Medications for Opioid Disorder:

Overview and Practical Considerations in the era of Synthetic Opioids

Oluwole Jegede MD PhD

Assistant Professor of Psychiatry

Addiction Physician

Yale Medicine/Connecticut Mental Health Center

Conflicts of interest

- No conflicts of interest to disclose

Learning Objectives

- At the end of this webinar, participants will be able to:
  - Summarize current trends in opioid use disorder (OUD) mortality and key epidemiologic patterns in the era of fentanyl.
  - Compare the mechanisms of action, dosing, monitoring, and adverse effects of medications for OUD (MOUD).
  - Apply a practical decision matrix to select MOUD based on patient factors, treatment setting, and clinical goals.
  - Identify common barriers to community-based MOUD prescribing and select strategies to address them.

Opioid Use Disorder (OUD)

- OUD is a chronic, relapsing, compulsive use of opioids resulting in functional impairments across all contexts.
- Third most prevalent SUD worldwide.
- In the U.S, 5.7 million people aged 12 or older had OUD in the past year.
- It often co-occurs with other SUD and psychiatric disorders

Of Opium, opiates and opioids

- Opium is a natural, unrefined substance obtained from the seed pod of the poppy plant which contains several opioid alkaloids

- Opiates are derived from the plant. They are natural or minimally modified plant derivatives.
  - Morphine
  - Codeine
  - Thebaine
  - Heroin (semi-synthetic, derived from morphine)

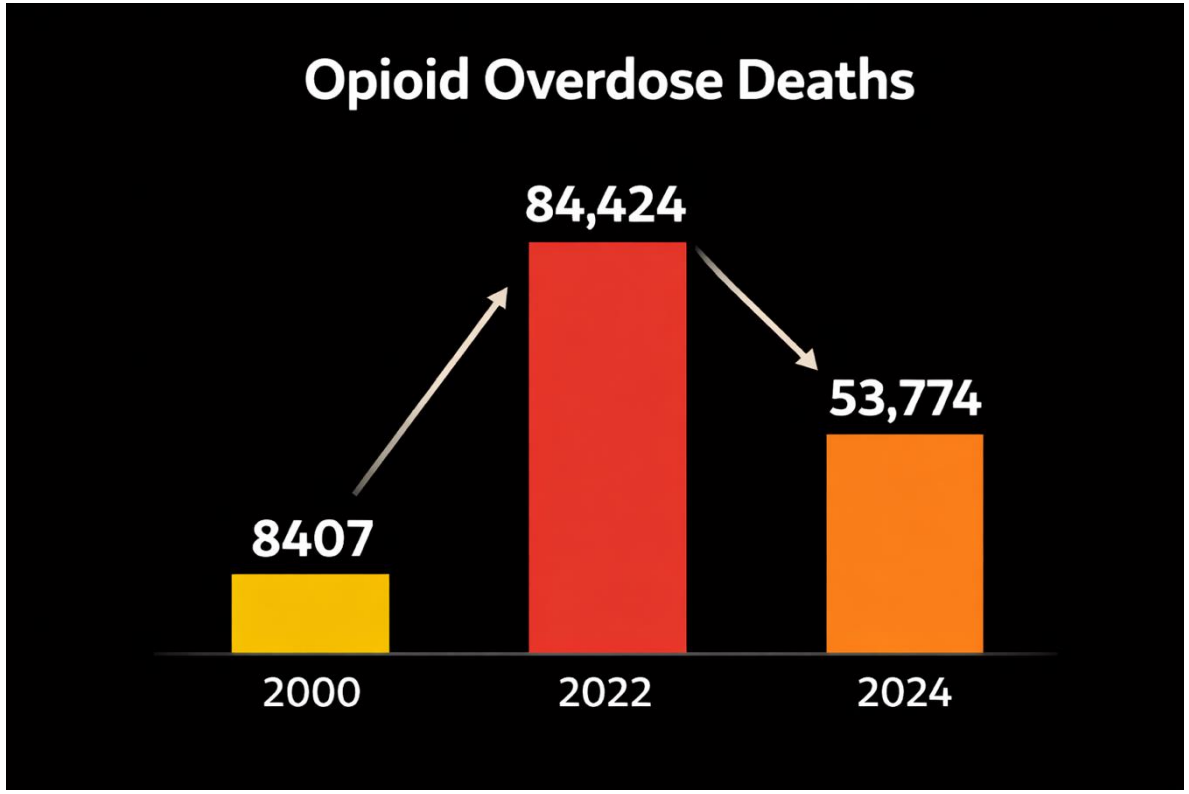
- Opioids refer to any substance — natural, semi-synthetic, or fully synthetic — that binds to opioid receptors (μ, κ, δ).

