OPIOIDS

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The ASAM Board Exam Study Course in Addiction Medicine

2022

Financial Disclosures

Soteri Polydorou, MD

No Disclosures

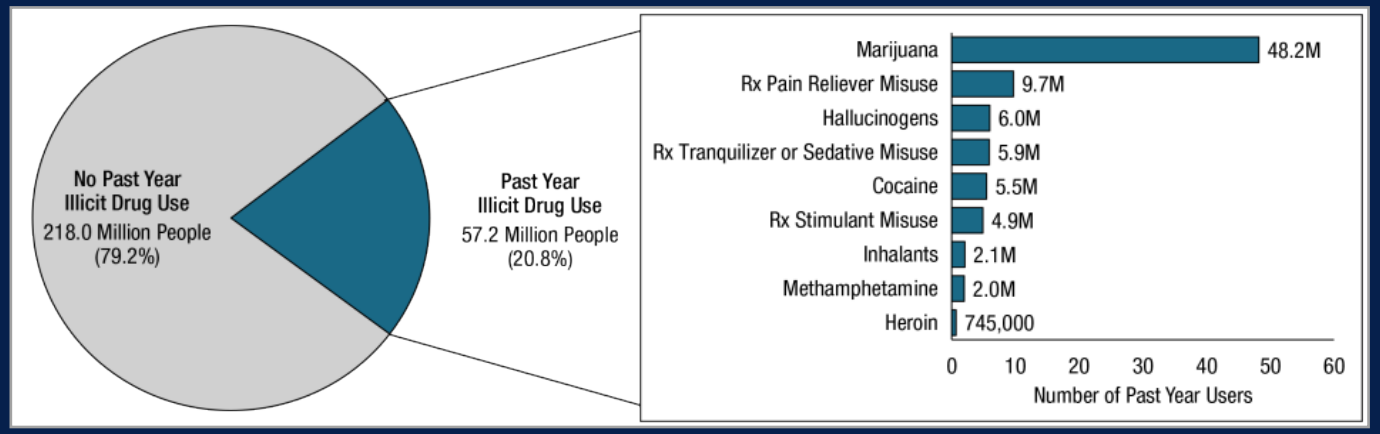
Outline

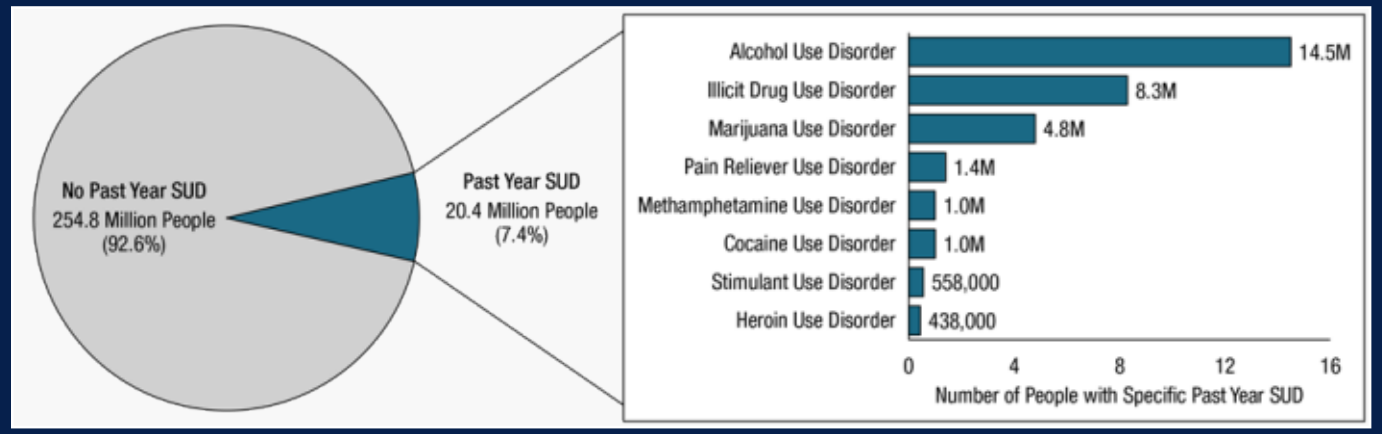
1. Opioid Use Trends
2. History
3. Regulations
4. Neurobiology
5. Intoxication and Withdrawal
6. Medications for Opioid Use Disorder

