Bridging the Gap: Updates in Substance Use Treatment in the ED

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Learning Objectives

- Discuss updates in treatment of alcohol use disorder and alcohol withdrawal in the ED
- Utilize novel strategies to start buprenorphine in challenging cases
- Understand navigation for between acute care and outpatient addiction treatment

Disclosures

No relevant financial relationship with commercial interests to disclose.

I will discuss off-label medications

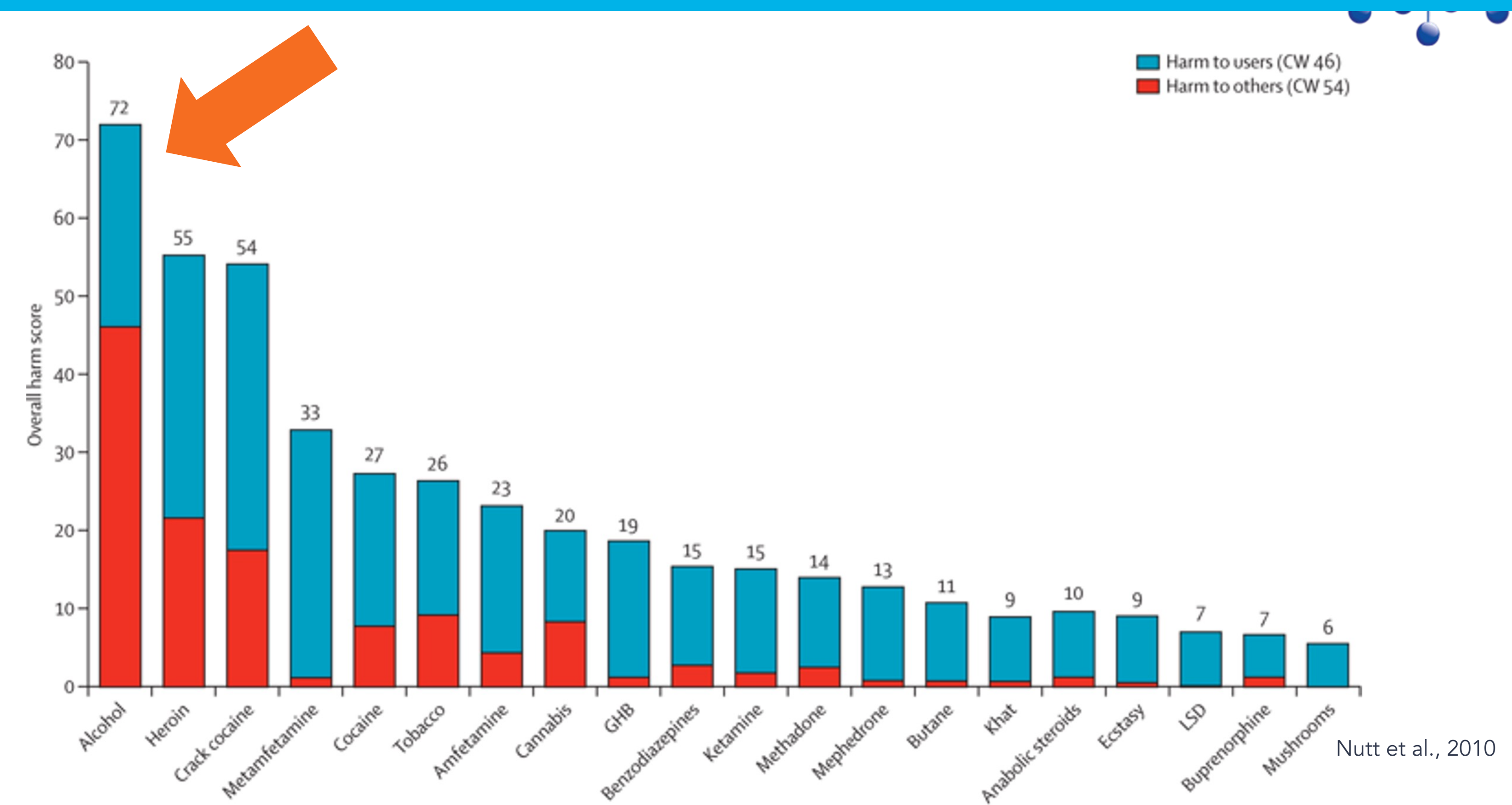
Receive Funding from:

NIH for NIDA Clinical Trial Network Studies: -0099 & -0131

PCORI evaluating linkage and retention techniques for patients with OUD

Alcohol Use Disorder: A worsening public health crisis

Alcohol use causes *most* harm compared to other substances.