Opioid Related Mortality

- Severe OUD is associated with 15 years decreased life expectancy, 10-17 times more likely to die prematurely and a 20% risk of overdose mortality.
- Within 12 months of hospital discharge, 8% die, a rate comparable to those who suffered heart attacks.
- The 2023 CT age-adjusted rate for unintentional **drug**-induced mortality was higher than the national average (33.3 versus 29.1/100,000).

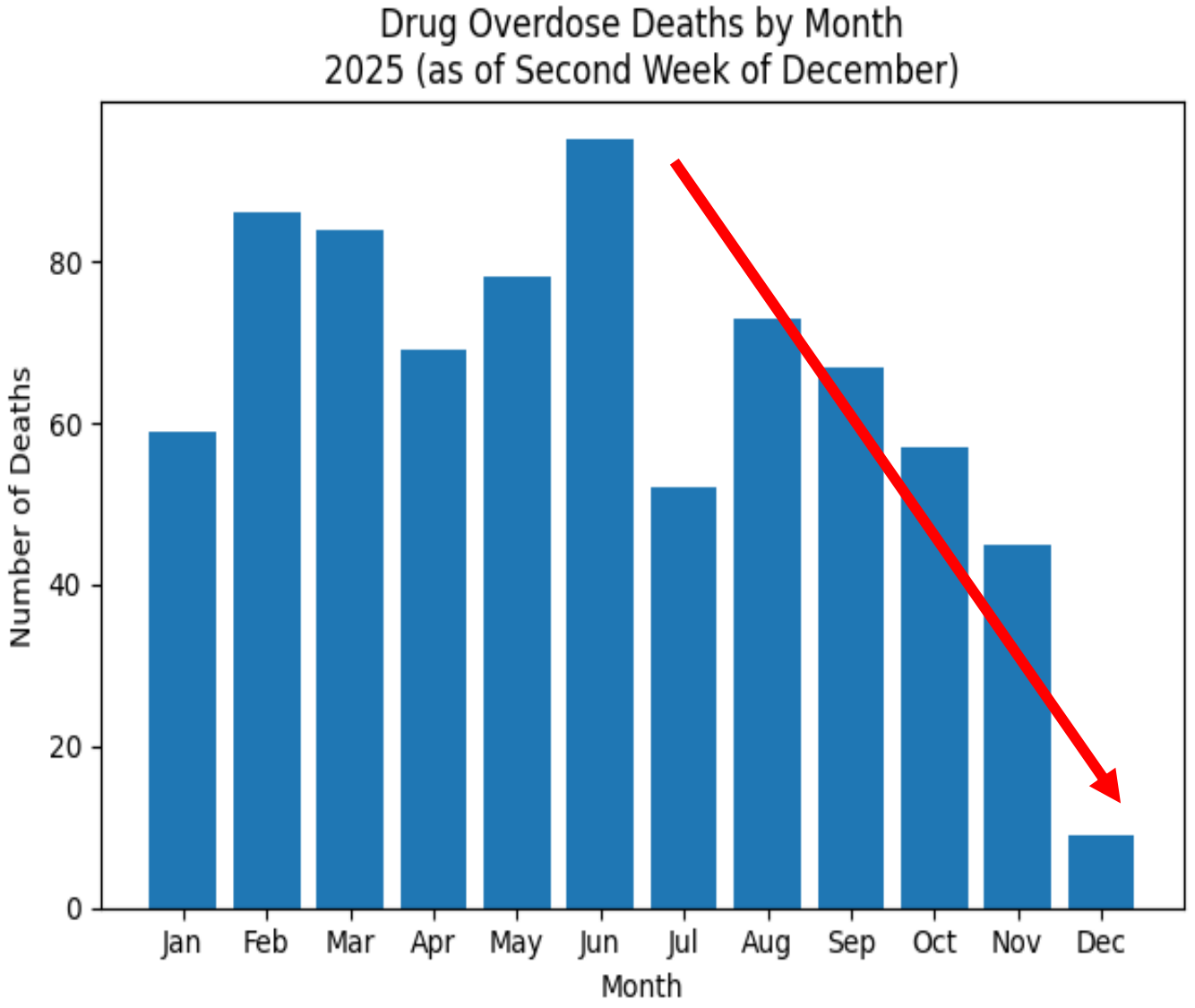
Herbert and Hill, 2024, Bahji et al, 2020, King et al, 2021, NSDUH, 2023

