ASAM REVIEW COURSE 2025

Opioid Use Disorder: Science, History, and Clinical Implications

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Financial Disclosure

Soteri Polydorou, MD

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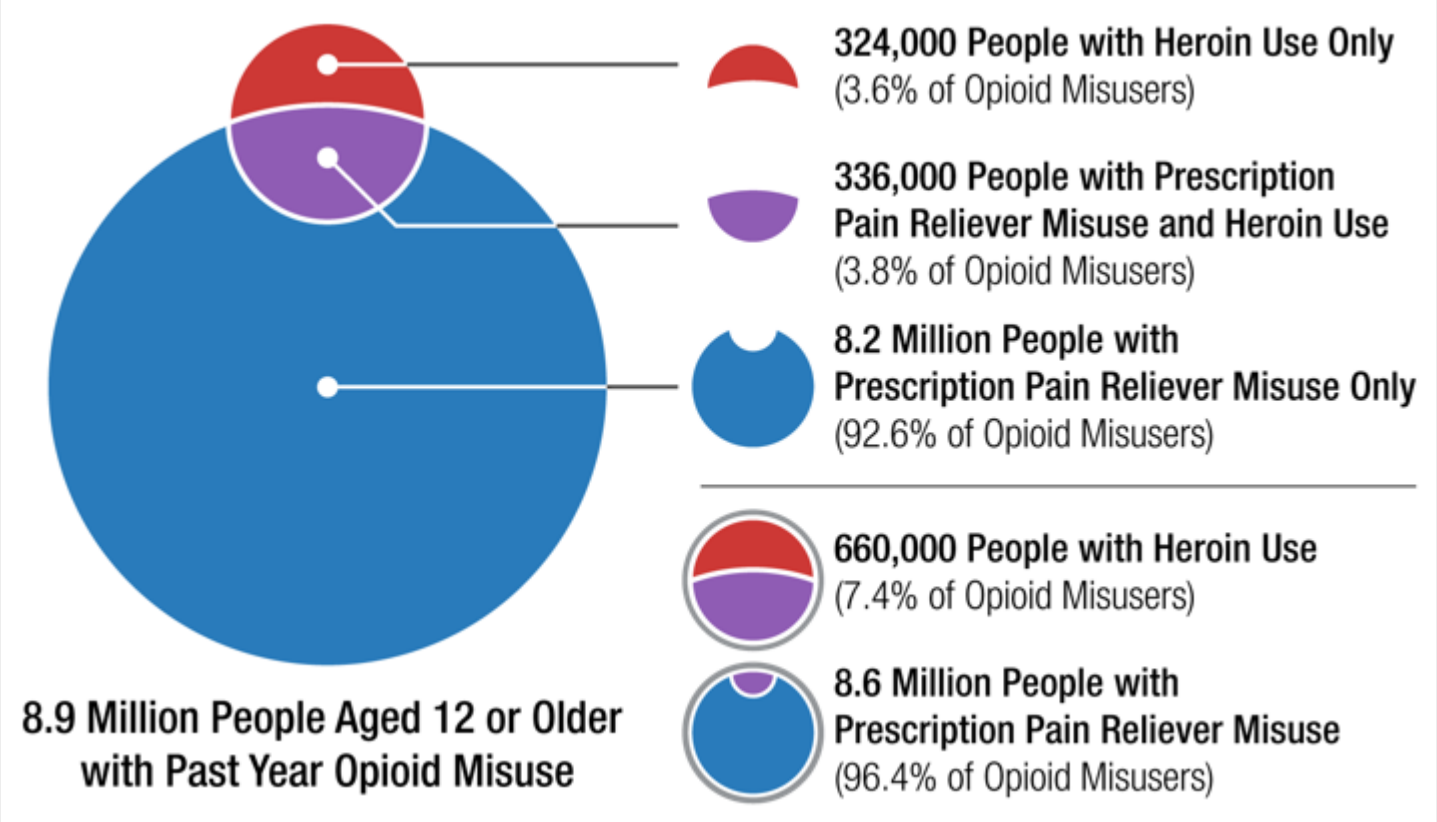
Outline

1. Opioid Use Trends
2. History
3. Regulations
4. Neurobiology
5. Intoxication and Withdrawal
6. Medications for Opioid Use Disorder

The Need for Treatment

- Opioid Use Disorder 5.7 million
  - Prescription opioid misuse 8.6 million in past year
  - Fentanyl 828,000 people in past year
  - Heroin use 660,000 in past year
    - >100% increase from 2004 to 2016
    - Lifetime use 5.7 million, doubled from 2002 to 2018
    - 4 of 5 new heroin users previously used prescription opioids
- 15-yr reduction in life expectancy



Lewer 2020; NSDUH 2023, SAMHSA

The Need for Treatment is Growing

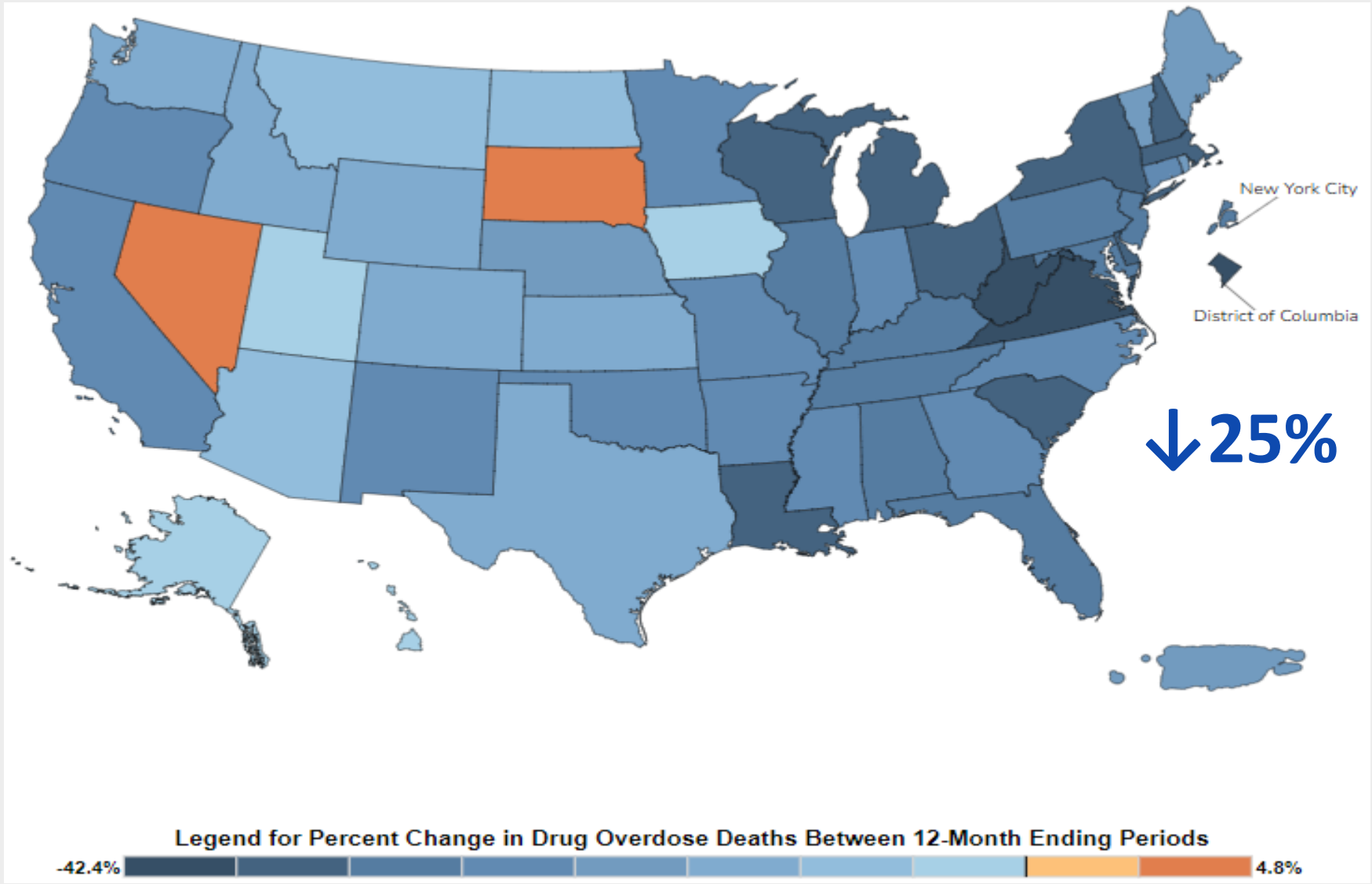
Nationally

- Nearly 80,000 lethal ODs in 2024
- Almost 70% of all overdose deaths involve an opioid
- Nearly 90% of fatal opioid overdoses involve synthetic opioids, fentanyl
- Heroin users, >100% increase from 2004 to 2016
- 4 out of 5 new recent heroin users previously abused prescription opioids
- >140 OD deaths from opioids daily in US
- 2010 to 2016 heroin related deaths increased by 500%
- 2015 to 2019 fentanyl related deaths increased by over 400%