Nutt et al., 2010

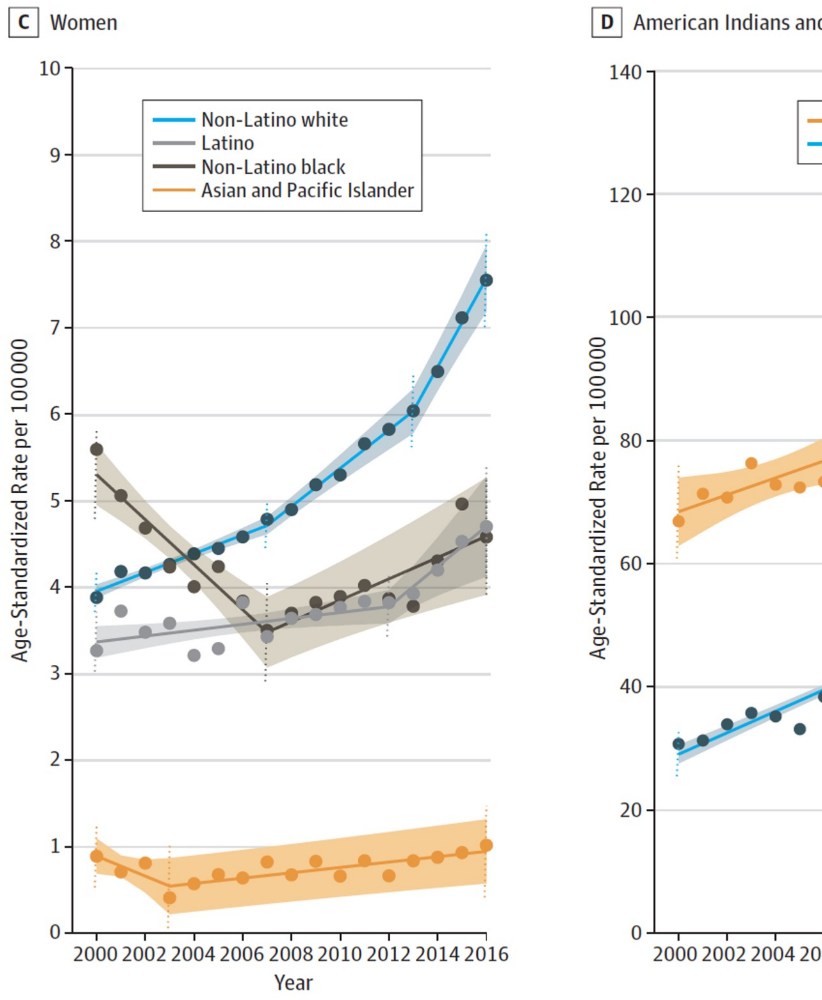
Racial & Ethnic Disparities

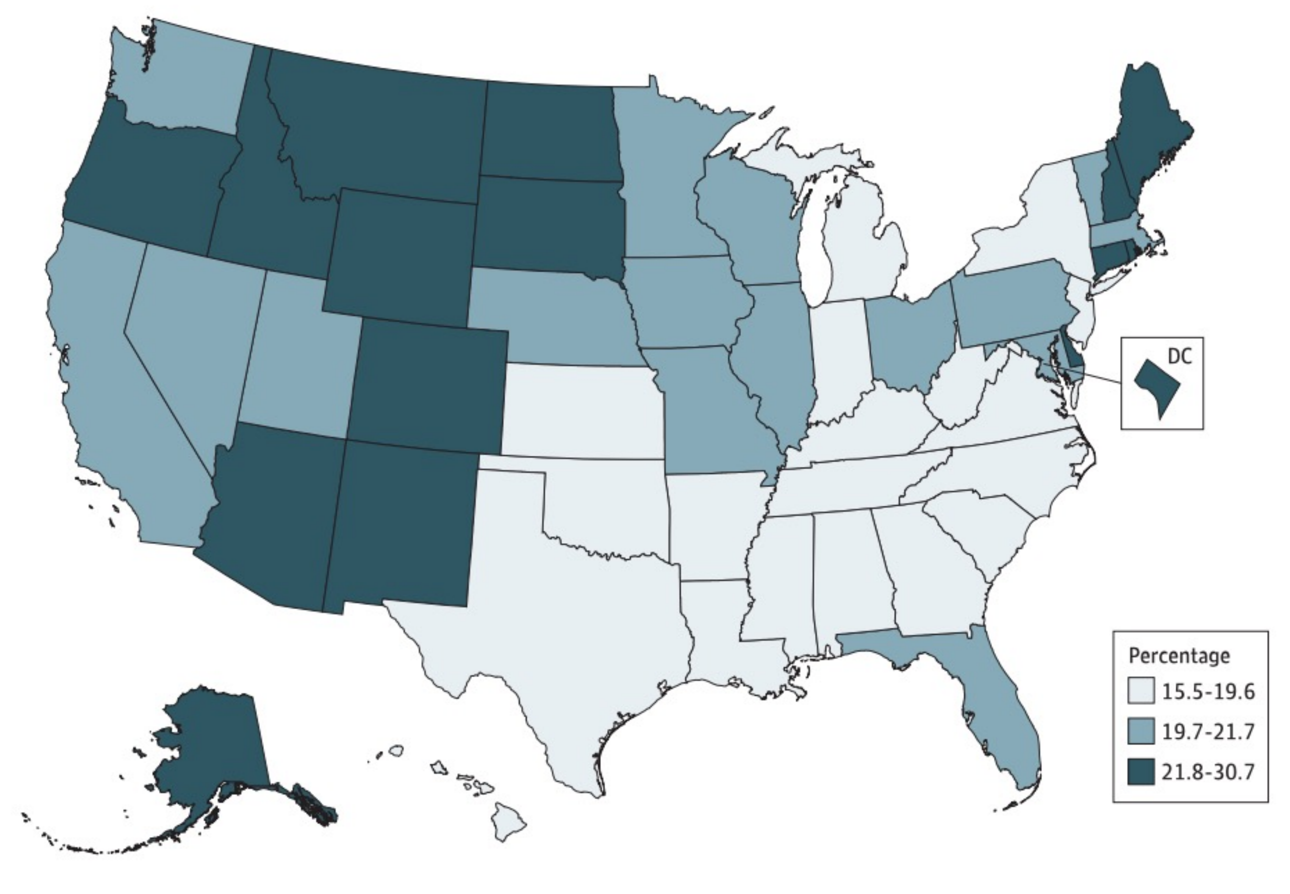
Mortality increasing for nearly all demographic groups

Largest increase in American Indian & Alaska Native individuals and non-Latinx White women

Specifically within AI/AN community, historical trauma, social determinants, and stigma need to be considered

Spillane 2020





Esser et al. Jama Open 2022.

Cross sectional study 694,600 deaths from 2015-2019

1 in 8 deaths for ages 20-64 attributable to excessive alcohol use

Harms of unhealthy alcohol use rose during first year of COVID-19 pandemic

Alcohol related deaths increased 25% during first 18 months of pandemic

Outpaced increases in all-cause mortality

Pollard et al JAMA
White et. al. JAMA

Patients with AUD often have psychosocial considerations impacting care

- 40% patients presenting to HGH ED have unhealthy alcohol use
  - Half documented in Epic
- Patients with unhealthy alcohol use have higher rates of:
  - Homelessness and unstable housing
  - Social/emotional/physical trauma history
  - Other substance use disorders

Anderson et al. J Addiction Med

Only **1 in 10** patients with AUD receive any treatment

Pharmacotherapy indicated for moderate-severe AUD

Only *1 in 20* are on medications for AUD.

Kranzler et al.

Alcohol withdrawal and use disorder management

- Alcohol withdrawal represents an opportunity to recognize and treat AUD
- Our treatment of withdrawal can have an impact on engagement in addiction treatment

“A condition in which the standard of care has a limited evidence base and has changed little over several decades.”

Smith et al, JAMA Open

A double-blind comparison of the efficacy and safety of lorazepam and diazepam in the treatment of the acute alcohol withdrawal syndrome.

Miller WC Jr, McCurdy L

Clinical Therapeutics, 01 Jan 1984, 6(3):364-371
PMID: 6722863

1984

Annals of Emergency Medicine
Volume 76, Issue 6, December 2020, Pages 774-781

Toxicology/original research

Lorazepam Versus Diazepam in the Management of Emergency Department Patients With Alcohol Withdrawal

Frank X. Scheuermeyer MD, MHSc [a, b], Isabelle Miles MD [a, b, c], Daniel J. Lane PhD [d], Brian Grunau MD,

Benzodiazepines

- Most consistently studied for severe withdrawal (usually vs placebo!)
- No clear superior BDZ
- Effective in preventing seizures from alcohol withdrawal
- Most common symptom triggered, though based on ambulatory setting
- May have lower BDZ usage in symptom triggered vs fixed dose

Holleck et al. JGIM 2019; Amato et al Cochrane

Phenobarbital

Typical dosing up to 20 mg/kg on day 1; often given 130-260mg q30min PRN

- Can be given has an initial 10 mg/kg load for moderate to severe withdrawal

Similar safety profile to BDZ when given as monotherapy or lower dose adjunct

When given as a high dose alongside high doses of benzos, concern for higher rates of hemodynamic issues

Long half life, may facilitates higher overall benzo equivalent dosing

Rosenson et al. J Emerg Med. 2013; Lebin et al. J Med Tox. 2022; Tidwell et al. Am J Crit Care 2018; Lee et al ACEP 2022

Phenobarbital

In individual trials compared to BDZ:

- Decreased ICU admissions and LOS
- One small RCT with fewer intubations
- Decreased ED recidivism in single center study from SF

Phenobarb as adjunct to BDZ:

- Either decreased hospital LOS or no significant difference
- Variable dosing of phenobarbital

Meta analysis: Similar safety and effectiveness to BDZ, low level of evidence overall

Rosenson et al. J Emerg Med. 2013
Lebin et al. J Med Tox. 2022
Tidwell et al. Am J Crit Care 2018
Lee et al ACEP 2022

Framework

1

Need “loading doses” and initial treatment with benzos or phenobarbital

2

After stabilization, minimize harms of medications

3

Consider treatment *in context of underlying substance use disorder*

Benzo-Sparing approaches may help acutely and improve drinking outcomes

- Gabapentin
- Carbamazapine
- Valproic Acid
- Ketamine
- Dexmedetomidine

Gabapentin

- Several retrospective cohort studies inpatient, two RCTs in ambulatory settings
- Can be used to promote abstinence in AUD patients with AWS history after withdrawal managment
- Use supported as adjunct by ASAM and VA Clinical Practice Guideline OR as monotherapy for low-risk patients

Gabapentin for AWS (and AUD)

Opportunity to consider in similar framework as buprenorphine for OUD:

Treat withdrawal and maintain for relapse prevention

Alcohol Withdrawal

600-900 mg PO TID

→

Alcohol Use Disorder

600-900 mg PO TID

Carbamazapine

9 RCT showing similar or better than BDZ, placebo, or other AEDs. All in low risk patients

Option in some inpatient protocols, but few studies in that setting

Use as adjunct supported by ASAM and VA CPG OR as monotherapy for low-risk patients

Maldonado et al

Valproic Acid

6 RCTs in outpatient detox settings (all old) showing benefit of VPA compared to BDZ, placebo, or carbamazepine.

Inpatient studies are retrospective and mixed results (either no benefit, or slightly favor VPA)

Use as adjunct supported by ASAM, VA CPG

Ketamine

NMDA-r antagonist, use as infusion in most studies

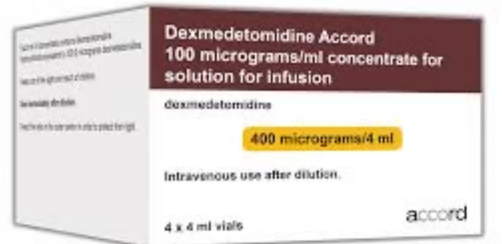
0.2-0.3mg/kg usual dosing, up to 1.6mg/kg/hr

Largely in ICU studies alongside high doses of BDZ

Associated with with rapid CIWA scores reduction in refractory AWS cases

Pizon et al 2018;
Wong et al 2014;
Shah 2018

Dexmedetomidine



Central alpha 2 agonist

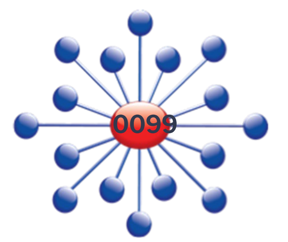
2 RCTs (n=51), 3 cohort studies (n=121)

No differences in hospital LOS*, BDZ requirements

More bradycardia in dex groups

Polintan et al 2022

AUD treatment for ED and hospitalized patients



SBIRT and motivational interviewing can have long term impact for patients

SUNs effective at linking patients to outpatient addiction treatmtent

Several studies describe AUD treatment interventions

Multiple studies show comprehensive inpatient consult services decrease LOS, readmissions

D'Onofrio et al; Barata et al
Anderson et al; Wei et al

Medications for AUD

FDA Approved

Naltrexone

Disulfiram

Acamprosate

Off-Label

Gabapentin

Topiramate

Baclofen

Naltrexone in Acute Care setting

Two cohort studies for hospitalized patients implemented XR-Naltrexone

- Found to have lower ED visits, readmissions

One ED study implemented PO and XR-Naltrexone

- High rates of treatment engagement, reduced drinking at follow up

Wei et al.
Kirchoff et al.
Anderson et al.

Naltrexone

Number needed to treat (NNT) 12 prevents return to heavy drinking

Effective in an office-based setting

Once daily dosing vs. monthly injection

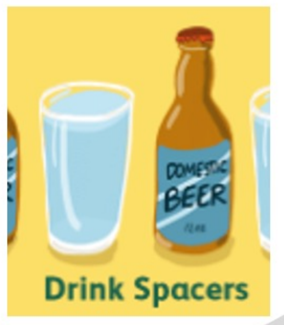
Extended-release is promising for acute care patients

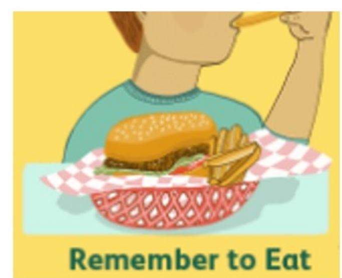
Combining behavioral harm-reduction treatment and extended-release naltrexone for people experiencing homelessness and alcohol use disorder in the USA: a randomised clinical trial

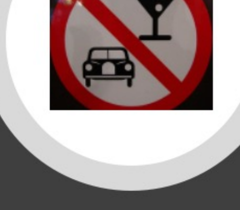
Susan E Collins, Mark H Duncan, Andrew J Saxon, Emily M Taylor, Nigel Mayberry, Joseph O Merrill, Gail E Hoffmann, Seema L Clifasefi, Richard K Ries

Harm reduction counseling + XR-NTX is Efficacious

Improved mental, physical quality of life; fewer drinks per day; lower harms from drinking







Harm Reduction for Alcohol

When you should *not* use Naltrexone

- Opioid use (clear history or naloxone challenge)
- Liver function tests >5x upper limit of normal (ULN) or decompensated cirrhosis*

Alcohol Summary

- Thoughtful approach to AWS may have acute and long term benefits
- Adjuncts may be a useful tool to spare benzos and start addiction treatment
- AUD treatment can and should be started in the ED

Linkage to care from Emergency Department to Addiction Treatment

- Initiating treatment should be paired with active efforts to link to ongoing treamtent
- Connection to clinics can be challenging in many settings

ED Substance Use Navigation

- Large body of evidence that bedside brief interventions for SUD in the ED has an impact long term outcomes
- Bup + navigation has high rate of follow up in clinical trials
- Substance use navigators (SUNs) are now widespread across CA and other parts of the country

What is a Substance Use Navigation?