National OUD mortality



CT overdose deaths: the hidden numbers

- In CT, of 774 confirmed drug overdose deaths for 2025:
- Fentanyl (69.9%; N=541)
- Carfentanil in increasing: 2023 (N=7)→ 2024 (N=10) → 2025 (29)
- In 2024, Black (46.6), Hispanic (29.6), White (25.2/100,000 population

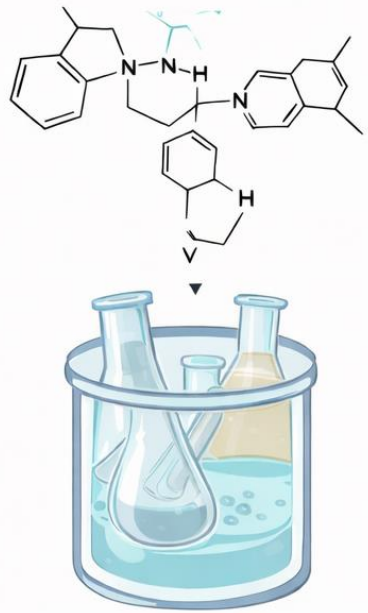


CT State Unintentional Drug Overdose Reporting System

Relative Potencies of Synthetic Opioids to Morphine

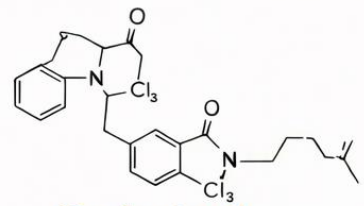
Morphine	Tramadol	Methadone	Fentanyl	Carfentanil
1x	**0.1x**	**~3x**	**50–100x**	**10,000x**

Fentanyl

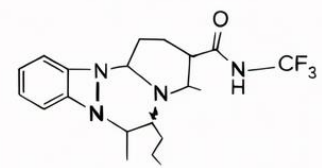


Simple modifications

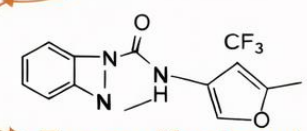
Synthetic Fentanyl Analogs



Carfentanil
100X Fentanyl



Acetylfentanyl
10X Fentanyl



Furanylfentanyl
5X Fentanyl

DOZENS OF ANALOGS

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Receipt of opioid use disorder treatments prior to fatal overdoses and comparison to no treatment in Connecticut, 2016–17

Robert Heimer [a,*], Anne C. Black [b,d], Hsiuju Lin [c], Lauretta E. Grau [a], David A. Fiellin [a,b], Benjamin A. Howell [b], Kathryn Hawk [a,b], Gail D'Onofrio [a,b], William C. Becker [b,d]

Results: Incidence rates for opioid poisoning deaths for those exposed to treatment ranged from 6.06±1.40 per 1000 persons exposed to methadone to 17.36±3.22 per 1000 persons exposed to any non-medication treatment. The estimated incidence rate for those not exposed to treatment was 9.80±0.72 per 1000 persons. With no exposure to treatment as referent, exposure to methadone or buprenorphine reduced the relative risk by 38% or 34%, respectively; the relative risk of non-medication treatments was equal to or worse than no exposure to treatment (RR = 1.27–1.77).

FDA-Approved Medications for Opioid Use Disorder (MOUDs)

Methadone

A

A Agonist

Buprenorphine

Buprenorphine / Naloxone

PA Partial agonist

Buprenorphine

Buprenorphine Naloxone

PA Partial agonist

Naltrexone

ANT

A Antagonist

Extended-Release Naltrexone

ANT

A Antagonist

The Patient: Case Vignette

- 34-year-old man; 10-year history of OUD. He has had multiple detox admissions
- He was released from jail 1 week ago after 3 months of incarceration.
- In clinic today, he reports:
  - Opioid cravings, poor sleep
  - Unstable housing but stays with a friend who also uses opioids
  - He declines buprenorphine stating, “I don’t want to be dependent on another drug.”