Leading Causes of Death in US 2023	Annual Deaths
Heart Disease	680,981
Cancer	613,352
Unintentional Injuries	222,698
Cerebrovascular Disease	162,639
Chronic Lower Respiratory Diseases	145,357
Alzheimer Disease	114,034
Diabetes Mellitus	95,190
Renal Disease	55,253
Chronic Liver Disease and Cirrhosis	52,222
COVID-19	49,932

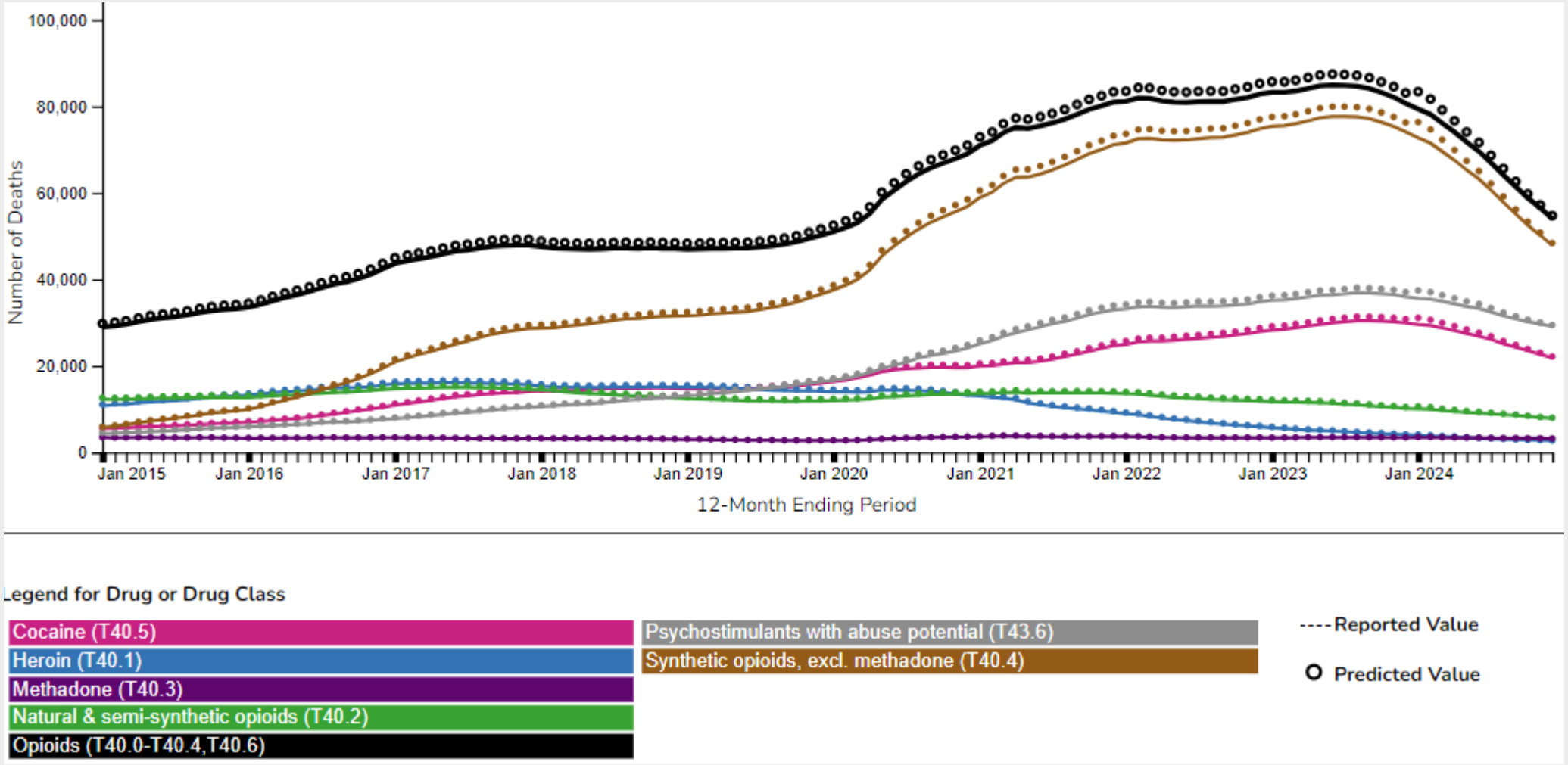
CDC, Health Alert Network, NSDUH, SAMHSA, CSAT, and DOHMH Bureau of Vital Statistics, National Center for health Statistics Data Brief 492 US Mortality 2022

Drug Overdose Deaths 12/2023 to 12/2024



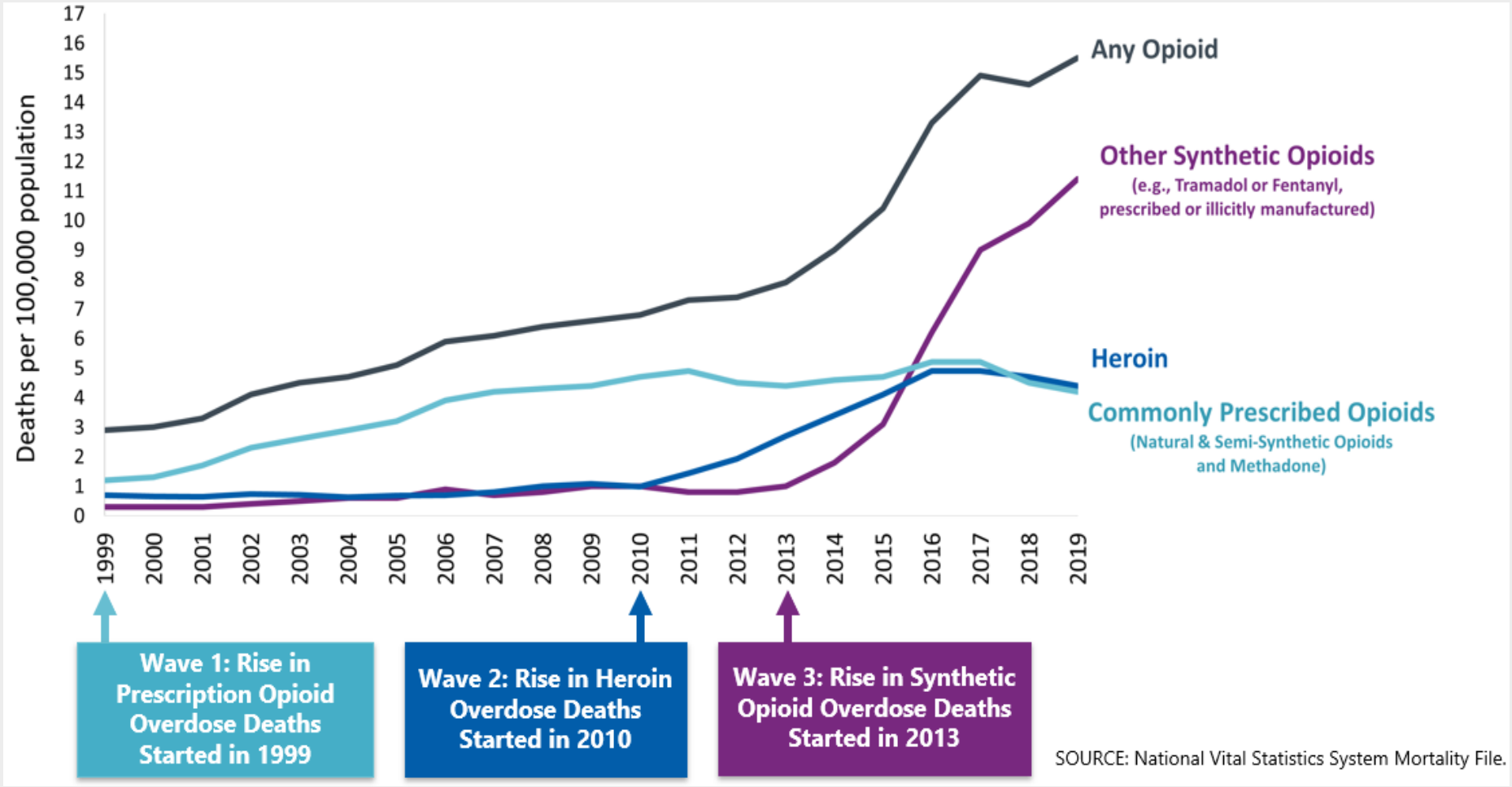
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

The Need for Treatment is Growing



Based on data available for analysis on 5/29/25, https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard

Three Waves of Opioid Overdose Deaths



cdc.gov/drugoverdose

Unintentional Opioid Overdose

Experienced (non-fatal)

- Lifetime 24% - 94% (mean 45%, median 47%, SD 14%)
- Past Year 9% - 36% (mean 18%, median 17%. SD 10%)

Witnessed (non-fatal and fatal)

- Lifetime 48% - 96% (mean 73.3%, median 70%, SD 14%)

1 Year All Cause Mortality

- 5% of Non-Fatal Opioid Overdose Presentations to ED or Hospital Admission

Martins S et al 2015, Leece P, et al. 2020, Weiner S et al. 2020

3400 BC

1898

1839

1935

U.S. Government Involvement

Congress passes multiple laws aimed at reducing the increase in heroin/morphine/opium addiction.