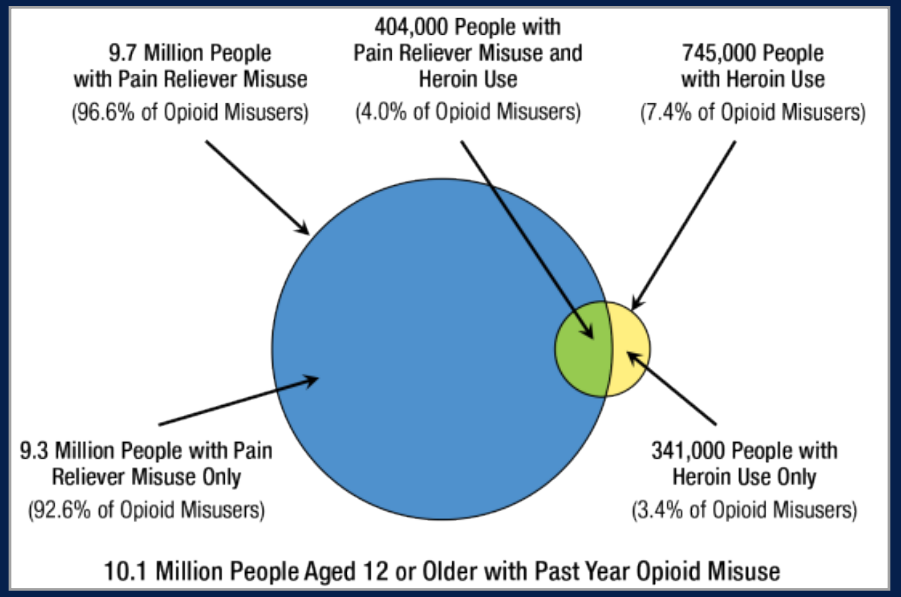
The Need for Treatment is Growing

Nationally

- SUDs affect 40 million people
- Cost $740 billion annually







NSDUH 2019, SAMHSA

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

The Need for Treatment is Growing

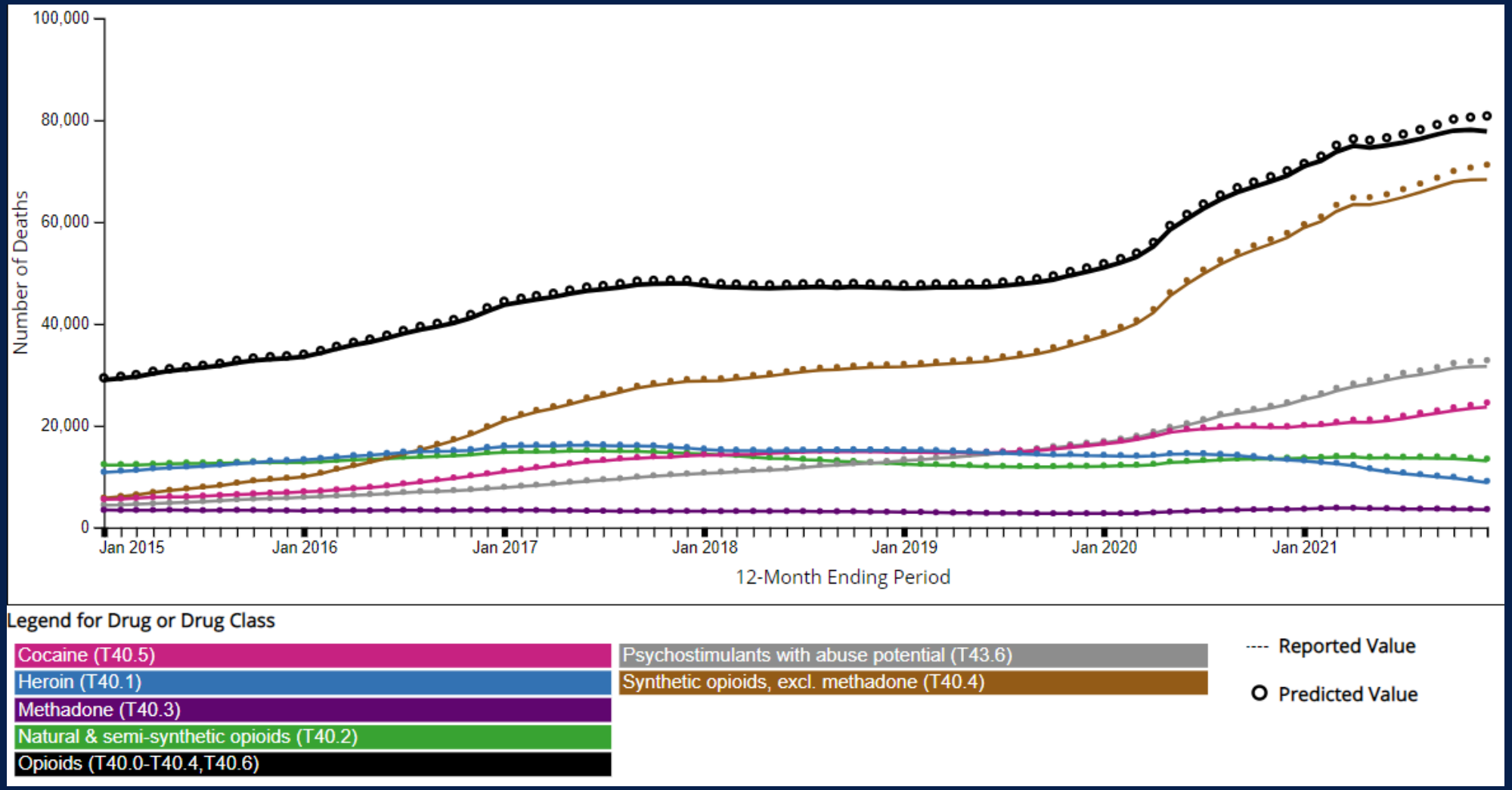
Nationally

- Over 100,000 lethal ODs in 2021, nearly 15% increase from 2020
- Almost 80% of all overdose deaths involve an opioid of which over 70% include 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, 2020	Annual Deaths
Heart Disease	696,962
Cancer	602,350
COVID	350,831
Accidents (unintentional injuries)	200,955
Stroke	160,264
Chronic Lower Respiratory Diseases	152,657
Alzheimer's Disease	134,242
Diabetes	102,188
Influenza and PNA	53,544
Renal Disease	52,547