	Bedside Counseling	Harm Reduction	ED-Initiated Pharmacotherapy	Low-Threshold Bridge Clinic
Bundled SUN Intervention	Motivational interviewing conducted by Substance Use Navigator Integration of social factors into recovery plan Strength-based navigation	Development of personal recovery plan integrating patient treatment goals (i.e. abstinence or decreased use) Harm reduction kits provided to patient at bedside	Nudge via EHR chat or in-person to emergency clinicians to use locally established ED treatment protocols for SUDs Navigate pharmacy barriers for discharge prescriptions	Directly schedule patients in clinic at patient preferred date and time Facilitate same day, post-discharge, clinic visits if desired Direct communication with addiction specialist for consultations when indicated

ED, **emergency department;** ***SUD,*** **substance use disorder;** ***SUN,*** **substance use navigator;** ***EHR,*** **electronic health record.**

ED Substance Use Navigation

- 1,328 patients discharged from HGH ED
- On-site SUNs with whole person care approach
- Some with lived experience, all from East Bay communities impacted by substance use
- 5 day a week low-threshold clinic, in-person or telemedicine
- Available to patients with any substance use disorder

Anderson et al Ann Emerg Med

ED Substance Use Navigation

30 day engagement in addiction treatment

- **50% with SUN vs 16% without SUN**

Medication for SUD administered

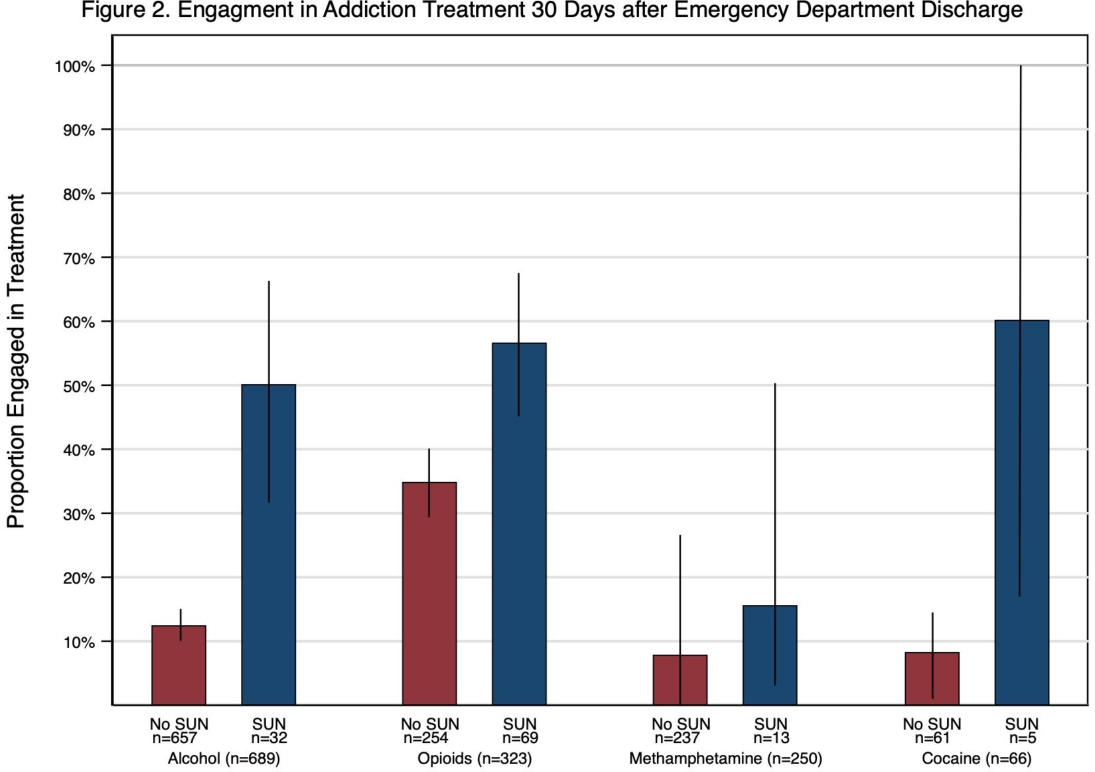
- **40% with SUN vs 17% without SUN**

Medication for SUD prescribed at discharge