- 1905-Opium banned
- 1906-Pure Food and Drug Act- labeling of all medications by pharmaceutical companies
- 1914-Harrison Narcotics Act (HNA)
  - 1919- Supreme Court sides with Treasury interpretation that physician prescribing of opioids for treatment of opioid addiction was violation of HNA
  - Later Supreme Court rulings from 1921 and 1926 reverses interpretation of HNA saying the federal government had overstepped its authority to regulate the practice of medicine

"We're from the F.B.I., going from house to house making sure that everyone is scared shitless."

U.S. Government Involvement

- 1970-Comprehensive Drug Abuse Prevention & Control Act (Controlled Substances Act)
- 1974 – Narcotic Addict Treatment Act of 1974
- 2000- Drug Addiction Treatment Act (DATA) of 2000– An Amendment to the Controlled Substances Act
  - Allows treatment of opioid dependence with narcotic schedule III, IV, V, or combinations of such drugs
  - Buprenorphine designated Schedule III and FDA approved for treatment of opioid dependence
  - Capacity to refer patients for counseling

U.S. Government Involvement

- 2016 Comprehensive Addiction and Recovery Act (CARA)
- 2018 Support for Patients and Communities Act
- 2020 HHS Public Health Emergency Declaration, DEA partners with SAMHSA (temporary)
- 2021 HHS Updates Practice Guidelines for the Administration of Buprenorphine for Treating OUD

By 2022, over 100,000 practitioners held waivers, 71,000 with 30-limit, 22,000 with 100-limit, <10,000 with 275-limit

2023 Consolidated Appropriations Act, Section 1262

Mainstreaming Addiction Treatment Act (MAT Act)

Buprenorphine DATA-Waiver is *ELIMINATED!*

Effective January 12, 2023

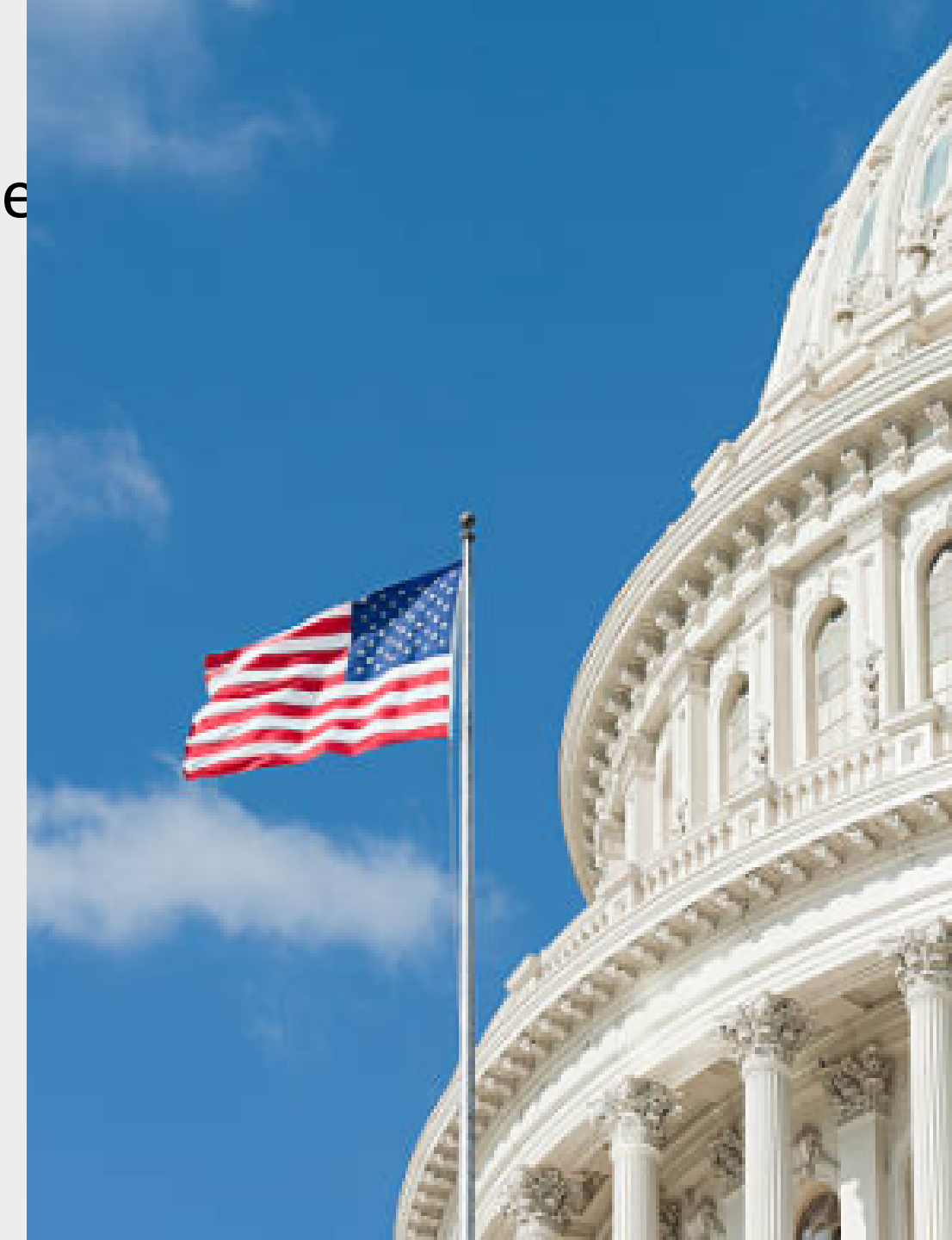
- A DATA-Waiver registration is no longer required to treat patients with buprenorphine for opioid use disorder
- Prescriptions for buprenorphine only require a standard DEA registration number
- No caps on the number of patients a prescriber may treat for opioid use disorder with buprenorphine
- The Act does not impact existing state laws or regulations that may be applicable

2024 HHS/SAMHSA 42CFR Part 8 Final Rule on Opioid Use Disorder Treatment

Opioid Treatment Programs ONLY

- Reduces barriers to receiving care
- Supports a patient-centered approach
- Promotes practitioner autonomy
- Removes stigmatizing and outdated language

https://www.federalregister.gov/documents/2024/02/02/2024-01693/medications-for-the-treatment-of-opioid-use-disorder



Highlights of the Final Rule

- Methadone: telehealth screening and full exam must be audio-visual, NOT audio only
  - 1st day methadone dose should not exceed 50mg, limited exceptions
- Buprenorphine: telehealth screening and full exam can be audio-visual or audio only
- Medication attendance schedule changes
- Allows medication units to be community pharmacies and allows them to offer take-home methadone
- Allows split dose as clinically indicated
- Allows Medical Directors to delegate responsibilities to other practitioners (NP/PA)
- Patient refusal of counseling does not preclude care at OTP

Methadone Take-Home Doses/Schedule

Take-home methadone schedules are significantly increased in regulation

- In treatment 0-14 days, up to 7 unsupervised take-home doses of methadone may be provided to the patient
- Treatment days 15-30, up to 14 unsupervised take-home doses of methadone may be provided to the patient
- From 31 days in treatment, up to 28 unsupervised take-home doses of methadone may be provided to the patient

Methadone Take-Home Doses/Schedule

In determining which patients may receive unsupervised doses, the medical director or program medical practitioner shall consider, among other pertinent factors that indicate whether the therapeutic benefits of unsupervised doses outweigh the risks, the following criteria:

1. Absence of active substance use disorders, other physical or behavioral health conditions that increase the risk of patient harm as it relates to the potential for overdose, or the ability to function safely;
2. Regularity of attendance for supervised medication administration;
3. Absence of serious behavioral problems that endanger the patient, the public or others;
4. Absence of known recent diversion activity; and
5. Whether take home medication can be safely transported and stored; and
6. Any other criteria that the medical director or medical practitioner considers relevant to the patient's safety and the public's health.

Overview

- Addictive drugs produce an enhancement in extracellular dopamine levels in the nucleus accumbens and other limbic structures as well as cortical areas.