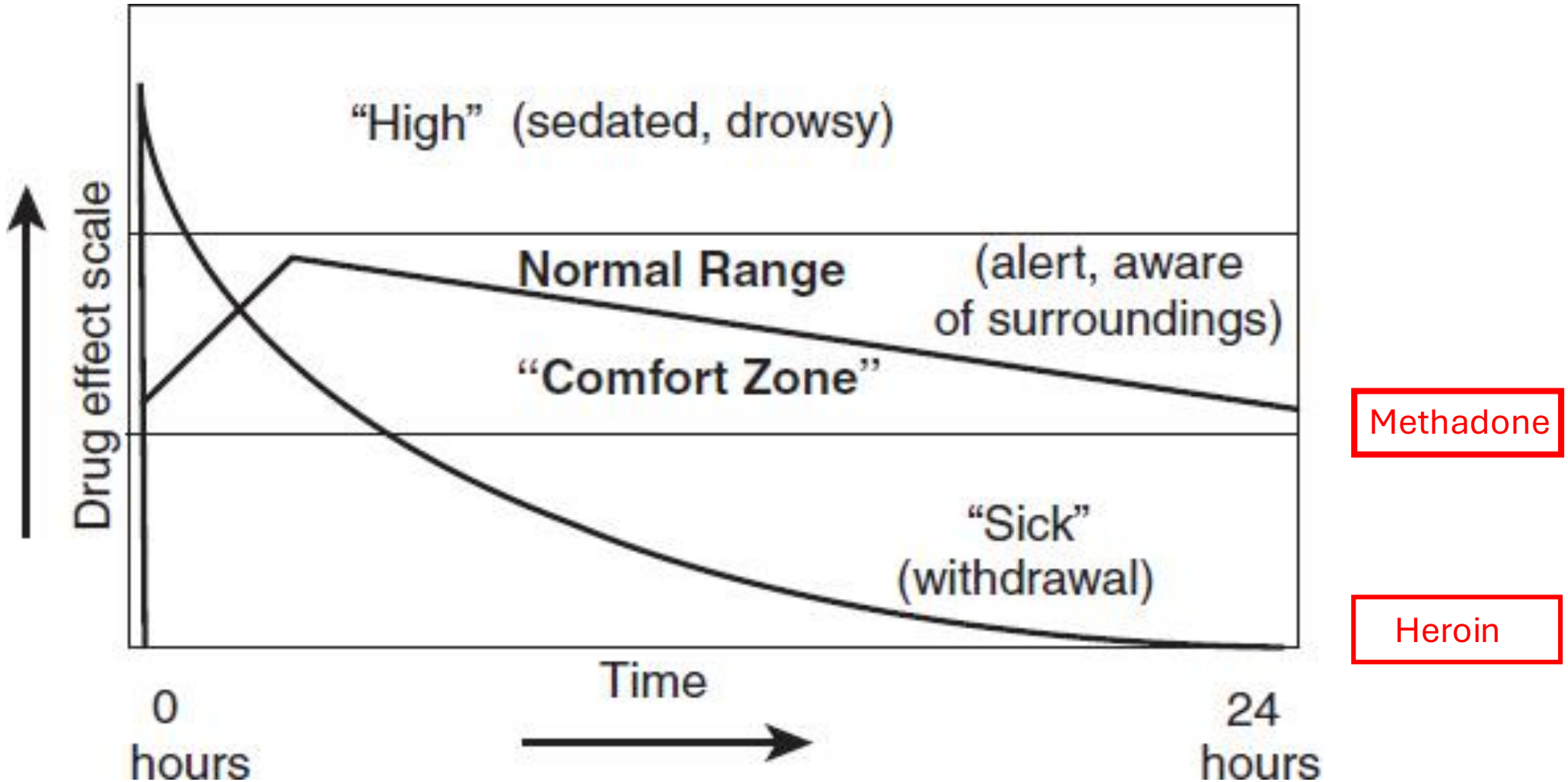
Despite overwhelming evidence that MOUD reduce mortality, only about 1 in 5 people with OUD in the U.S. receive **medication treatment** each year

METHADONE

- Methadone has the largest, oldest evidence base of all MOUD
- Full μ-opioid receptor agonist
- Long-acting, once-daily dosing
- Strongest evidence for ↓ overdose mortality

Methadone: patient selection

- Patient preference- shared decision making
- Prior buprenorphine non-response
- High opioid tolerance (HPSO e.g., fentanyl)
- Pregnancy (when already stable on methadone or high tolerance)
- Chronic pain
- Need for structure (integrated counseling)



Methadone

Heroin

Key Practical: dosing and safety

- Delivered only through opioid treatment programs (OTP)
- Initiating dose: 10-30 mg escalating by 5-10 mg, 50-60 mg (2025 guidelines)
- Maintenance dose at least 80 mg/day
- Underdosing → continued use & dropout
- QTc prolongation: monitor selectively
- Risk ≪ untreated OUD

In the era of fentanyl,
Methadone is a Public Health Intervention

- Methadone is drug overdose prevention at scale.
- Full agonism → no precipitated withdrawal
- Better retention in patients with high opioid tolerance
- Methadone's mortality benefit is driven more by retention than by abstinence.
- Note: Subtherapeutic methadone dosing increases overdose risk.