- **47% with SUN vs 21% without SUN**

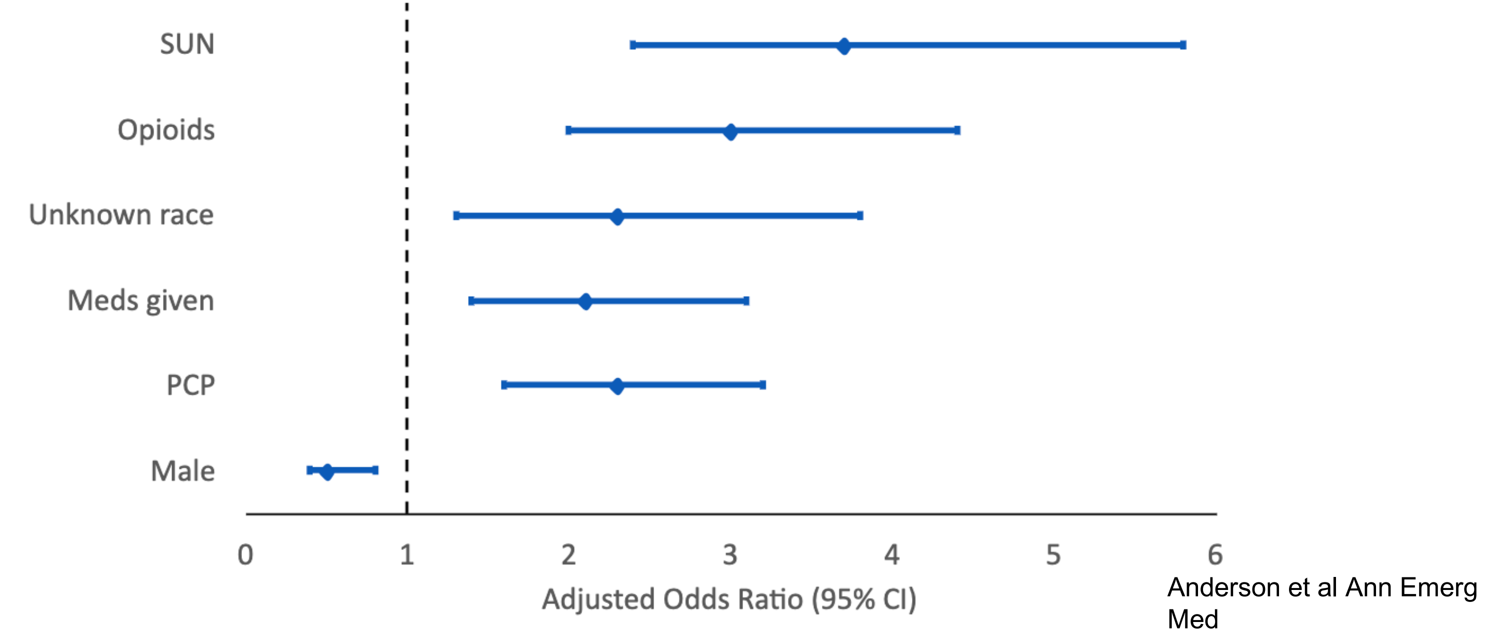
Anderson et al Ann Emerg Med

ED Substance Use Navigation



Anderson et al Ann Emerg Med

ED Substance Use Navigation



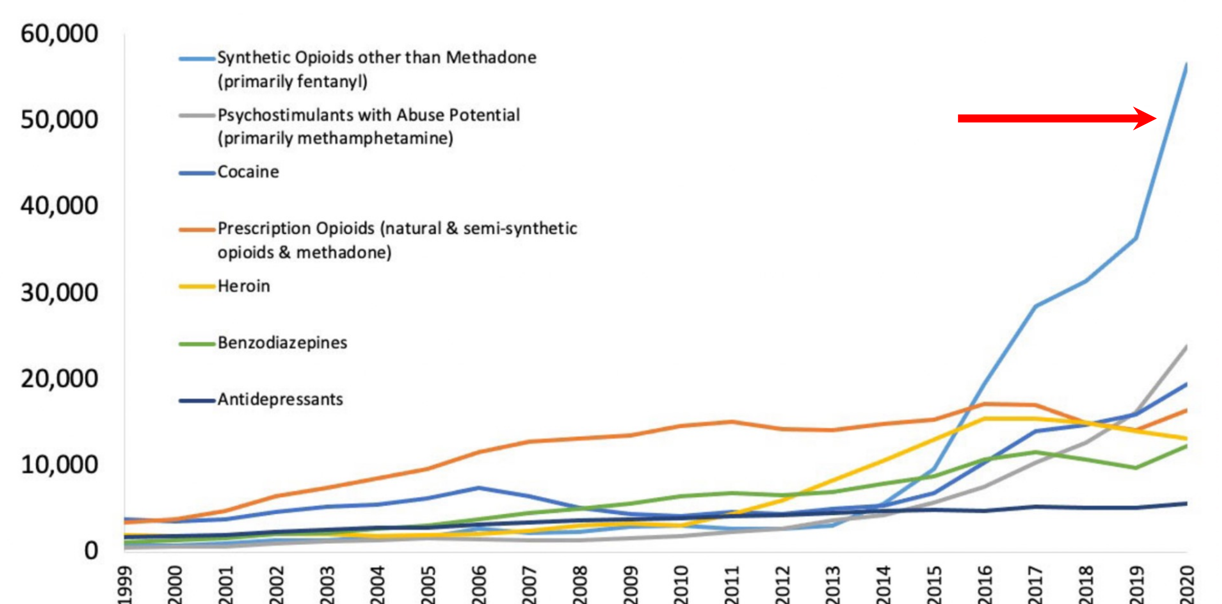
Anderson et al Ann Emerg Med

ED Substance Use Navigation

- Substance use navigation is independent predictor of engaging in addiction treatment after acute care
- A whole person care approach may be a useful framework to use
- Care from SUNs that is culturally competent from the community will improve efforts

Opioids

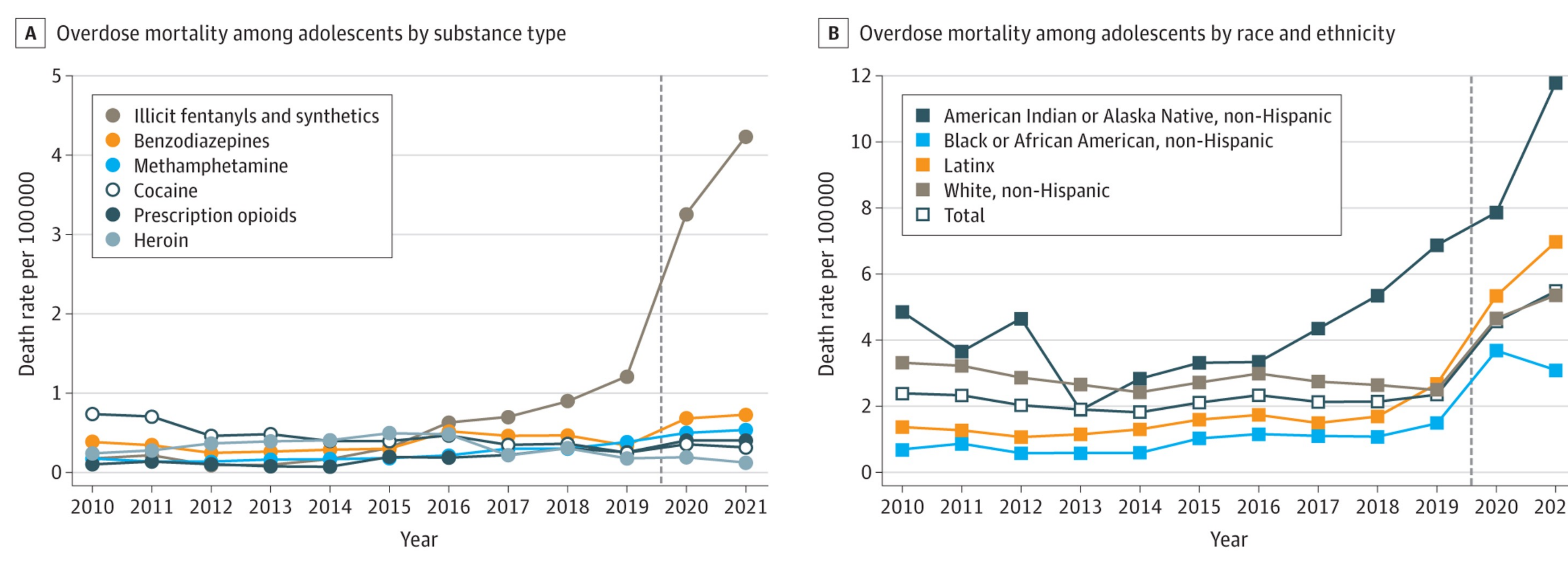
The Problem: Overdose deaths are *skyrocketing*



- **91,799** overdose deaths in 2020
- **107,622** overdose deaths in 2021
- **110,000** overdose deaths in 2022
- **112,000** overdose deaths 2023
- Annual drug overdose deaths exceed those from motor vehicle crashes, gun violence, and HIV at its peak
- **Fentanyl** use and overdose is **on the rise** in our region

Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021
Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2022.

Trends similar among adolescents and worsening disparities



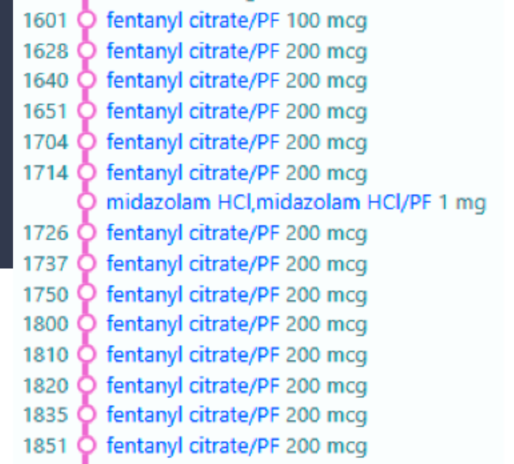
Friedman J, Godvin M, Shover CL, Gone JP, Hansen H, Schriger DL. Trends in Drug Overdose Deaths Among US Adolescents, January 2010 to June 2021. JAMA. 2022;327(14):1398–1400. doi:10.1001/jama.2022.2847

Medication treatment for opioid use disorder *reduces the risk of death from any cause by more than 50%* and represents the standard of care.