- Endorphin-Opioid Receptor binding results in an increase in dopamine release in the mesolimbic and mesocortical pathways but unlike exogenous Opioid-OR binding the effect is less robust and does not result in habituation.

Terminology

Endorphins - describes the whole class of endogenous opioid ligands

- Beta-endorphin, enkephalin, dynorphin

Opioid - describes entire class of non-endogenous (natural or synthetic) and endogenous compounds that bind to one or more types of opioid receptors

- Methadone, fentanyl, oxycodone

Opiate - describes compounds naturally derived from the poppy plant

- Morphine, codeine

Opium Poppy: Papaver Somniferum

Alkaloid Content

- **Morphine,** 7-25%, opiate analgesic, named after Morpheus, the Greek God of dreams
- **Noscapine**, 4-15%, central acting antitussive, no morphine-like effect of dependence or tolerance
- **Codeine**, 1-6%, opiate analgesic
- **Thebaine**, 1-6%, important intermediate for the synthesis of semisynthetic opioids e.g., buprenorphine, oxycodone
- **Papaverine**, 1-5%. smooth muscle relaxant

***Poppy Seeds**: UDS → ⊃ Opiates, Morphine, Codeine (cut-off dependent)*

Endogenous Opioids & Opioid Receptors

Endorphin Class	Opioid Receptor Type
Beta-endorphin Endomorphin	Mu Opioid Peptide Receptor
Dynorphin	Kappa Opioid Peptide Receptor
Enkephalin	Delta Opioid Peptide Receptor
Orphanin/Nociceptin (opiate-like)	*Nociceptin/Orphanin FQ Peptide Receptor, Opioid Receptor Like-1*

Multiple opioid receptor polymorphisms identified

Opioid Receptors

All Opioid Receptors

Seven transmembrane domain

G protein-coupled

Primarily inhibitory pathways

Mu Opioid Receptor (OPRM) Activation (predominantly beta-endorphin)

Reduces cAMP

Inhibits transporter release of GABA, glycine, and glutamate

- Inhibition of GABA in ventral tegmental area (VTA)→increases dopamine release throughout mesolimbic (amygdala, ventral pallidum, hippocampus, NAcc)-mesocortical (prefontal cortex, orbitofrontal cortex, anterior cingulate) dopaminergic fields.

Opioid Receptors

Mu Opioid Receptor (OPRM) Activation (predominantly beta-endorphin)

- Widely dispersed across a wide variety of brain regions, including cortex, striatum, thalamus, hippocampus, locus coeruleus, ventral tegmental area, nucleus accumbens, amygdala

- Mu receptors also mediate rewarding properties of non-opioid drugs of abuse including cannabinoids, alcohol and nicotine, or even natural reinforcers such as social interactions

- Physiologic effects of **intoxication** and **withdrawal**

Opioid Receptors

Kappa Opioid Receptor (OPRK) Activation (predominately dynorphin A)

- Identified in various CNS regions such as the nucleus accumbens, caudate–putamen, olfactory tubercle, bed nucleus of the stria terminalis, medial preoptic area, paraventricular nucleus, supraoptic nucleus, dorsomedial, and ventromedial hypothalamus, amygdala, midline thalamic nuclei, periaqueductal gray, raphe nuclei, parabrachial nucleus, locus coeruleus, spinal trigeminal nucleus, and the nucleus of the solitary tract.

- Mediates **dysphoric** activities of both opioids and cannabinoids and therefore opposes mu receptors in regulating the hedonic tone and modulating stress-induced relapse.

Opioid Receptors

Delta Opioid Receptor (OPRD) Activation (predominately enkephalin)

- Identified in various CNS regions including thalamus, amygdala, NAcc, locus coeruleus, VTA, and others
- Lack of familiar opioid characteristics like respiratory depression, reinforcing effects as measured in self-administration studies, and opioid (mu or kappa) withdrawal symptoms.
- Delta receptors are less directly involved in hedonic control.
- Distinct from mu and kappa receptors, delta receptors may play a role in emotional responses and show **anxiolytic** activity along with benefits in analgesia resulting from inflammatory states.

Role of Endorphin Systems in Normal Physiologic Functions

- Endogenous response to pain
- Neuroendocrine functions
  - Stress-response systems including HPA axis
  - Reproductive function including HPG axis
- Immunologic function
- Gastrointestinal function
- Cardiovascular function
- Pulmonary function
- Mood, affect, cognition

Additional Opioid Effects

- CNS → Sedation, Analgesia, Euphoria
- GI → Constipation, Nausea
- Endo → ↓Testosterone, ↑Prolactin , ↓ FSH, LH
- Urinary → Retention
- Cardiovascular → Vasodilatation, ↑ QTc
- Miosis
- Tolerance Varies

Opioid Potency

Opioid	*Relative Potency*	*Lethal Dose*
Morphine	1x	1 Pea
Diacetylmorphine (heroin)	2x	1 Sunflower Seed
Fentanyl	100x	1 Sesame Seed
Sufentanil	500x	1 Grain of Sand
Carfentanil	10,000x	0.5 Grain of Salt

Role of Medications in the Treatment of Opioid Use Disorder

Overdose

- Acute intervention, possible reversal, and close monitoring

Withdrawal/Early Stabilization

- Reduction and stabilization of withdrawal symptoms
- Opportunity to initiate and engage in ongoing addiction treatment

Maintenance Therapy

- Prevents or eliminates withdrawal
- Diminishes or eliminates drug craving and use of illicit opioids
- Blocks or attenuates the effects of heroin and other abused opiates
- Risk/harm reduction, reduces overdose risk
- Increased treatment retention and engagement in comprehensive rehabilitation
- Decreased medical and psychiatric symptoms, improves health, reduced risk of HIV and Hep C infection
- Improved social determinants such as employment, family relations
- Decreased criminal behavior

Opioid Overdose

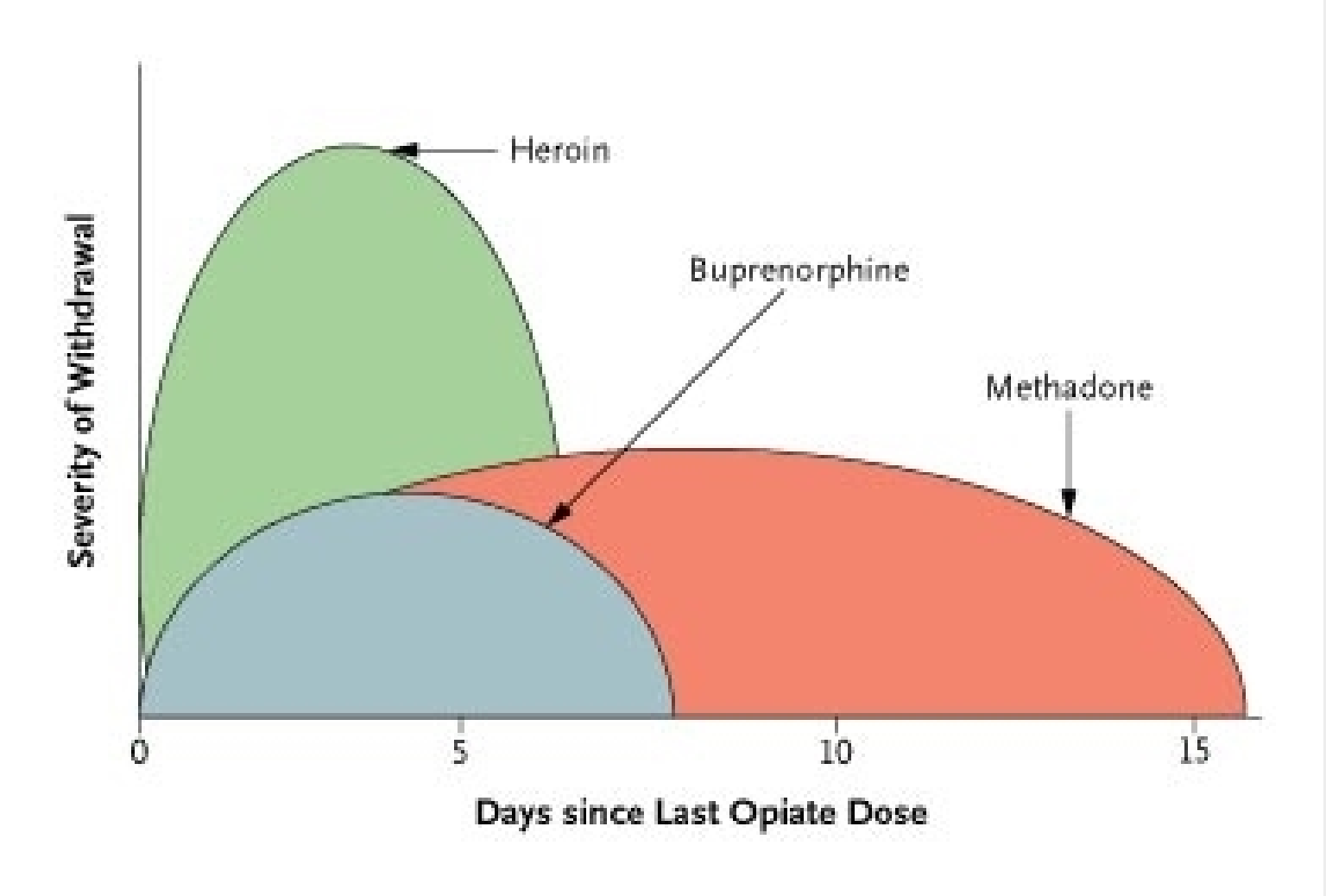
Classic Triad Seen In Overdose

- ***Miosis***
- ***Decreased level of Consciousness/Coma***
- ***Respiratory Depression (With Prolonged ↓ PO2)***
- Pulmonary Edema (Non-cardiogenic)
- Seizures
  - Meperidine, Tramadol