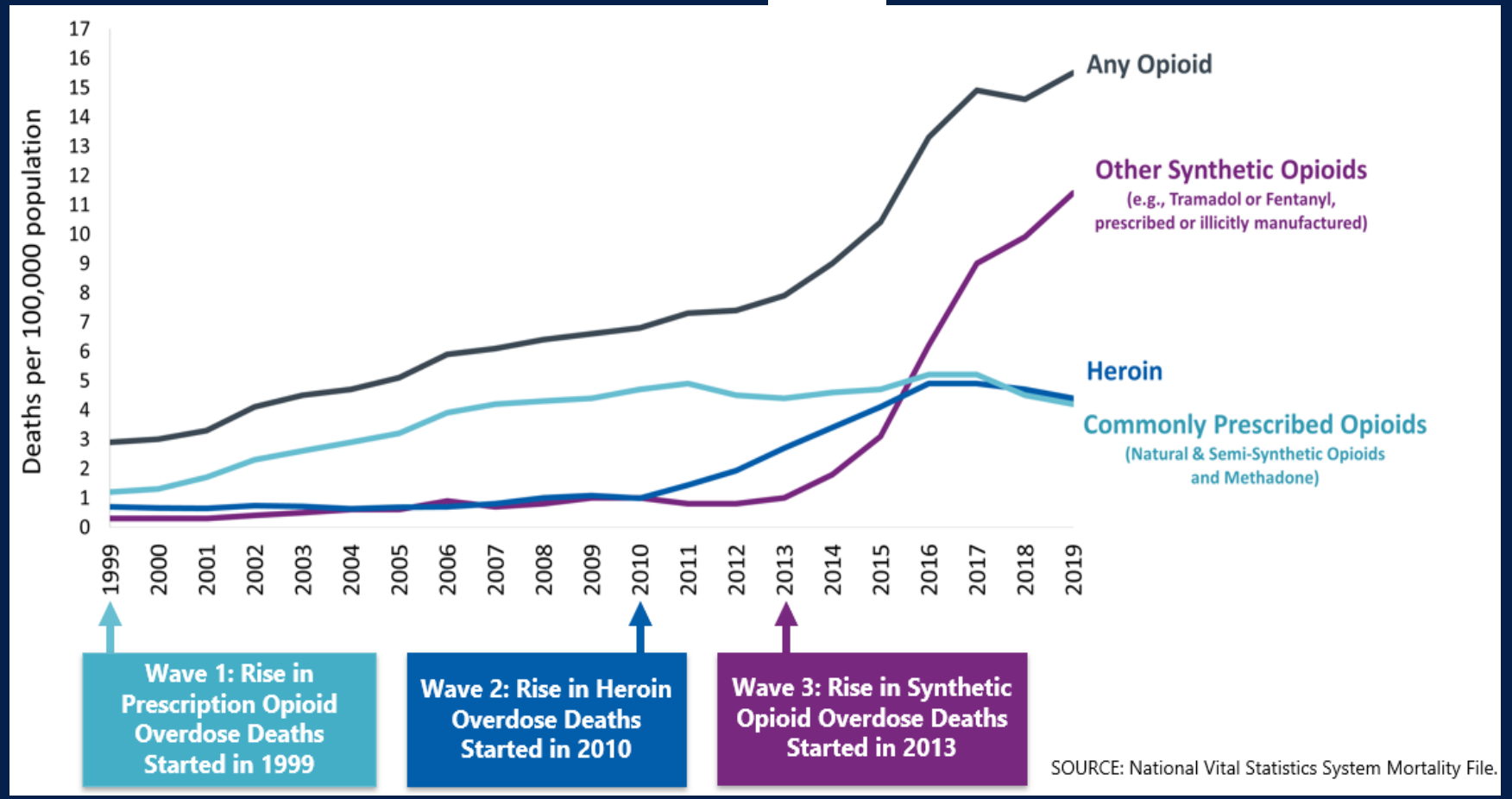
CDC, Health Alert Network, NSDUH, SAMHSA, CSAT, and DOHMH Bureau of Vital Statistics