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Case: Why is the Patient High Risk?

- **Loss of Tolerance**
  - 90 days abstinent
  - Prior dose now potentially lethal
- **Fentanyl-Contaminated Supply**
  - Heightened overdose risk
  - Other synthetic analogs
- **Polysubstance Risk**
  - Benzodiazepines
  - Alcohol
  - Synergistic respiratory depression
- **High-Risk Transition Period**
  - First 2 weeks post-incarceration = highest overdose mortality
- **No MOUD Protection**
  - No stabilized receptor occupancy
  - No tolerance buffer
- **Social Determinants of health**
  - Unstable housing
- **Structural Vulnerability**

BUPRENORPHINE

- Partial μ-opioid receptor agonist
- High receptor affinity, slow dissociation
- FDA-approved for OUD and pain (separate indications)
- This combination—*partial agonism* + *high affinity*—is what makes buprenorphine unique.

Buprenorphine formulations

- Sublingual tablets/films (Subutex, Suboxone)
- Extended-release injection (Sublocade)
- Implant (Probuphine – discontinued)
- Combination with naloxone to deter misuse

Buprenorphine: patient selection

- Patient preference-desires office-based treatment
- High risk of overdose/prior overdose history
- Cardiac (QTc prolongation)/ respiratory disease
- Polysubstance use (esp. sedatives)
- Unstable housing (less clinic attendance burden)
- Co-occurring MDD

Buprenorphine pharmacodynamics

- Buprenorphine is a semi-synthetic opioid
- **μ (mu)-opioid receptor (MOR) partial agonist**
- κ (kappa) opioid receptor (KOR) antagonist
- δ (delta) opioid receptor (DOR) antagonist
- Weak partial agonism at ORL1

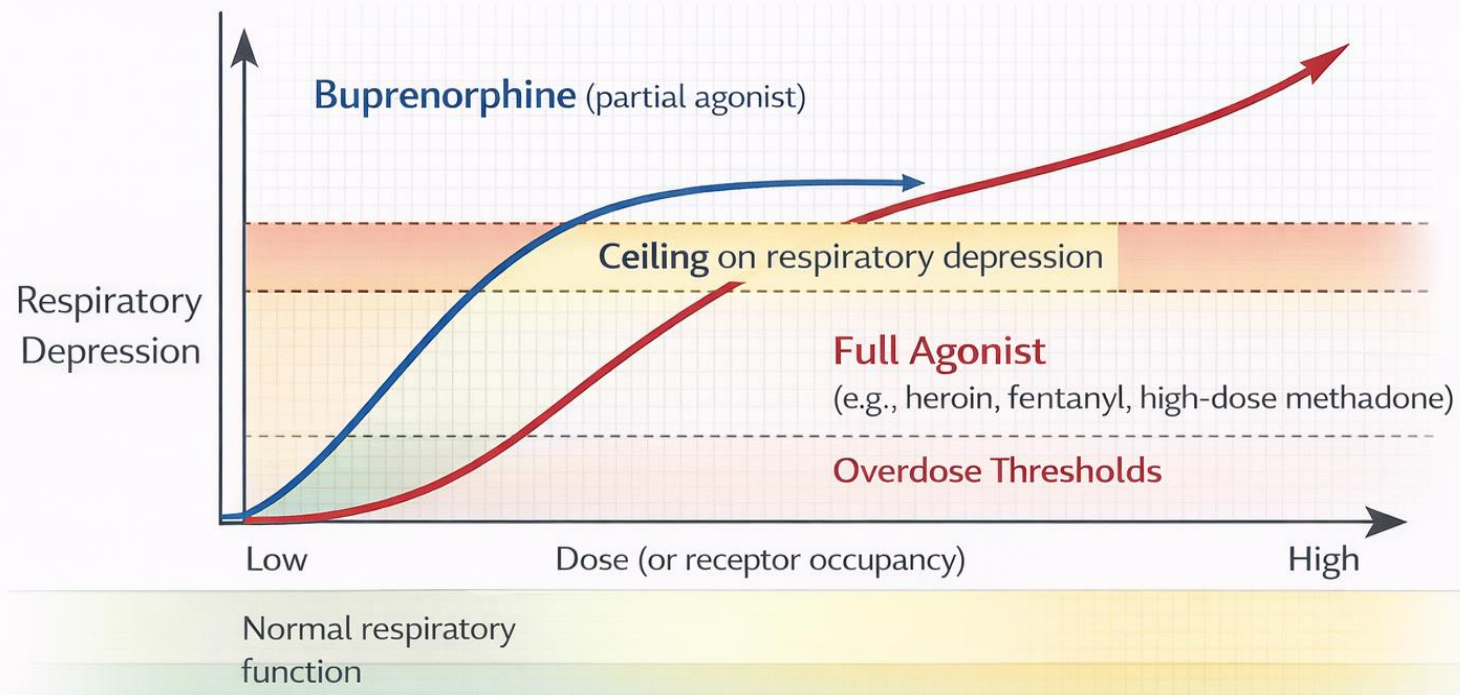
Antidepressant properties?