Management of Opioid Overdose

- Ventilatory support if needed
- Parenteral Naloxone
- If IV access, bolus 0.04mg-2mg with escalating doses q2-3min titrated to
  - RR>10/min
  - Improved level of consciousness
  - No withdrawal
  - If needed ongoing IV infusion 2/3 of initial bolus dose/hr.
- If no IV access, 0.4-2mg SQ or IM and observe
- Intranasal administration of 2 doses of Naloxone 4mg in OD Prevention Kits

Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone



Kosten and O'Connor, 2003

Clinical Opiate Withdrawal Scale (COWS)

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time _____/_____/_____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Journal of Psychoactive Drugs Volume 35 (2), April - June 2003

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

Opioid Withdrawal

- Buprenorphine—DEA licensed prescribers, no longer limited to those with DATA waivers, MD/DO/PA/NP, OTP
- Methadone—Hospitalized, OTP, very limited other OP
- Symptomatic Meds, e.g., Clonidine, Lofexadine, NSAIDS, Imodium, B/Zs
- 72 Hour Rule: Methadone Dispense Only

Table 2. Medication Treatment for Opioid Withdrawal.*

Protocol	Examples	Effects and Comments
Medication		
Opioid agonists	Methadone (20 to 35 mg daily) or buprenorphine (4 to 16 mg daily), tapered over several days or weeks	Withdrawal symptoms are decreased in severity. Methadone and other opioid agonists are currently restricted to inpatient settings or licensed programs; buprenorphine is now approved by the FDA for this purpose.
Nonopioid drugs	Clonidine (0.2 mg 3 times daily) or lofexidine (0.2 mg twice daily), administered for approximately 10 days for heroin and 14 days for methadone	Withdrawal symptoms are decreased in severity. Lofexidine is less likely to produce hypotension but is not currently approved by the FDA for this purpose.
Rapid and ultra-rapid detoxification	Protocols include a variety of medications: opioid antagonists (noloxone or naltrexone), clonidine, sedatives, antiemetic agents, analgesics, anesthetics	Withdrawal is precipitated with an opioid antagonist, and symptoms are managed with a variety of adjuvant medications. Patients are awake or lightly sedated for rapid detoxification; they are under heavy sedation or general anesthesia for ultra-rapid detoxification. Both methods require special training, equipment, or both. Research on efficacy is limited.

* FDA denotes Food and Drug Administration.

Pitfalls Opioid Analgesic ODs

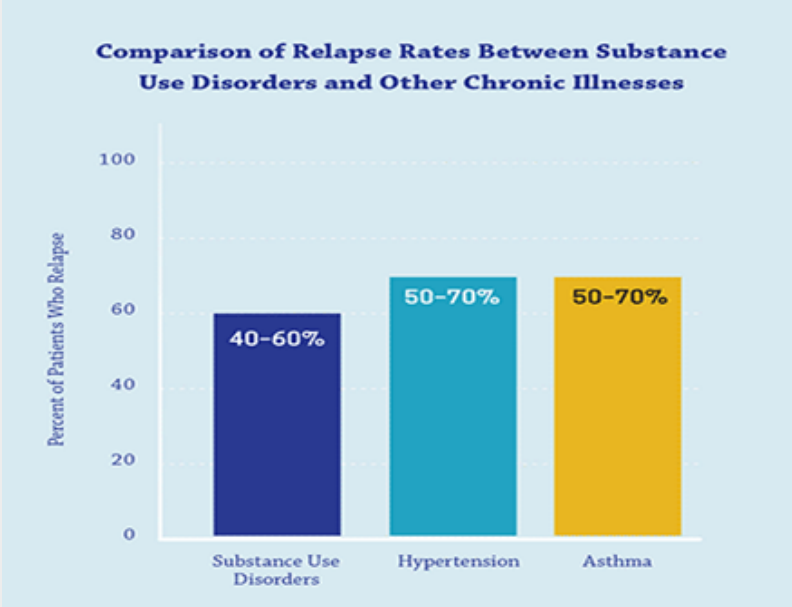
- Need for repeated naloxone treatment with longer acting opioids (methadone), and more potent opioids (fentanyl, carfentanil)
- Check for Fentanyl Patch under clothing
- Fentanyl chest wall/skeletal muscle rigidity
  - Rapid respiratory arrest
  - Most common with rapid IV administration, not dose related
  - Ventilation, naloxone, neuromuscular blocking agent
- Xylazine and Medetomidine (**non-opioid sedative**, alpha2 adrenergic agonist) identified with illicit fentanyl, sedating, naltrexone not effective, withdrawal not addressed by methadone/buprenorphine treatment, associated with complex/severe wounds
- Alert to possible acetaminophen or other OD

Atypical Opioids of Note

- ✓ **Nitazenes (isotonitazine, metonitazine, etc)** synthetic high potency opioids, developed originally in 1950s, never approved for use, identified in illicit drug supply since ~2020s, elevated OD risk potential
- ✓ **Mitragynine (Kratom)** low dose (1-5g) stimulant resembling caffeine/cocaine, high dose (5-15g) opioid effects, analgesic/sedation reversed by naloxone, possible assoc with hepatic cholestasis—dose dependent
- ✓ **Tianeptine** antidepressant similar to TCAs, mu and delta agonist, anticholinergic
- ✓ **Meperidine** → Normeperidine → Neuroexcitation, MAO interactions Serotonin Syndrome
- ✓ **Tramadol** weak mu, ↑ 5HT, ↑ NE, Seizures, (Sched. IV), serotonin syndrome
- ✓ **Tapentadol** mu agonist, ↑ NE (5HT), serotonin syndrome

Opioid Use Disorder Treatment Outcome*

Methadone Maintenance	**50 – 80%**
Buprenorphine-Naloxone Maintenance	**40 – 70%****
Naltrexone Maintenance (oral, depot)	**10 – 20%, 20-60%*****
“Drug Free” (no pharmacotherapy)	**5 – 20%**
Short-term Detoxification (any mode)	**5 – 20% (limited data)**