The Need for Treatment is Growing

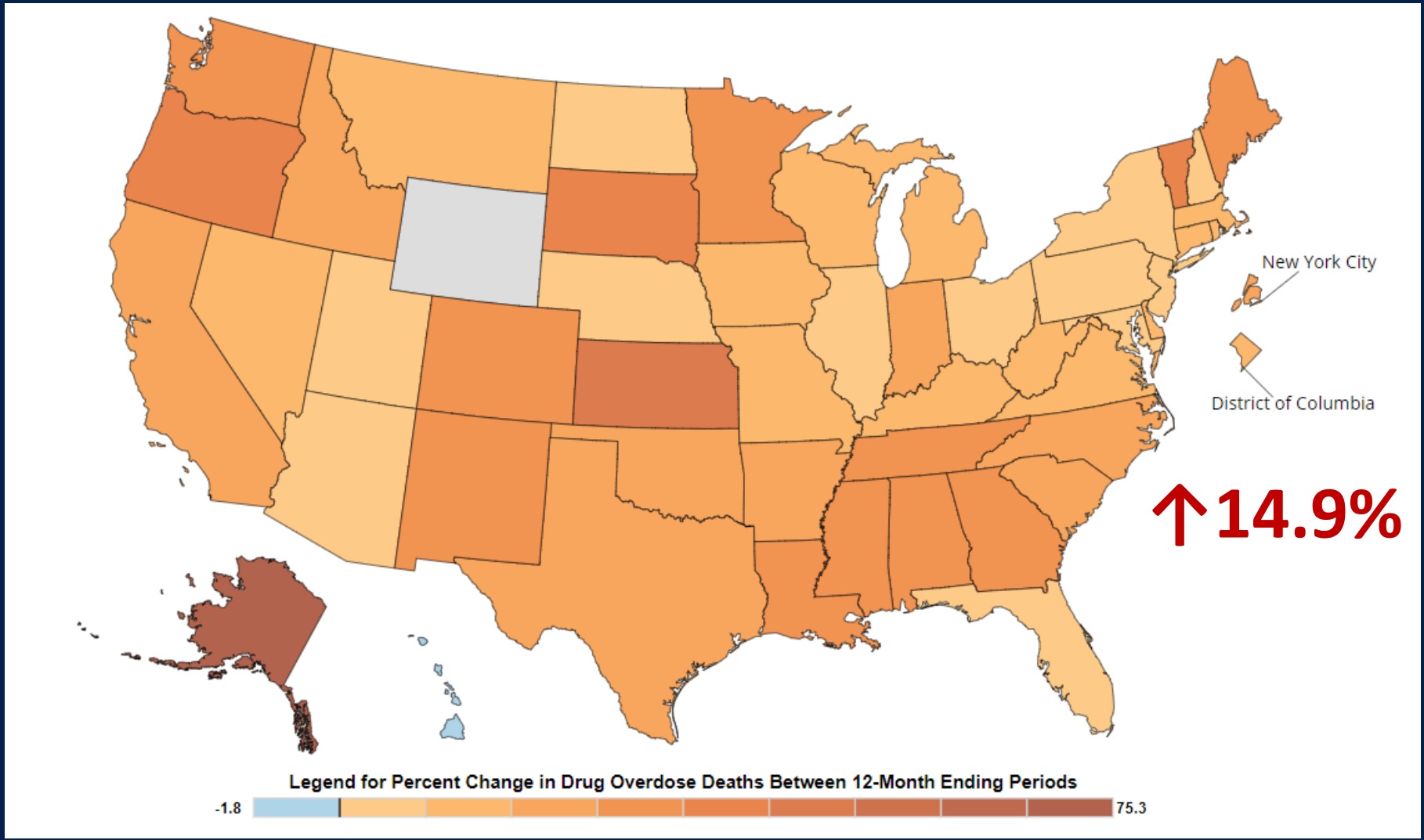


Based on data available for analysis on 5/12/22,
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard

Three Waves of Opioid Overdose Deaths

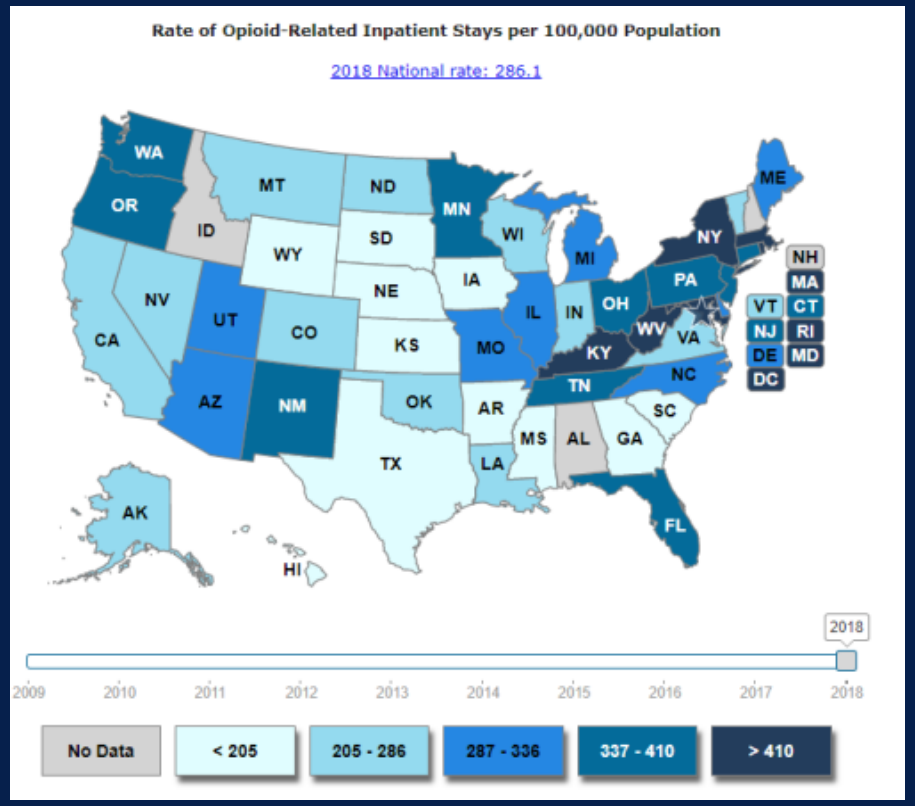


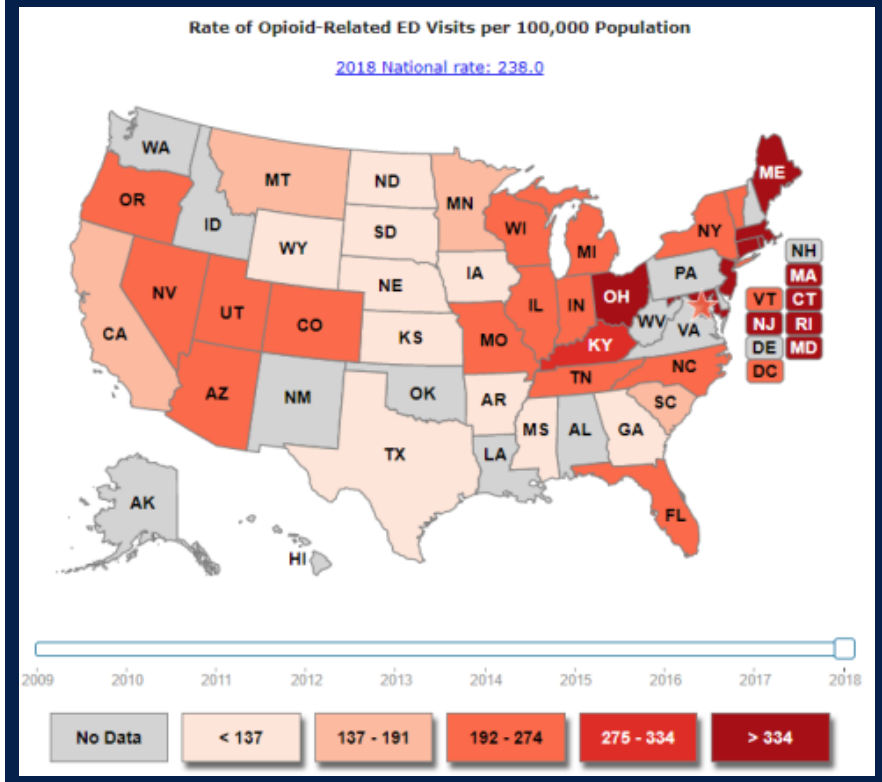
Drug Overdose Deaths 2021



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

Opioid Related Inpatient Stays and ED Visits





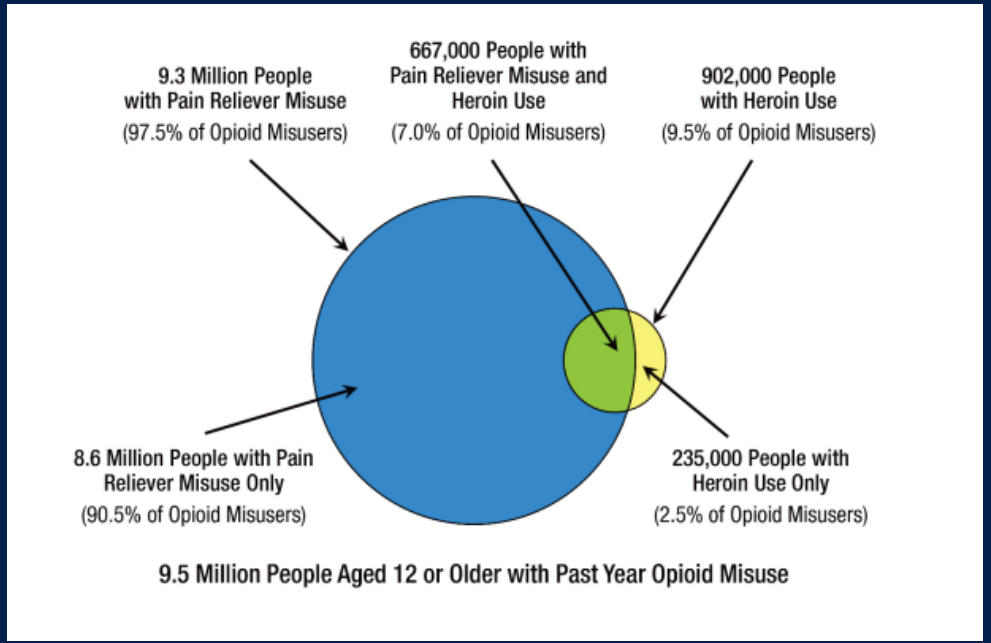
Agency for Healthcare Research and Quality (AHRQ), Healthcare Cost and Utilization Project (HCUP), https://www.hcup-us.ahrq.gov/