- κ-opioid receptor (antagonist)
  - Blocks dynorphin signaling
  - Reduces stress-induced dysphoria
  - Reduces anhedonia
  - May reverse stress-mediated depressive circuitry

Buprenorphine Ceiling Effect

- Increasing doses beyond a point do not increase opioid effect
- This lowers:
  - Overdose risk
  - Sedation
  - Reinforcing euphoria
- The ceiling may be insufficient for very high tolerance (e.g., fentanyl exposure)
- Reduces all-cause and overdose mortality by ~50%

Buprenorphine Ceiling Effect & Respiratory Protection



Partial agonism creates a ceiling on respiratory depression, while full opioid agonists continue to suppress respiration in a dose-dependent manner, leading to overdose.

Pharmacokinetics

- Bioavailability: ~30% sublingual
- Peak: 1-4 hours
- Half-life: ~24-60 hours
- Metabolized by CYP3A4 to norbuprenorphine

Contraindications and Cautions

- Allergy to buprenorphine
- Severe hepatic impairment
- Dental issues: tooth decay, cavities, oral infections/abscess, and tooth loss
- Necrotic injection site (ER formulation)
- Concomitant sedative use (e.g., benzodiazepines)

Adverse Effects

- Common: constipation, nausea, headache
- Serious: respiratory depression (rare), liver enzyme elevation
- Precipitated withdrawal

REVIEWS

The Impact of High-Potency Synthetic Opioids on Pharmacotherapies for Opioid Use Disorder: A Scoping Review

Jegede, Oluwole MD, MPH; De Aquino, Joao P. MD; Hsaio, Connie MD; Caldwell, Ebony MD; Funaro, Melissa C. MS; Petrakis, Ismene MD; Muvvala, Srinivas B. MD, MPH

Author Information

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BUY CME TEST EARN CREDIT Editor's Choice

- Fentanyl exposure among individuals on MOUD remains high
- MOUD, buprenorphine and methadone, retains efficacy and are linked to a decreased risk of overdoses and mortality even when exposed to HPSO.
- Precipitated withdrawal is a challenge to buprenorphine induction in people exposed to fentanyl

Standard Buprenorphine Induction

Phase	Timing	Buprenorphine Dose (SL)	Clinical Goal
Initiation	Start (COWS ≥ 8–12)	**2–4 mg**	Begin withdrawal relief
Titration	Every 1–2 hrs on Day 1	**+2–4 mg as needed**	Suppress ongoing withdrawal/cravings
Day 1 Total	End of Day 1	**8–12 mg** (up to **16 mg** if needed)	Achieve comfort, avoid precipitated withdrawal
Stabilization	Day 2	**12–16 mg once daily**	Prevent withdrawal & cravings
Early Maintenance	Days 3–7	**16–24 mg/day**	Sustain stabilization & retention
Dose Adjustments	Ongoing	Split dosing if pain; increase within range if cravings persist	Optimize function & adherence

Low-Dose (Micro) Induction

- Micro-induction allows safe initiation of buprenorphine without withdrawal by gradually increasing receptor occupancy while tapering full agonist opioids.
- Induction is started while the patient is still using FAO
- Mechanistically- gradual opioid receptor occupancy
- Smooth LDI may involve concomitant and cautious use of clonidine, benzodiazepine or Benadryl and other psychosocial support.

Precipitated Withdrawal

- Iatrogenic displacement of FAO by a POA
- Symptoms: dysphoria, nausea/vomiting, muscle aches, lacrimation/rhinorrhea, pupillary dilation, sweating, diarrhea, yawning, fever, insomnia.
- Risk factors:

Medical Conditions	Chronic kidney disease, cirrhosis (through impaired CYP450 metabolism)
Opioid Use	Methadone, fentanyl (chronic use)
Other Substance Use	Benzodiazepine use

Spadaro, A., Long, B., Koyfman, A., & Perrone, J. (2022). Buprenorphine precipitated opioid withdrawal: prevention and management in the ED setting. *The American journal of emergency medicine*, *58*, 22-26.