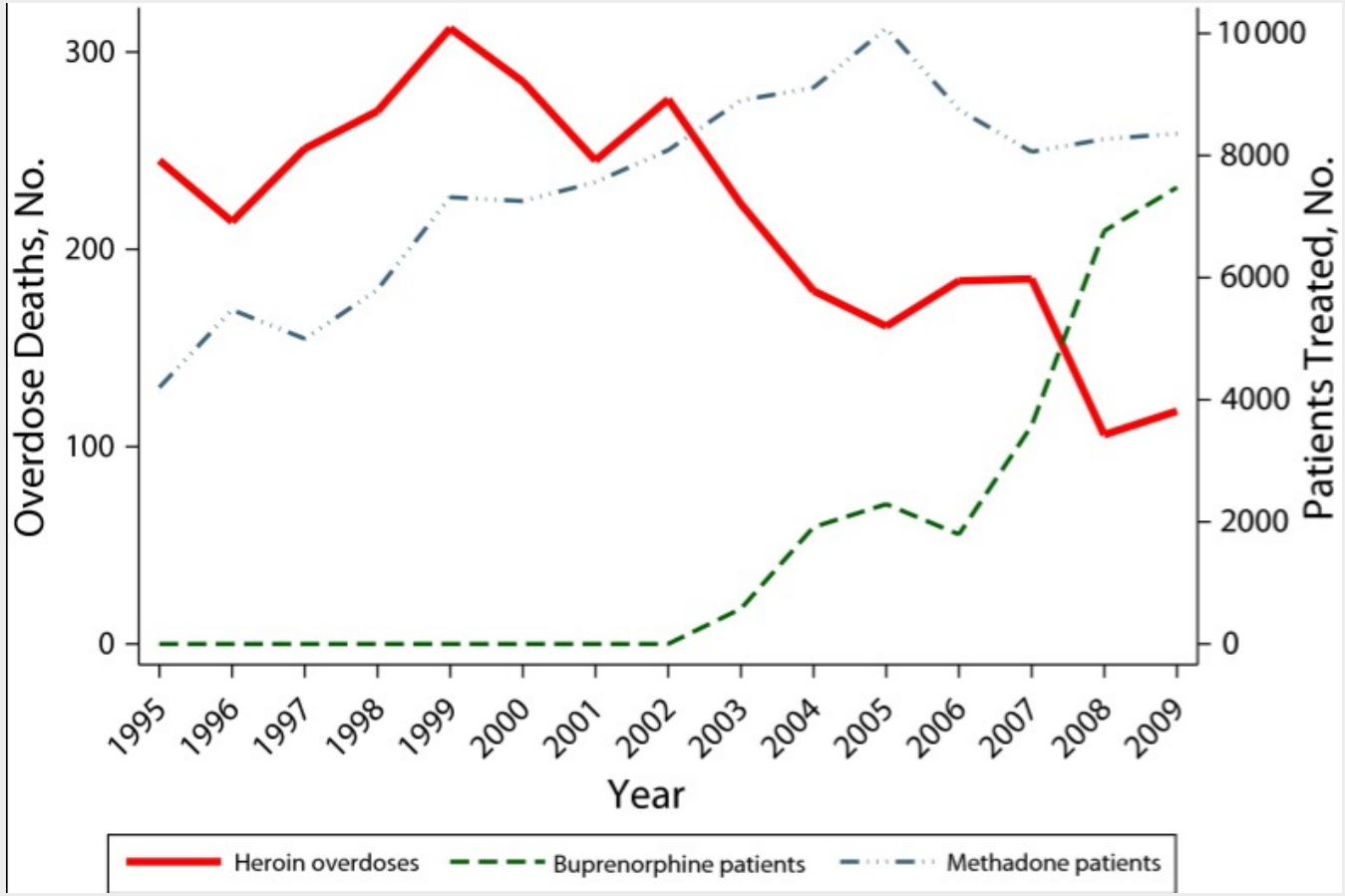
** One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates*
*** Effective dose 16-24mgs equal to 60 to 80 mg/d or possibly greater of methadone.*
**** 6 month treatment with extended release naltrexone*

Methadone and Buprenorphine maintenance treatment reduces overdose risk by 37-86%

>350,000 in OTPs on methadone and est. >800,000 on buprenorphine

Kreek 1996, 2001, 2003, 2006, Krupitsky 2011, Fudala 2003, Weiss 2011, Woody 2008, Mattick 2009, Lee 2016+2017, CSAT

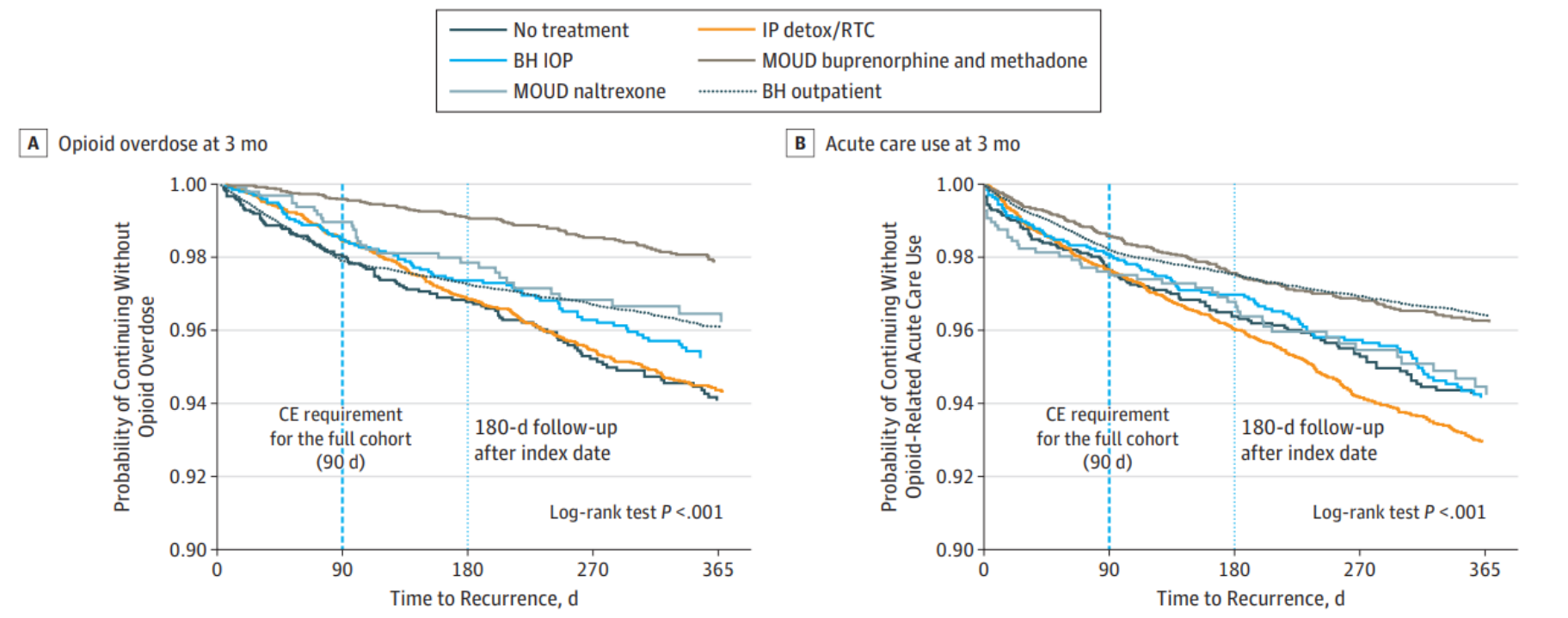
Access to Treatment



Buprenorphine treatment was associated with a 37% annual decline in heroin overdose deaths.

Schwartz RP. Am J Public Health 2013

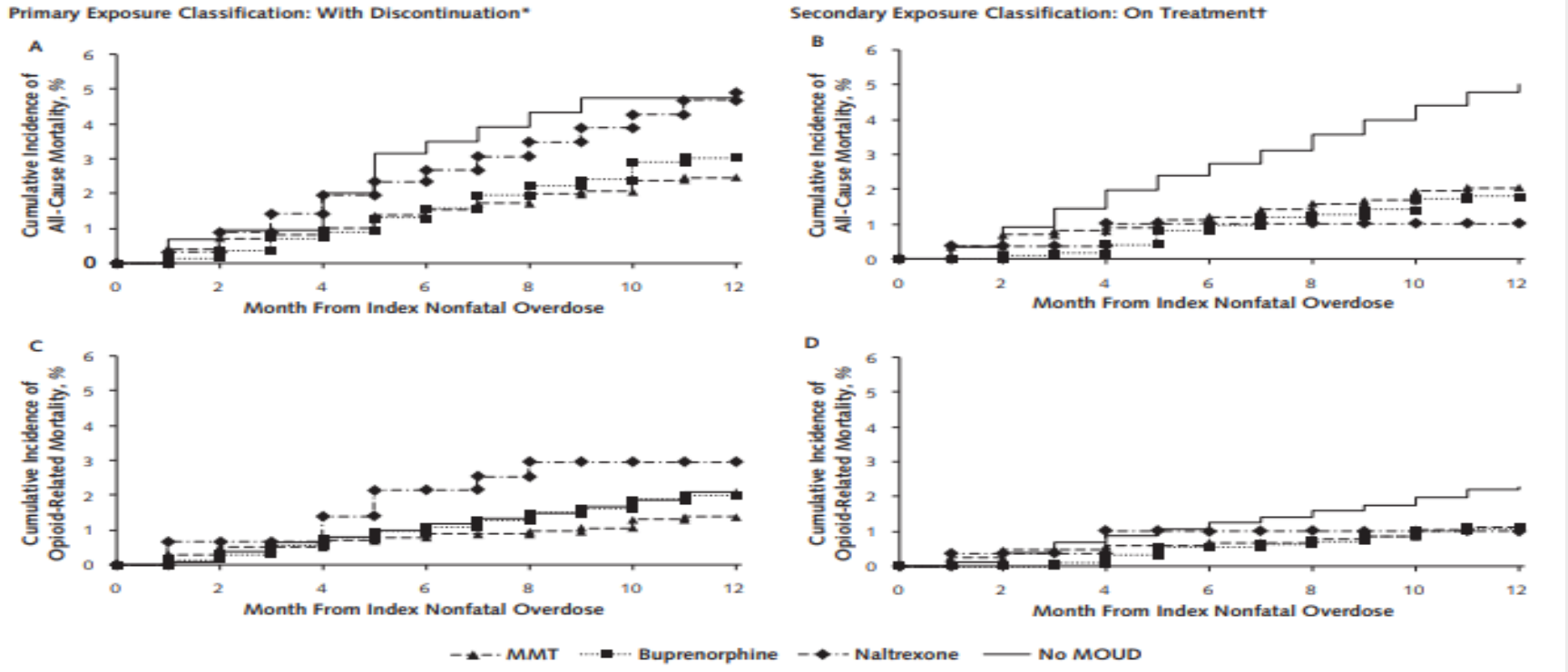
Access to Treatment



Treatment with buprenorphine or methadone was associated with reduced risk of overdose and serious opioid-related acute care use at 3 month and 12 month follow up.