***Yet*, only about 1 in 5 people with OUD receive any medication treatment.**

Santo T, Clark B, Hickman M, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021;78(9):979–993. doi:10.1001/jamapsychiatry.2021.0976
Jones CM, Han B, Baldwin GT, Einstein EB, Compton WM. Use of Medication for Opioid Use Disorder Among Adults With Past-Year Opioid Use Disorder in the US, 2021. JAMA Netw Open. 2023;6(8):e2327488. doi:10.1001/jamanetworkopen.2023.27488

Landscape has changed



- Typical patient who says “I smoke 2g of fentanyl a day”
  - Smoking fentanyl has >90% bioavailability
  - Purity is approximately 20% in SF drug testing programs
- 2g of fentanyl = 2,000,000 mcg x 20% = **400,000 mcg of fentanyl daily**
- Patients managed with iOAT in Canada receive 2000-4000mcg iv fentanyl q1h prn

Starting Buprenorphine

- Typical approach
- Novel strategies

Case 1: Typical Buprenorphine Initiation from Fentanyl

- 22 yo F smoking fentanyl for 3 years
- Presents to ED with a COWS of 14, large pupils, yawning, piloerection

Case 1: Typical Buprenorphine Initiation from Fentanyl

- 22 yo F smoking fentanyl for 3 years
- Presents to ED with a COWS of 14, large pupils, yawning, piloerection

- Receives 16mg SL bup → COWS 10
- Repeats 16mg SL bup 2 hours later → COWS 2

- Discharged with gabapentin, trazodone
- Returns to clinic next day feeling better, reports hot flashes in evening

Case 1: Typical Buprenorphine Initiation from Fentanyl

- Opts to continue SL bup at 32mg daily without fentanyl use
- After month 2 switches to XR-Bup (300mg sublocade)
- Remains engaged in treatment 6 months later

Home-Based Simplified Bup Start Guide

- Great for uncomplicated starts
- ***Need 2 objective withdrawal signs***
- Advise >24 hours
- *Utilize other supportive meds*

Wait, Withdraw, Dose

Starting Buprenorphine (Bup), "Subs," Suboxone

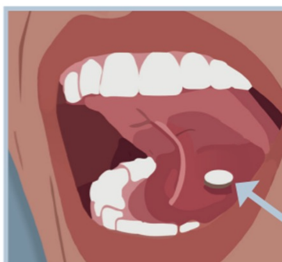
1. Plan to take a day off and have a place to rest.
2. Stop using and wait until you feel sick from withdrawals (at least 12 hours is best).
3. Dose an 8mg tablet or strip UNDER your tongue.
4. Repeat dose (another 8mg) in an hour to feel well.
5. Start 16mg per day the next day.

If you have started Bup before:

- If it went well, that's great! Just do that again.
- If it was difficult, talk with your care team to figure what happened and find ways to make it better this time.

If you have never started Bup before:

- Gather your support team and if possible take a "day off."
- You are going to want space to rest. Don't drive.
- Using cocaine, meth, alcohol or pills actually makes starting Bup harder, but that is up to you. Be safe.



Place dose under your tongue (sublingual).

Case 1: Typical Buprenorphine Initiation from Fentanyl

- Common adjuncts to buprenorphine initiation (“kick pack”)
  - Gabapentin 600mg po q8h PRN anxiety/insomnia
  - Clonidine 0.2mg po q8h prn withdrawal
  - Pramipexole 0.25mg po q8h prn restlessness

Case 1: Typical Buprenorphine Initiation from Fentanyl

- Most recent data in "fentanyl era" shows higher dose SL bup (at least 24mg) associated with 20% improved retention in care

- Reflects our clinical practice

Figure 2. Time to Buprenorphine Treatment Discontinuation in the 180 Days After Initiation, by Daily Dose Starting on Day 0 (Primary Analysis)

Daily dose
16 mg
24 mg

Survival probability
1.0
0.8
0.6
0.4
0.2
0

Log rank $P = .01$

0
50
100
150
200
Time since initiation of treatment, d

No. at risk					
16 mg	3264	1176	803	624	0
24 mg	690	350	270	222	0

Chambers et al. JAMA Open

Novel Strategies for Buprenorphine Initiation

- Prior precipitated withdrawal
- Low withdrawal tolerance
- >2-3g/day of fentanyl and co-occurring meth use
- Transition from methadone > 40mg

Case 2: ED visit for non-fatal fentanyl overdose

- 23 yo M living in encampment in W Oakland
- Smokes 1g/day fentanyl, uses meth daily
- Found with RR 6, somnolent, hypoxic → EMS gave 0.5mg iv naloxone

Non-Fatal overdose is the STEMI of Addiction Medicine

- ED visit for non-fatal overdose should activate a system of care similar to "heart alert"

Landmark Study from Massachusetts Patients with OUD:

- 5% died within 1 year
- 1/5 die in the first month
- Average age 39 years old

STEMI in PCI Era:
- 7% mortality within 1 year
- ½ within first month

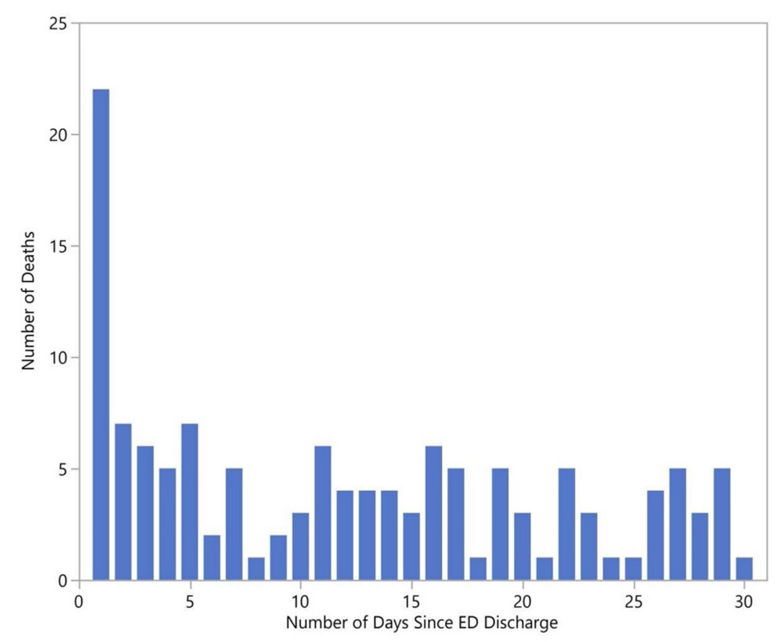


Figure 2:
Number of deaths after emergency department treatment for non-fatal overdose by number of days after discharge in the first month, by day, n=130.