5-Day Buprenorphine Micro-Induction (LDI) Schedule

Day	Morning Dose (SL)	Evening Dose (SL)	Daily Total	Full-Agonist Opioid
Day 1	0.5 mg	—	**0.5 mg**	Continue usual use
Day 2	0.5 mg	0.5 mg	**1 mg**	Continue
Day 3	1 mg	1 mg	**2 mg**	Continue
Day 4	2 mg	2 mg	**4 mg**	Continue or begin taper
Day 5	4 mg	4 mg	**8 mg**	**Stop full agonist**

Kaliamurthy, Hermes, Jegede 2022

>24 mg buprenorphine fentanyl users

- Buprenorphine activates MOR less strongly than FAO, so higher doses may be needed to generate sufficient opioid tone.
- Chronic fentanyl exposure produces very high opioid tolerance, requiring stronger receptor signaling to suppress withdrawal.
- Higher buprenorphine levels improve receptor blockade against fentanyl, reducing reinforcing effects if relapse occurs.
- Higher doses maintain higher steady-state buprenorphine concentrations, improving craving suppression and retention.

Greenwald MK et al, 2003, 2014; Nasser AF, et al, 2014

Monitoring and Follow-up for patients on buprenorphine

- Clinically meaningful urine drug screens
- Monitor adherence using Buprenorphine: Norbuprenorphine
- Monitor craving, and withdrawal assessments
- Oral hygiene (acidic SL bup, decrease saliva production)
- Hepatic function tests
- Provide psychosocial support

ER buprenorphine

Sublocade

- Stable on SL bup x7days*
- STAT 300 mg x 2 months THEN maintenance 100-300 mg
- SC abdomen*
- Delays of up to 2 weeks may not have significant clinical impact

Brixadi

- Single dose SL bup
- Weekly dose-8, 16, 24, 32 mg; monthly dose-64, 96,128 mg
- SC buttock, thigh, abdomen, upper arm
- Monthly dose can be administered +/- 1 week

Case: To detox or not to detox?

- Detox eliminates opioid tolerance
- Does NOT treat:
  - Craving
  - Neurobiological adaptation
  - Environmental risk
  - Relapse vulnerability
- Detox without MOUD → **high relapse rates (60–90% within months)**
- Post-detox period → **markedly elevated overdose risk**
- Mortality risk highest in first weeks after abstinence

NALTREXONE

- μ-opioid receptor antagonist
- Blocks opioid effects
- No agonist activity
- Oral daily or extended-release injectable (XR-NTX)

Naltrexone: patient selection

- FDA approved for MOUD
- Naltrexone can be an effective MOUD for a narrow but important subgroup
  - patients who can complete detox (7-10 days opioid free)
  - remain adherent and
  - have strong external structure.

Harris MTH et al, 2026, Volpe DA et al. 2011

Naltrexone dosing and Adverse Effects

- Oral naltrexone should be administered initially at a dosage of 25 mg/d to minimize adverse effects.
- Extended-release naltrexone – Vivitrol 380 mg Q28 days
- AE- GI symptoms including nausea (most common- >30%), vomiting, decreased appetite, abdominal pain.
- Vivitrol- injection site symptoms including injection site nodule and swelling (most common 69%), tenderness and pain.

Hepatic injury: much ado about nothing?

- Naltrexone is not a “hepatotoxic drug”
- Naltrexone metabolite 6-β-naltrexol is cleared hepatically
- The hepatotoxicity came from early obesity studies (300 mg/day).
- At standard doses (50 mg/day oral):
  - Mild ↑ AST/ALT can occur
  - Typically, asymptomatic
  - Usually reversible
  - Rarely progresses to clinically significant hepatitis

Mechanisms of hepatic injury across MOUDs

Medication	Primary Hepatic Risk Mechanism
Buprenorphine	Mitochondrial stress, dose-related, IV misuse risk
Naltrexone	Dose-related hepatocellular toxicity at high doses
Methadone	Not hepatotoxic (QT prolongation instead)

Baseline and Ongoing Laboratory Monitoring

Test	Timing	Rationale
LFTs (AST, ALT, total bilirubin)	Baseline	Assess hepatic function before starting
Repeat LFTs	1–3 months after initiation, then every 6–12 months or sooner if symptomatic	Detect hepatotoxicity
Urine drug screen	Before starting and as clinically indicated	Confirm opioid-free status
Pregnancy test (if applicable)	Baseline	Safety in women of childbearing potential