Wakeman et al. JAMA 2020

Access to Treatment



12 months after a nonfatal overdose, compared with no MOUD, both methadone and buprenorphine were associated with decreased all-cause mortality and opioid-related mortality

Larochelle et al. Annals of Internal Medicine 2018

Buprenorphine

Onset of action 30-60min

Peak effect 90-100min, half-life 24-42 hr

Metabolism via CYP 3A4 isoenzyme

- Those on CYP 3A4 inhibitors (azole, antifungals, macrolide antibiotics, and HIV protease inhibitors) should be closely monitored, and dose adjustments may need to be made
- Those on CYP 3A4 inducers (phenobarbital, carbamazepine, phenytoin, and rifampin) should also be monitored, and dose adjustments may need to be made

Can alter liver enzymes

- Liver function should be monitored periodically depending upon any recent symptoms or history of hepatitis
- Consider dose reduction or transition to mono formulation if ≥3x upper limit of normal

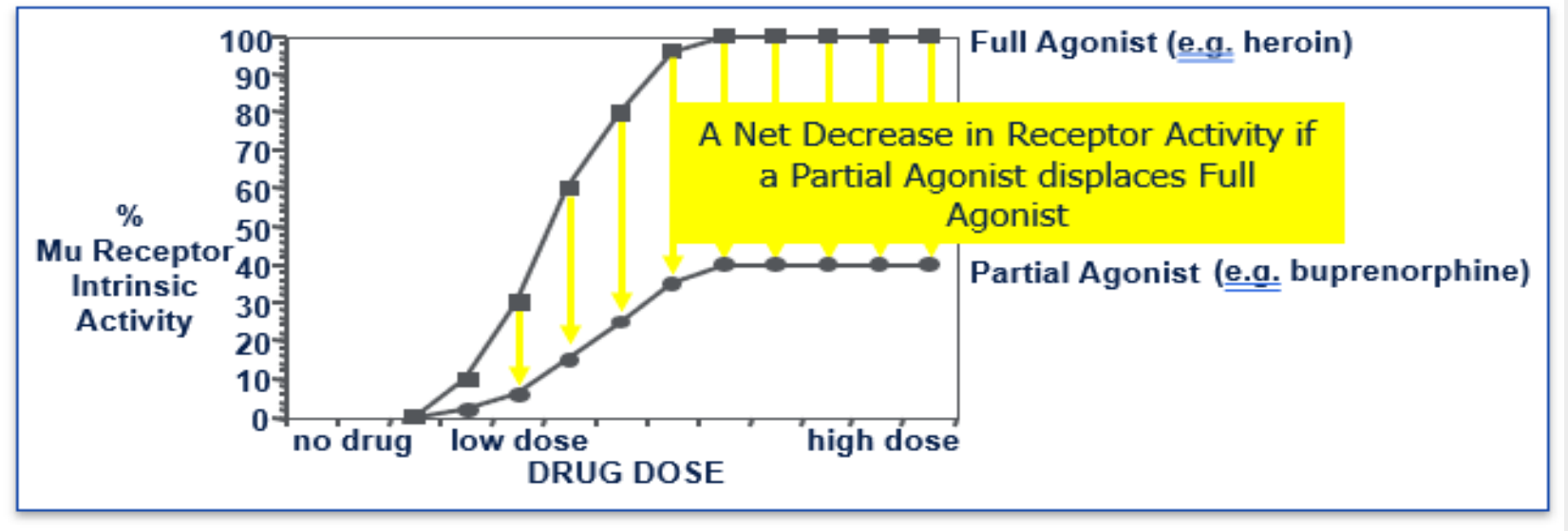
Pregnancy

- MOTHER study, mono (without naloxone) formulation, reduced morphine/NAS/hospitalization

Buprenorphine

Multiple FDA Approved Formulations for OUD: SL film or tablet, monthly SQ

- Partial agonist of the μ-opioid receptor and antagonist of the κ-opioid receptor.
  - ***High affinity*** for μ-opioid receptor
    - Competes with other opioids and inhibits their effects
  - ***Slow dissociation*** from μ-opiate receptor
    - Prolonged therapeutic effect
- At low doses, acts as an agonist; in patients dependent on high doses of chronic opioids sudden initiation at high doses results in antagonist clinical effects.



Initiation

Opiate Withdrawal Symptoms

- 6-18 hrs after last use of short-acting opioids (heroin, oxycodone), or 24-48 hrs after longer-acting opioids (methadone)
- Clinical Opiate Withdrawal Scale (COWS) score of ≥8-10

Day 1: Start with buprenorphine (+/-naloxone) 2-4 mg SL

- Consider additional 2-4mg after 1-2 hrs if continued elevation of COWS and no precipitated withdrawal
- May consider additional 2-4 mg 6 hrs later if OWS persist
- FDA Approved Total Day 1 dose 8 mg, but may clinically increase dose further based on persistent OWS

Day 2: Provide total day 1 dose (routinely given as single dose)

- May increase by 4mg twice daily for ongoing symptoms (8 mg total)
- Total Day 2 dose 16 mg

Adjuvant medications:

- Clonazepam 0.5 to 1mg tid prn, Clonidine 0.1 to 0.2mg q4 prn, Trazadone 100mg qhs prn, NSAIDS, Antiemetics/GI (promethazine 25mg IM, loperamide 4mg PO, octreotide 50 mcg SQ), IVF

Low/Micro Dosing Inductions: Typically utilize 0.5mg initial dose while patient continues on full opioid agonist. Slow titration to maintenance doses over 3-7 days with d/c of full opioid agonists.

Initiated at-home with physician instructions, during hospitalizations, or ED assessments

SAMHSA Treatment Improvement Protocol 63; Salapenka et al. 2022; robbins et al. 2021; Penn Medicine https://penncamp.org/clinical/micro-dosing/

Low-Dose (Micro-Dose) Buprenorphine Initiation

Conventional Low-Dosing Initiation Protocol				
Day	Buprenorphine buccal*		Buprenorphine SL^	Full agonist
1	150 mCG – 1 film daily	OR	0.5 mG daily	Continue
2	150 mCG – 1 film BID	OR	0.5 mG BID	Continue
3	450 mCG – 1 film daily	OR	0.5 mG TID	Continue
4	STOP		2 mG daily	Continue
5	0		2 mG BID	Continue
6	0		4 mG BID	Continue
7	0		12 mG daily	STOP
8+	0		Titrate as needed	STOP
*Each buccal 150 mCG film is equivalent to buprenorphine 0.3 mG ^Doses < 2 mG achieved by patient cutting prescribed 2 mG SL film in 4 pieces BID=twice daily; TID=three times daily				

Rapid Low-Dosing Initiation Protocol				
Day	Buprenorphine buccal*		Buprenorphine SL	Full agonist
1	150 mCG every 4 hours	OR	0.5 mG every 4 hours	Continue
2	450 mCG every 4 hours	OR	1 mG every 4 hours	Continue
3	STOP		2 mG every 4 hours	Continue
4	0		Titrate as needed	STOP
*Each buccal 150 mCG film is equivalent to buprenorphine 0.3 mG				

Buprenorphine

Generic name	Brand Name	Route	Doses
Buprenorphine	Subutex	Sublingual tablets	2 mg; 8 mg
Buprenorphine/naloxone	Suboxone	Sublingual film	2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg
Buprenorphine/naloxone	Suboxone	Sublingual tablets	2 mg/0.5 mg; 8 mg/2 mg
Buprenorphine/naloxone	Zubsolv	Sublingual rapid-dissolve tablets	0.7 mg/0.18 mg; 1.4 mg/0.36 mg; 2.9 mg/0.71 mg; 5.7 mg/1.4 mg; 8.6 mg/2.1 mg; 11.4 mg/2.9 mg
Buprenorphine extended-release injection for subcutaneous use	Brixadi	Subcutaneous	Weekly: 8 mg/0.16 mL; 16 mg/0.32 mL; 24 mg/0.48 mL; 32 mg/0.64 mL Monthly: 64 mg/0.18 mL; 96 mg/0.27 mL; 128 mg/0.36 mL
Buprenorphine extended-release injection	Sublocade	Subcutaneous	Monthly: Initiate 300 mg/1.5 mL after tolerance established of at least 4mg bup, 2nd injection as early as 1 week and up to 1 month after initial injection; then ongoing 100 mg/0.5 mL maintenance dose monthly (can increase to 300 mg)