Weiner et al Ann Emerg Med
Hosseiny et al Inter Card

Case 2: ED visit for non-fatal fentanyl overdose

- 23 yo M post overdose
- Recurrent respiratory depression and hypoxia reversed with low-dose buprenorphine
- Admitted for mild hypoxia thought to be from aspiration
- Used "cross taper with continuation of full agonist" to transition to XR-Bup by hospital day 2

7:30am EMS naloxone

8:30am COWS 4 post naloxone

10:00 Recurrent resp depression

Reversed with 0.1 iv Bup q30min x 6

11:30 COWS 10

200mcg IV Fent

COWS 3

Initiated Bup cross taper

300mg XR-Bup on HD #2

Case 2: Inpatient Cross Taper

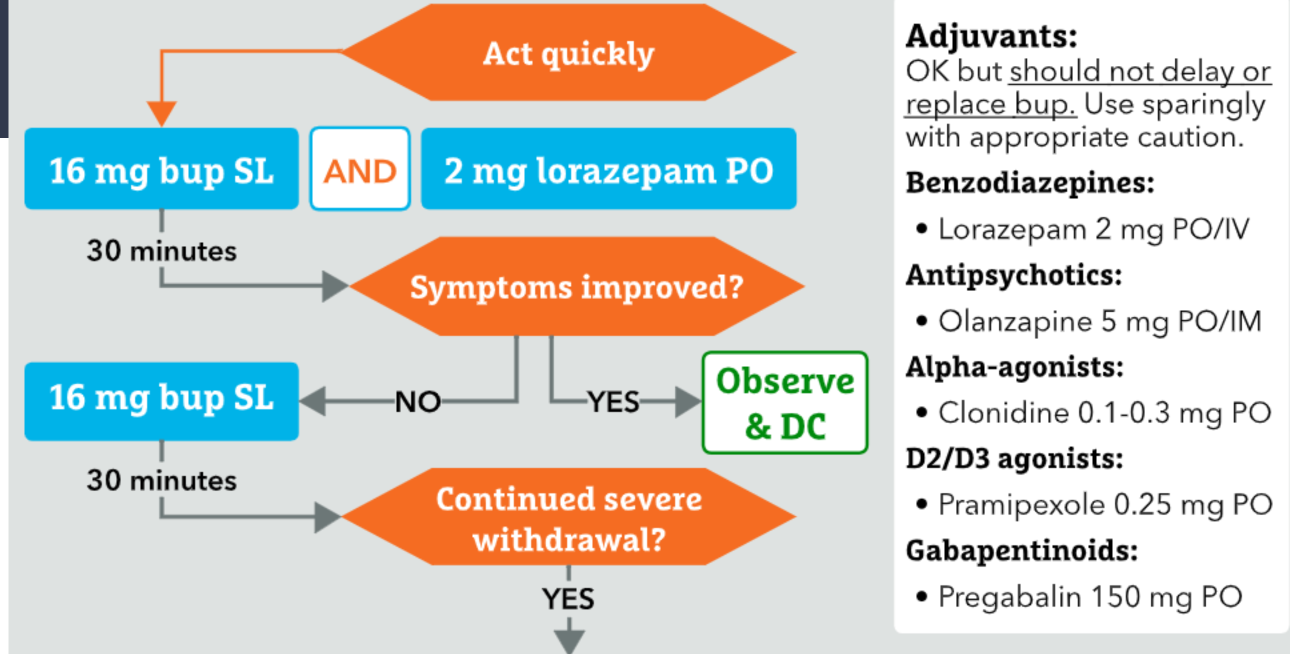
Full agonist opioid*	Full agonist opioid	Full agonist opioid
1. MorphineER 30-60 mg PO Q 8h scheduled 2. Morphine IR 15-30 mg PO Q 2h PRN 3. Morphine 10-20 mg IV Q 2h PRN ** increase or decrease based on clinical assessment of tolerance. See reverse for equivalent opioids (e.g hydromorphone)*	*Increase for pain and withdrawal.* *Decrease for sedation*	*Increase for pain and withdrawal.* *Decrease for sedation*
Buprenorphine	**Buprenorphine**	**Buprenorphine**
1 mg SL *(1/2 of 2 mg tab)* Q 6 hrs for 4 doses. **If dose(s) are missed** (e.g.sleep), continue when awake for 4 total doses.	1 mg SL *(1/2 of 2 mg film)* Q 3 hrs for 8 doses	8 mg SL TID *or* 300mg XR Buprenorphine

Case 2: ED visit for non-fatal fentanyl overdose

- Transition from overdose with high mortality within 1 month → 1 month of long-acting injectable buprenorphine
- High-value care for high-risk patient – especially compared to typical approaches to overdose
- Inpatient and ED can use full agonists to support withdrawal management

Case 3: Precipitated withdrawal to XR

- 44 yo F with fentanyl use disorder, 2g/day smoking and uses meth by injection
- Presented to ED with COWS of ~12, 1 objective sign of withdrawal (mid-range pupils), last use 20 hours prior
- COWS post 8mg SL bup x 2 → COWS of ~25


Treatment of bup precipitated withdrawal
(Sudden, significant worsening of withdrawal soon after bup administration.)
Act quickly
16 mg bup SL
AND
2 mg lorazepam PO
30 minutes
Symptoms improved?
NO
YES
16 mg bup SL
Observe & DC
30 minutes
Continued severe withdrawal?
YES
Adjuvants:
OK but should not delay or replace bup. Use sparingly with appropriate caution.
Benzodiazepines:
• Lorazepam 2 mg PO/IV
Antipsychotics:
• Olanzapine 5 mg PO/IM
Alpha-agonists:
• Clonidine 0.1-0.3 mg PO
D2/D3 agonists:
• Pramipexole 0.25 mg PO
Gabapentinoids:
• Pregabalin 150 mg PO
Escalate level of care to manage potential moderate to deep sedation including cardiac, pulse oximetry, and end tidal CO2 monitoring:
1. Ketamine (0.3 mg/kg IV slow push q 15 minutes and/or infusion).
2. Fentanyl 200 mcg IV q10 minutes. Total dose of > 2000 mcg has been reported.
After clinical resolution, observe and discharge with bup Rx and/or XR-bup

Buprenorphine SL
Initial treatment: 8mg + 8mg
POW treatment: 16mg SL
Total 32mg SL
(Plus Lorazepam 2mg PO x1)

Ketamine brief infusions
30mg then 40mg
Total 70mg IV
(Plus versed 1mg IVx 1)

Fentanyl 200mcg IV boluses
Total 3,000 mcg over 5 hrs

After Fentanyl (restless)
Clonidine 0.3mg PO x1
Pramipexole 0.5mg PO x 1

Sleep under ED observation

Next morning
Sublocade 300mg SC

02/26

Time	Event
1121	Arrived
1255	gabapentin 900 mg
	buprenorphine HCl 8 mg
1256	acetaminophen 650 mg
1257	ibuprofen 600 mg
1306	hCG, quantitative, pregnancy
	Hepatitis C Antibody with Reflex to Viral Load
	SYPHILIS SCREENING PANEL
	HIV Ab/Ag with reflex to viral load
1319	buprenorphine HCl 8 mg
1323	C. trachomatis / N. gonorrhoeae, DNA probe
1405	lorazepam 2 mg
	buprenorphine HCl 16 mg
1441	ketamine (KETALAR) 10 mg/mL 30 mg in sodium... 30 mg
1517	fentanyl citrate/PF 100 mcg
1518	ketamine (KETALAR) 10 mg/mL 40 mg in sodium... 40 mg
1601	fentanyl citrate/PF 100 mcg
1628	fentanyl citrate/PF 200 mcg
1640	fentanyl citrate/PF 200 mcg
1651	fentanyl citrate/PF 200 mcg
1704	fentanyl citrate/PF 200 mcg
1714	fentanyl citrate/PF 200 mcg
	midazolam HCl,midazolam HCl/PF 1 mg
1726	fentanyl citrate/PF 200 mcg
1737	fentanyl citrate/PF 200 mcg
1750	fentanyl citrate/PF 200 mcg
1800	fentanyl citrate/PF 200 mcg
1810	fentanyl citrate/PF 200 mcg
1820	fentanyl citrate/PF 200 mcg
1835	fentanyl citrate/PF 200 mcg
1851	fentanyl citrate/PF 200 mcg
2021	fentanyl citrate/PF 200 mcg
2033	clonidine HCl 0.3 mg
2057	pramipexole di-HCl 0.5 mg