General Principles Guiding Choice of MOUD

- **Physiologic dependence**
- **Prioritize retention**
  - The best medication is the one the patient will stay on
- **Assess overdose risk**
  - High respiratory risk (benzos, COPD, prior OD)
- **Treatment context**
  - Needs daily structure / benefits from OTP oversight → methadone
  - Needs flexibility / limited transportation → buprenorphine
  - Mandated or abstinence-based environments → naltrexone (with caution)
- **Evaluate co-occurring pain**
  - Significant chronic pain → methadone or higher-dose buprenorphine
  - Avoid naltrexone if opioid analgesia may be needed
- **Medical comorbidity**
  - Prolonged QTc → avoid methadone
  - Advanced hepatic failure → avoid naltrexone
  - Severe untreated psychiatric instability → caution with antagonist therapy
- **Patient preference**
- **Structural vulnerability**
  - Housing instability, incarceration history, fragmented care

Harm Reduction

- Naloxone Distribution
  - Prescribe to every patient with SUD
  - Train patient + family
- Safer Use Counseling
  - Avoid using alone
  - Test dose first
  - Avoid mixing with alcohol/benzodiazepines
  - Carry naloxone
- Fentanyl Test Strips
  - Detect contamination
  - Associated with safer behavior
- Xylazine Test Strips
  - Detect contamination
  - Associated with safer behavior
- Syringe Services Programs
  - Reduce HIV/HCV transmission
  - Increase engagement in treatment
  - Gateway to MOUD
- Low-Threshold MOUD Access
  - Same-day buprenorphine
  - No mandatory counseling
  - Flexible follow-up

Community-Based MOUD Prescribing

- Clinical complexity in community settings
- Structural and social drivers
- Stigma and Trust
- Treatment flexibility and adaptation
- Regulation and logistical hurdles

Clinical Complexity in Community Settings

- **Co-occurring disorders**: Higher prevalence of untreated psychiatric illness, trauma, and chronic pain.
- **Polysubstance use**: Especially stimulant use (e.g., cocaine, methamphetamine) and benzodiazepine alongside opioids.
- **Medical comorbidities**: More frequent, undiagnosed and often poorly managed (HIV, HCV, liver disease, COPD, etc.).

Structural and Social drivers

- **Housing instability**: medication adherence and safe storage.
- **Transportation and treatment access**: Missed appointments, trouble accessing pharmacies.
- **Criminal-legal involvement**: Interruptions in treatment, stigma, parole/probation requirements.

Stigma and Trust

- **Racial disparities** in SUD treatment
- **Patient mistrust**: Due to past trauma or discriminatory care in healthcare and legal systems.
- **Provider and system stigma**: Even within community health centers, some staff may resist MAT.

Treatment Flexibility and Adaptation

- **Induction approaches**: Home-based, office-based, low-barrier, micro-induction.
- **Dosing considerations**: May need higher or split doses due to comorbid HPSO, stimulant use or poor absorption.
- **Urine drug screening**: challenges around ethics, justice and clinical utility

Regulatory and Logistical Hurdles

- **Prior authorizations**: For buprenorphine formulations (especially ER).
- **Documentation burden**: More intense when dealing with insurers, Medicaid, and housing programs.
- **Pharmacy availability**: Pharmacies reluctant to stock or dispense buprenorphine, specialty pharmacies for LAI, challenge with some LDI formulations.

Interdisciplinary Collaboration

- Interdisciplinary collaboration:
  - Physicians
  - Social workers
  - Nurses
  - APRN/PA
  - Psychologists
  - Outreach workers
  - Peer recovery specialists
  - Legal advocates
  - Pharmacies

Patient-Centered Innovations

- **Mobile units and street outreach**: Bringing buprenorphine to the patient (Street Psychiatry, ACT, InMOTION)
- **Telehealth**: Especially effective post-COVID for stable patients.
- **Bridge clinics / low-threshold access**: MAT clinic, Drop-in, same-day starts are increasingly valued.

Advocacy and Policy Awareness

- Recognize racial disparities in MOUD
- Importance of:
  - Advocating for funding for wraparound services
  - Understanding changing DEA/State regulations
  - Being a voice against local NIMBYism or stigma
- **NIMBYism:** community resistance to opening:
  - MAT (Medication for Addiction Treatment) clinics
  - Syringe services
  - Recovery housing or sober living facilities
  - Mobile outreach vans

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Mentors and collaborators

Ismene Petrakis MD

Srinivas Muvvala MD MPH

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Sara Becker PhD

Carla Rash PhD

Brian Kiluk PhD

Theddeus Iheanacho MD

Daniel Sarpong PhD

Ayana Jordan MD PhD

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