The Need for Treatment is Growing

Opioid Use Disorder 2.9 million

- Prescription opioids 2.3 million
- Heroin use 691,000
  - >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 2020, SAMHSA

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Martins S et al 2015

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

Opportunities to Reduce Risk

Individual

Education

OD Prevention Rescue Kits

MAT

Treatment Availability

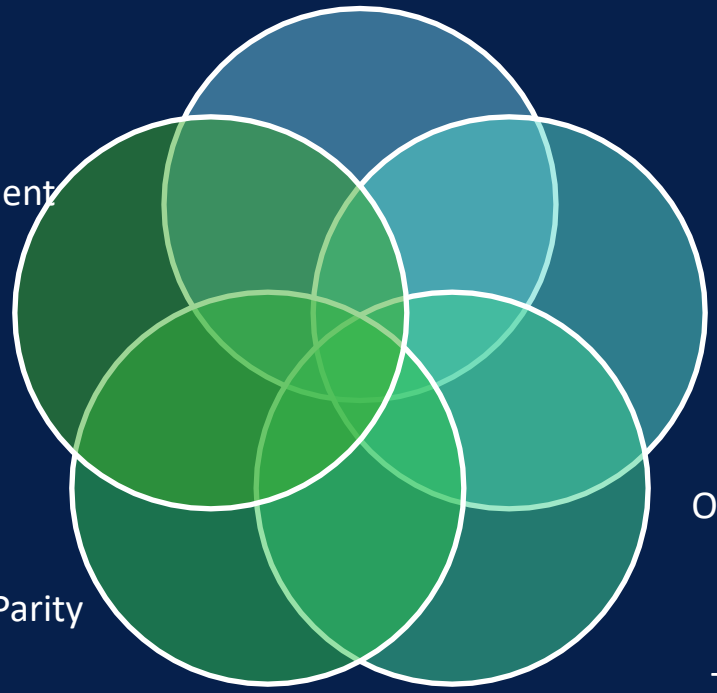
Family & Friends

Education

OD Prevention Rescue Kits

Medication Safety

Encourage Treatment Engagement



Community

Increase Awareness

Medication Safety

Reducing Stigma

Harm Reduction

Government

MAT Access

Insurance Coverage

Mental Health and Addiction Parity

Research Funding

PMP Optimization

Prescribers

Education

OD Prevention Rescue Kits

MAT

Identification of SUDs

Treatment Coordination

Hawk K et al 2015

3400 BC

1898

1839

1935

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
- **Papaverine**, 1-5%. smooth muscle relaxant
- **Poppy Seeds**: UDS→ ⊃ Opiates, Morphine, Codeine (cut-off dependent)

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

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

- Approved training programs
  - Complete eight hours of training provided by a pre-approved society or by a society approved by State Medical Licensing Boards or by the Secretary of HHS
  - Providers Clinical Support System, ***PCSSNOW.ORG***
- Apply for waiver from Center for Substance Abuse Treatment (CSAT)
- 2006 – Patient limit increases to 100
- 2016 Comprehensive Addiction and Recovery Act (CARA)
  - Expands buprenorphine prescribing to PA and NP, qualify after taking 24hr of training, until 2021.
  - SAMHSA authorizes patient limit increase to 275

U.S. Government Involvement

- 2018 Support for Patients and Communities Act
  - Expands buprenorphine prescribing to Clinical Nurse Specialists, Certified Registered Nurse Anesthetists, and Certified Nurse Midwives until 10/1/23
  - Increases number of patients to 100 that can be treated by certain physicians in the first year of obtaining a waiver under specific conditions.
- 2020 HHS Public Health Emergency Declaration, DEA partners with SAMHSA (temporary)
  - Controlled Substances (in accordance with DATA 2000 waivers) can be prescribed using telemedicine or telephone without first conducting an in-person examination while HHS PHED in effect
  - OTP utilization of methadone continues to require an initial on-site examination, but attendance restrictions related to time in treatment have been temporarily modified.

U.S. Government Involvement

- 2021 HHS Updates Practice Guidelines for the Administration of Buprenorphine for Treating OUD
  - Provides an alternative Buprenorphine Waiver Notice of Intent allowing providers to treat up to 30 patients to forego training requirement, as well as certification to counseling and other ancillary services.
    - https://buprenorphine.samhsa.gov/forms/select-practitioner-type.php

Over 100,000 practitioners hold waivers, 71,000 with 30-limit, 22,000 with 100-limit, <10,000 with 275-limit

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

DEA Announcement

March 23, 2022 — For Immediate Release

Contact: Media Relations

Phone Number: (571) 776-2508

DEA's Commitment to Expanding Access to Medication-Assisted Treatment

WASHINGTON – Today, Administrator Anne Milgram announced the Drug Enforcement Administration's continued commitment to expanding access to medication-assisted treatment to help those suffering from substance use disorder.