02/27

Time	Event
1101	ketorolac tromethamine 15 mg
	clonidine HCl 0.3 mg
1238	Discharged

Case 3: Precipitated withdrawal to XR

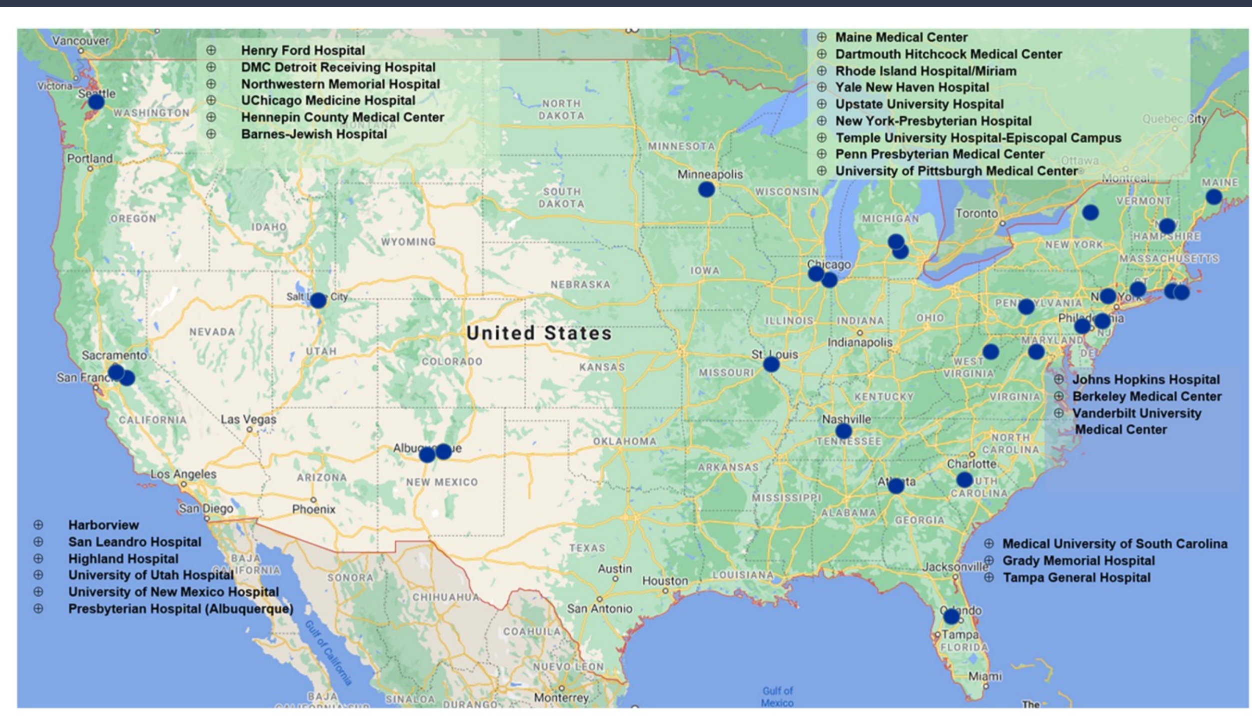
- Precipitated withdrawal protocols available and can help
- Most improve with oral/IM benzo and additional SL bup
- Once recognized and treated, goal is XR-Bup
- Rescue for severe or refractory cases is frequent pushes of fentanyl titrated to comfort
- >60% of patients with precipitated withdrawal remain engaged in care at 30 days (AHS Bridge)

Case 4: Direct to Injection

- 38 year old female with OUD, smokes 1g/fentanyl daily
- Presents with COWS of 7, last use 30 hours prior
- Randomized as part of clinical trial to 24mg Buprenorphine CAM2038 (Brixadi)

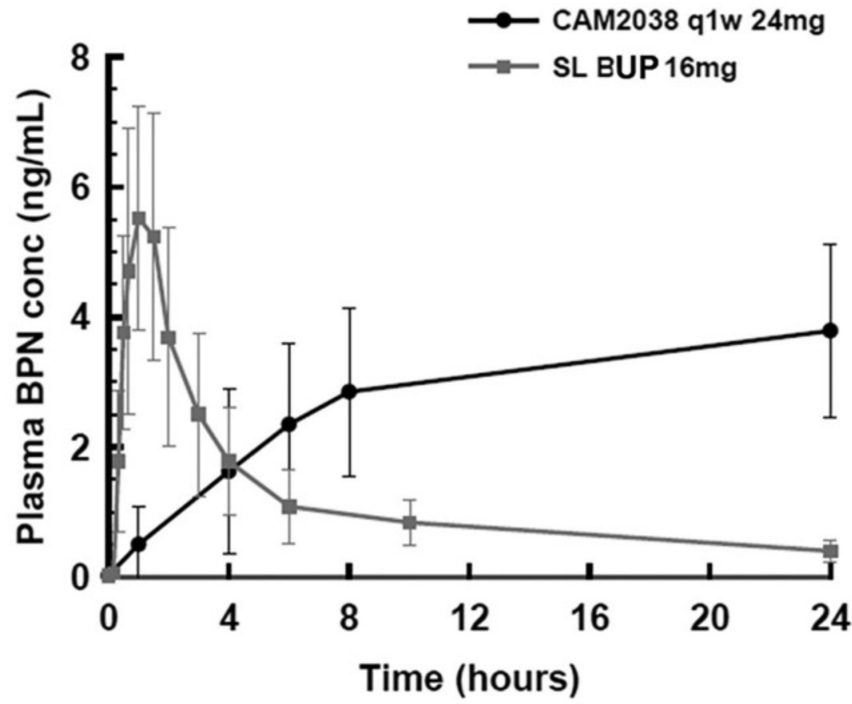
Case 4: Direct to Injection

- Multicenter RCT, nearing 2000 enrollments
- Bup SL vs XR
- Primary outcome 7 day follow up
- COWS 4+ eligible for XR vs home start
- COWS 8+ eligible for XR vs SL induction



Case 4: Direct to Injection

- Brixadi now approved by FDA, covered by MCAL
- Weekly or monthly formulations
- On-label use after 4mg SL bup



Case 4: Direct to Injection

- Tolerates injection well, COWS decreases to 2 within 2 hours
- Presents to clinic 5 days later, has not used fentanyl
- Receives month long injection of buprenorphine
- Remains engaged in addiction treatment 4 months later

Summary: Opioids

- Fentanyl has made OUD a more fatal disease and novel approaches to starting buprenorphine are utilized
- Precipitated withdrawal protocols can help improve treatment (CA Bridge has multispecialty endorsed protocol)
- Injectables a promising opportunity for ED patients

Summary

- Alcohol use disorder treatment should be integrated into withdrawal management for ED and hospitalized patients
- ED Substance Use Navigators can improve linkage to care and treatment outcomes
- Buprenorphine is a life saving medication with novel treatment approaches in the era of high-potency illicit opioids

Thanks!