Naltrexone

- Long-acting, competitive, non-selective opioid-antagonist with high affinity to mu-opioid receptors.
- Metabolism via CYP450
- Excretion predominately urine (53-79%), partial feces. 2% excreted unchanged
- Active metabolite 6-beta-naltrexol
- Half-life 4 hours for naltrexone and 13 hours for 6-beta-naltrexol
- High doses may be associated with hepatic toxicity, contraindicated if elev transaminases

Naltrexone

Antagonist of the μ-opioid receptor

- Withdrawal treatment for those with physical dependence
- POC toxicology
- Induction protocol

Oral formulation FDA approved 1984

- Once daily, 3xweek alternative
- Low adherence limits use to highly motivated populations *(Cornish 1997, Roth 1997)*

Long-acting formulation, Naltrexone-XR 380mg IM monthly, FDA approved for OUD in 2010, *Preferred Formulation*

- More effective than placebo *(Comer 2006, Krupitsky 2011, Tiihonen 2012)*
- More effective than treatment as usual in criminal justice population *(Lee 2016)*
- Lower medical/surgical related hospitalizations but not overall healthcare utilization found in those in criminal justice system as compared to TAU. *(Lee 2018)*
- Non-inferior to buprenorphine, when randomization occurred after opioid detoxification or those successfully inducted onto XR-NTX. *(Tanum 2017, Lee 2018)*
- Reported ODs in studies is low, however most did not report how overdose events were measured particularly those lost to follow-up. *(Jarvis 2018)*

➢ *Consider OD risk from interrupted antagonist treatment*

Methadone

- Approved by FDA 1972 for opioid dependence
- Mu opioid receptor agonist and NMDA antagonist (reduces development of tolerance)
- 2 enantiomers in equal amounts
  - *l (R)* active, *d (S)* inactive
  - Rapidly absorbed orally with detectable plasma levels at 30min but has a delayed onset of action with peak levels at 2-4 hours with sustained levels for 24 hours.
- Metabolized by CYP450 – several isoforms:
- CYP2D6 – may explain group who need very high doses
- Excreted in urine and feces
  - Avoids accumulation and reduces risk of toxicity for those with renal or liver dysfunction
- Half-life 24-36 hrs but may range from 4-91 hrs
  - **Avoid rapid titration!**

Methadone

- 2006 Black Box Warning – risk of QTc prolongation and possibly torsades de pointes/polymorphic VT, dose dependent
- Common side effects: ***constipation, diaphoresis, to a lesser extent sexual dysfunction***
- Safety profile well established including during pregnancy
- ***Beware Opioid Conversion Tables!***
- **Serum Level** – clinical presentation should direct dosing decisions but SML can serve as aid
  - Peak level drawn 2-4 hours after dosing
  - Trough level drawn prior to daily dosing ~24hrs
  - Peak SML less than twice trough

Methadone

1. Initial dose 10-20mg PO (50% dose IM), 20mg eliminates severe withdrawal, first 24hr dose 20-30mg TDD (not routinely recommended to exceed 40mg in first 24 hours, recent 42CFR Part 8 up to 50mg)
2. Craving reduced by increasing methadone dose by 5-10mg q three to seven days (80-120mg or greater)
3. “Blocking dose” (often 80-120mg or greater): tolerance that inhibits the euphoric high

After stabilization, methadone and buprenorphine do not produce euphoria or sedation.

ASAM 2017, 2015, SAMHSA TIP 63

The Basics for all OTPs

- Comprehensive Assessments
- Treatment Plans
- Toxicology Testing
- Diversion Control
- Multiple MAT options: methadone, buprenorphine, naltrexone
- New attendance schedule flexibility for medication dispensing
- Guest Medication
- Confidentiality, 42 CFR Part 2
- Regulatory Oversight

OUD - Fentanyl

	Buprenorphine	Naltrexone-XR	Methadone
Initiation after last opioid use	Traditional: 1-3 days LDB: same day HDB: 1-3 days	7-14 days for opioid detoxification	Same day
Induction withdrawal risk	Low-Moderate Precipitated withdrawal and post-acute withdrawal may last longer with subtherapeutic dosing	Moderate Precipitated withdrawal if given before completion of acute withdrawal treatment/detoxification Protracted withdrawal may persist 1-2 wks post-induction	Low Mild withdrawal may persist during early titration
Time to full therapeutic dose	1-3 days or longer	1-day post-administration	≥1 week, or longer
Craving Reduction	Moderate Ceiling partial agonist effect	Variable Mechanism of anti-craving effect poorly understood	High Dose-related full agonist effect

Medication and Treatment Setting – Selection Considerations

- Abstinence to Harm Reduction Continuum
- Chronic Pain or foreseeable need for opioid analgesia
- Pregnant or planning pregnancy
- Recent Overdose or high risk for overdose behavior
- Medical and Psychiatric Co-occurring Disorders
- Diversion Risk
- Additional substance use disorders
- Alternatives

Which endogenous opiate receptor type predominantly influences the development of acute opiate withdrawal symptoms?

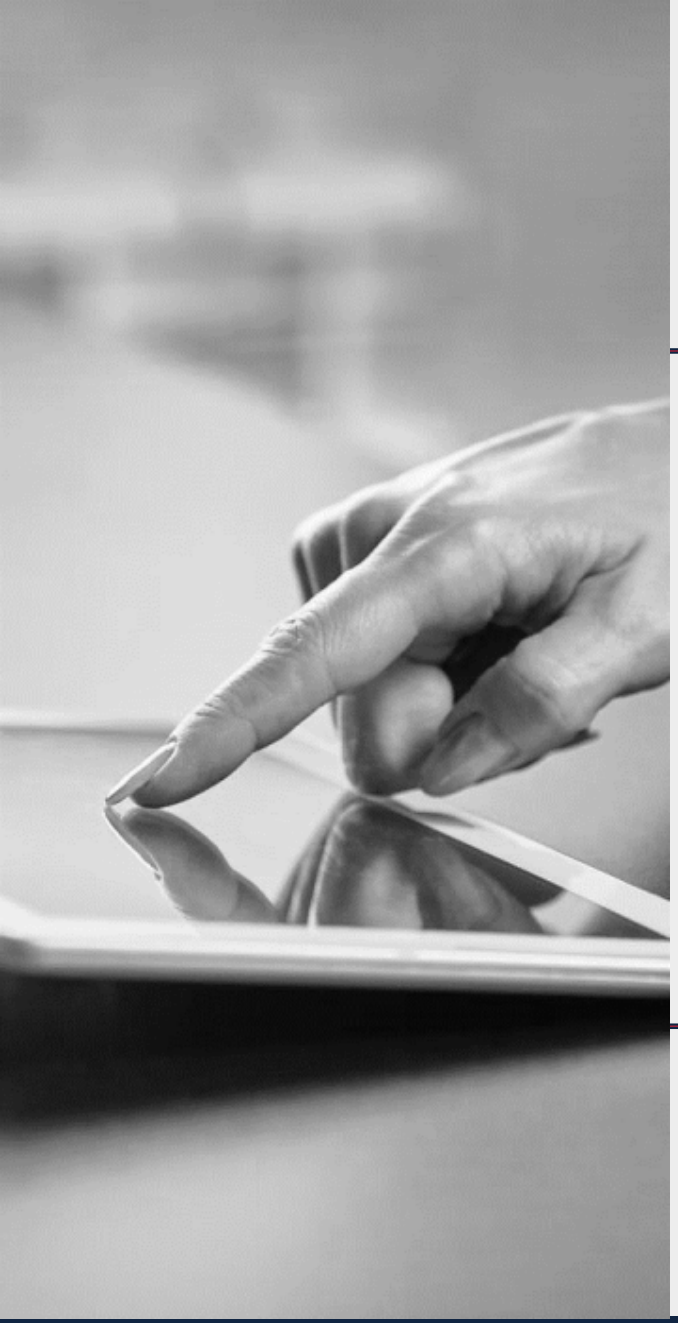
A. GABA B receptor
B. Mu opiate receptor
C. Kappa opiate receptor
D. Serotonin 5HT-2A receptor

The federal 2024 HHS update to 42 CFR Part 8 authorizes the following at accredited Opioid Treatment Programs EXCEPT?

A. Up to 7 unsupervised take-home doses of methadone for patients recently admitted
B. Medical Directors may delegate some responsibilities to other practitioners
C. Counseling is required for patients obtaining care at OTPs
D. Medical exam requirement modified to facilitate treatment initiation

Which of the following is the correct order from most to least relative opioid potency?

A. Fentanyl, carfentanil, diacetylmorphine, morphine
B. Diacetylmorphine, carfentanil, fentanyl, morphine
C. Carfentanil, fentanyl, diacetylmorphine, morphine
D. Morphine, diacetylmorphine, carfentanil, fentanyl



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