"In this moment, when the United States is suffering tens of thousands of opioid-related overdose deaths every year, the DEA's top priority is doing everything in our power to save lives," said Administrator Milgram. "Medication-assisted treatment helps those who are fighting to overcome substance use disorder by sustaining recovery and preventing overdoses. At DEA, our goal is simple: we want medication-assisted treatment to be readily and safely available to anyone in the country who needs it."

Recently, DEA, in collaboration with federal, state, and local partners, has been championing a number of initiatives to expand access to medication-assisted treatment for those suffering from opioid-related substance use disorder.

- Beginning in March 2022, practitioners working in hospitals, clinics, and emergency rooms will be able to request an exception allowing them to dispense a three-day supply of medication-assisted treatments, including buprenorphine and methadone, to treat patients experiencing acute opioid withdrawal symptoms.
- DEA, in partnership with the Department of Health and Human Services, is engaging in regular outreach with pharmacists and practitioners to express support for the use of medication-assisted treatment for those suffering from substance use disorder.
- In July 2021, DEA implemented a new regulation increasing the number of mobile methadone treatment facilities in an effort to expand access to treatment in remote and underserved communities.
- In response to the COVID-19 public health emergency, DEA implemented temporary regulations allowing medication-assisted treatment to be prescribed by telemedicine. DEA is working to make those regulations permanent.

DEA is committed to continuing to work with our federal, state, and local partners to find more ways to expand access to medication-assisted treatment. DEA hopes that these efforts will help people across the country gain access to these lifesaving medicines.

For more information, visit DEA's Diversion Control Division website.

Email DEA Exception Requests:
ODLP@dea.gov

Subject Line:
Request for Exception to Limitations on Dispensing for OUD

https://www.dea.gov/press-releases/2022/03/23/deas-commitment-expanding-access-medication-assisted-treatment

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

Endogenous Opioids & Opioid Receptors

Opioid 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

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.

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.

Genetics/Pharmacogenomics

Multiple polymorphisms identified in opioid receptor genes and other coding regions which have clinical effect.

- OPRM1 chromosome 6; OPRK1 chromosome 8; OPRD1 chromosome 1
- OPRM1 Gene→SNP,rs1799971: **A118G** (Adenine to Guanine substitution)
- → Asn40Asp(Substitution in the receptor extracellular domain) →
- ↑(?) Binding beta endorphin, ↑ risk OUD, AUD, ↓(?) Analgesic Response
- CYP 2D6: Codeine→Morphine, Hydrocodone→Hydomorphone, Oxycodone→Oxymorphone (Asian heritage: ↓↓ 2D6 Other Groups ~ 10% PM)
- Methadone: CYP 3A4, 2D6, 2B6
- COMT (enzyme) The most widely studied variant is **158Met**, where a G to A nucleotide substitution at codon 158 results in an amino acid change from valine to methionine. Patients with Met/Met genotype have lower morphine requirements than those with a Val/Val expression.

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

Opioids of Note

- Fentanyl ↑ Temp → ↑Skin Absorption
- Meperidine → Normeperidine→ Neuroexcitation, MAO interactions Serotonin Syndrome
- Tramadol weak mu, ↑5HT, ↑NE, Seizures, (Sched. IV), serotonin syndrome
- Tapentadol mu agonist, ↑ NE (5HT), serotonin syndrome
- Kratom, low dose (1-5g) stimulant resembling caffeine/cocaine, high dose (5-15g) opioid like effects, analgesic/sedation reversed by naloxone, possible assoc with hepatic cholestasis—dose dependent
- Tianeptine, antidepressant similar to TCAs, mu and delta agonist, anticholinergic

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

Management of Opioid Overdose

- Ventilatory support if needed
- Parenteral Naloxone
- If IV access, bolus 0.1mg/min 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, 0.4-0.8mg SQ or IM and observe
- Naloxone OD Prevention Kits

