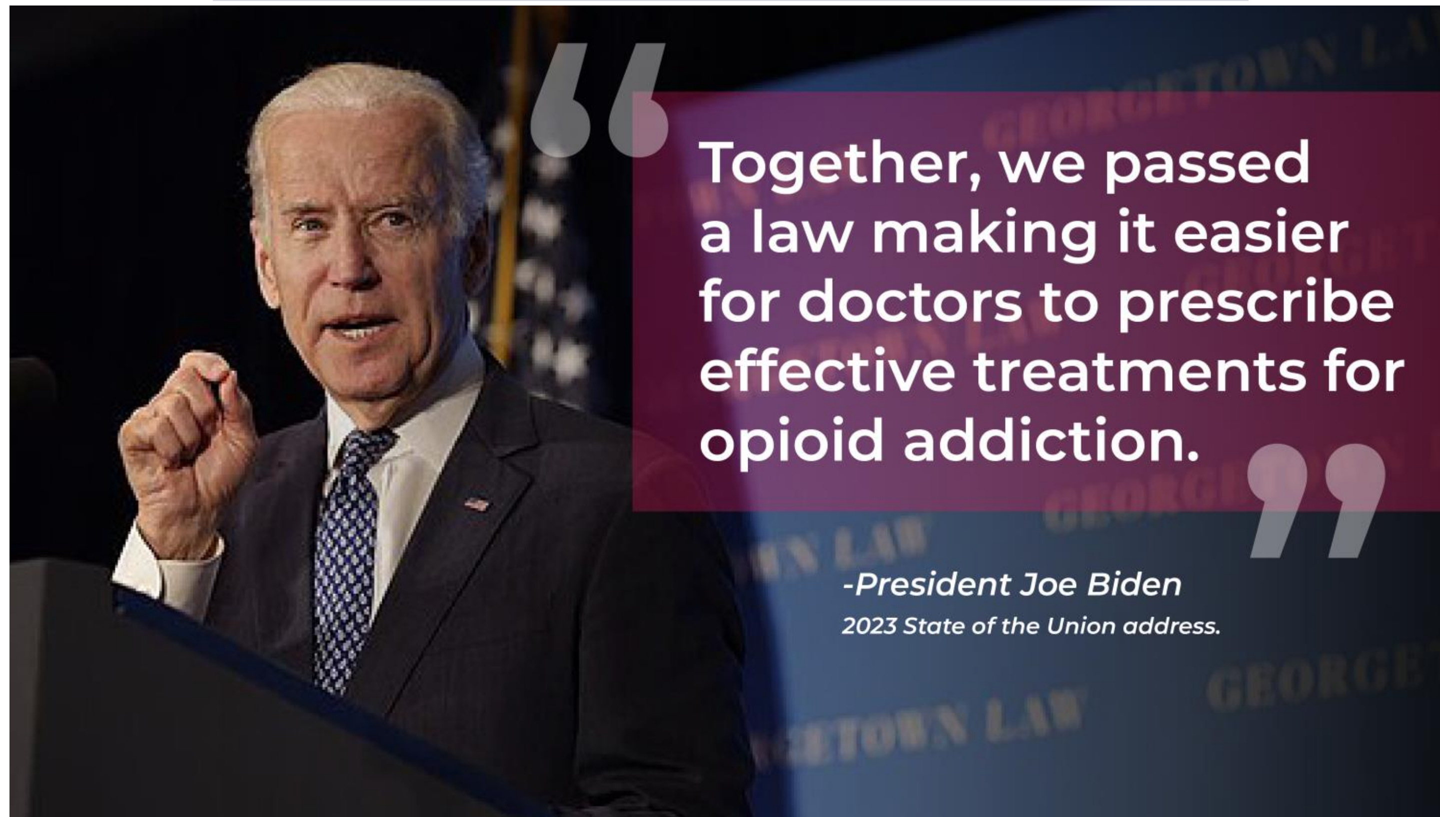
- In heart of hospital, 50 ft from ED
- Staffed by addiction specialists, primary care, and ID physicians
- On-demand treatment including walk-ins (AUD/OUD)
- Recovery coaches / Resource specialist / Social worker

Longer-term SUD treatment

JANUARY 25, 2023

White House Hosts Event to Mark Removal of Barriers to Addiction Treatment

ONDCP ▸ BRIEFING ROOM ▸ PRESS RELEASES



DEA waiver is no longer needed to prescribe buprenorphine

- **All practitioners who have a DEA registration that include Schedule III drugs can now prescribe buprenorphine**
- After June 2023, DEA and SAMHSA will still require that all DEA registrations complete a training in OUD treatment which will be required for those newly applying or renewing their registration
- No caps or limits will be imposed
- There may be **state laws** that prohibit physicians from prescribing

Updated regulations for Opioid Treatment Program (OTP) which provide methadone maintenance

- Methadone maintenance has been around since the 1970s with minimal changes to the rules

- Updated rules since April 2024

  - Remove requirement for 1 year of OUD history
  - Can initiate treatment at higher doses
  - Receipt of medication no longer contingent on counseling
  - Permit take-home doses much earlier in treatment
  - Audio-visual telehealth visit permitted for methadone initiation
  - Permit NPs and PAs to order MOUD for dispending at OTP

Summary

- Opioid epidemic continues to be a public health crisis, made worse by COVID
- Buprenorphine is highly effective in preventing overdoses, and improving lives
- Novel induction strategies are needed in the “fentanyl-era”
- Liberalization of regulations now permit greater access to life-saving treatments

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