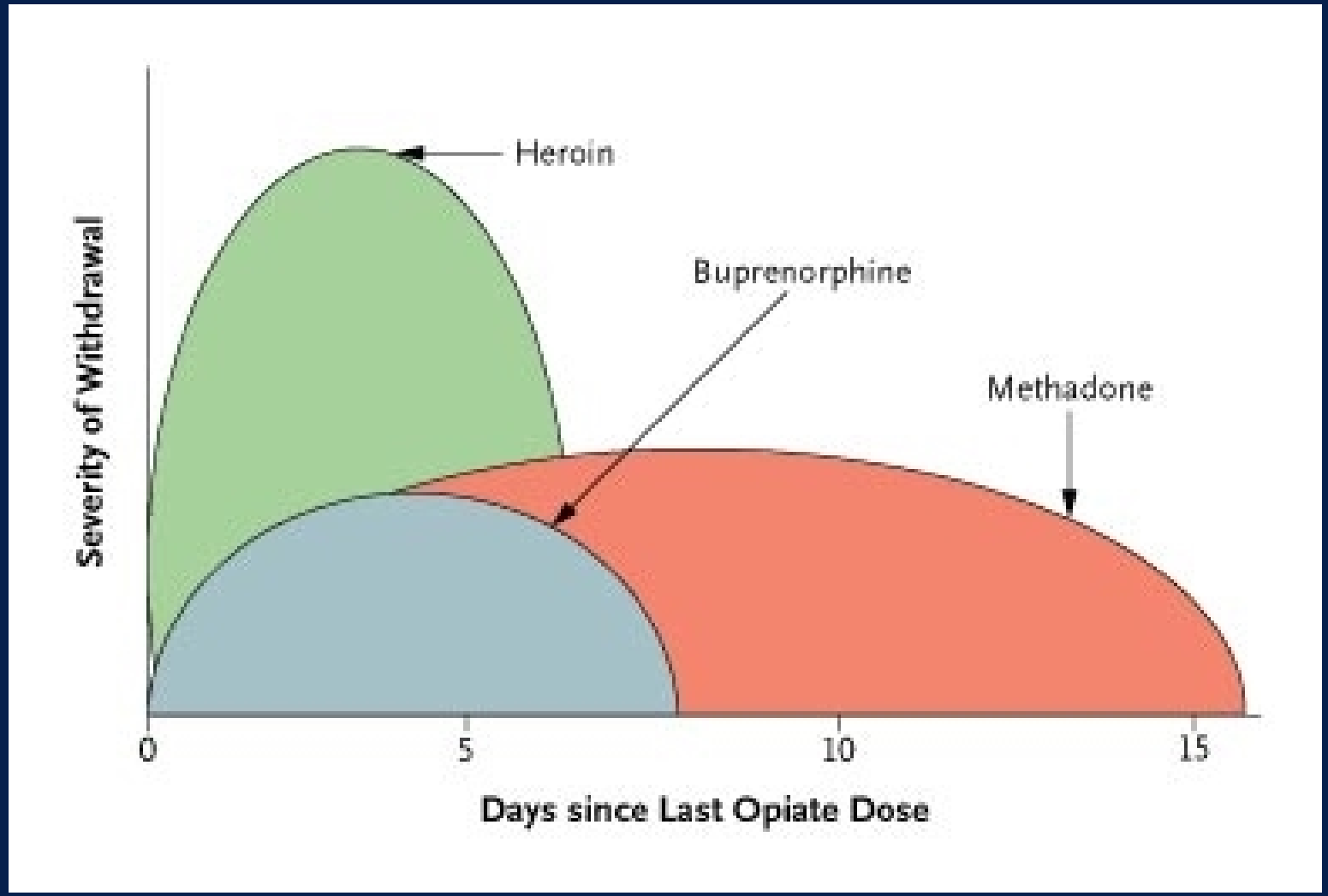
Opioid Overdose Education and Naloxone Distribution (OEND) Programs

- Improved trainee Strang 2006 knowledge of OD safely and effectively administer naloxone
- Some evidence suggests trainees reduced IV use and were more likely to enter treatment 6 months after training. Seal 2005.
- Chicago, OD deaths reduced after introduction of OOPPs. Maxwell S 2006
- Mass, ↓27% in OD deaths low implementation (1-100/100k) vs ↑46% in high implementation (>100/100k). Walley AY 2013.
- But still…
- Study of >500 MDs reported 54% would NEVER consider prescribing naloxone to an IVDU. Beletsky L 2007.

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
    - Most common with rapid IV administration, not dose related
    - Ventilation, naloxone, neuromuscular blocking agent
- Observation
- Alert to possible acetaminophen or other OD

Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation o 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.

Clinical Opiate Withdrawal Scale (COWS)

- Methadone—Hospitalized, OTP, very limited other licensed OP
- Buprenorphine—Hospitalized, Recent HHS Practice Guideline change to Notice of Intent, Waivered MD/DO/PA/NP, OTP
- Symptomatic Meds, e.g., Clonidine, NSAIDS, Imodium, B/Zs
- 72 Hour Rule: Dispense Only

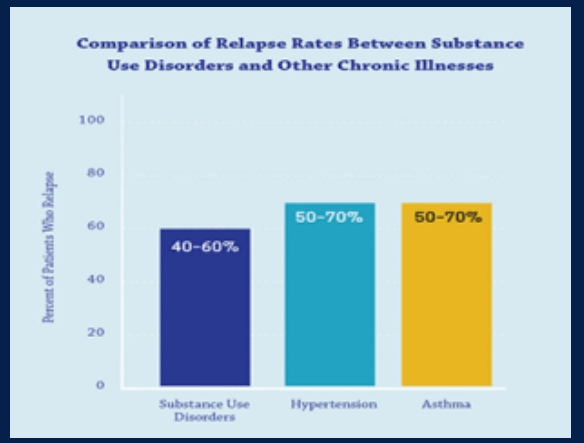
Table 2. Medication Treatment for Opioid Withdrawal.*

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.

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)



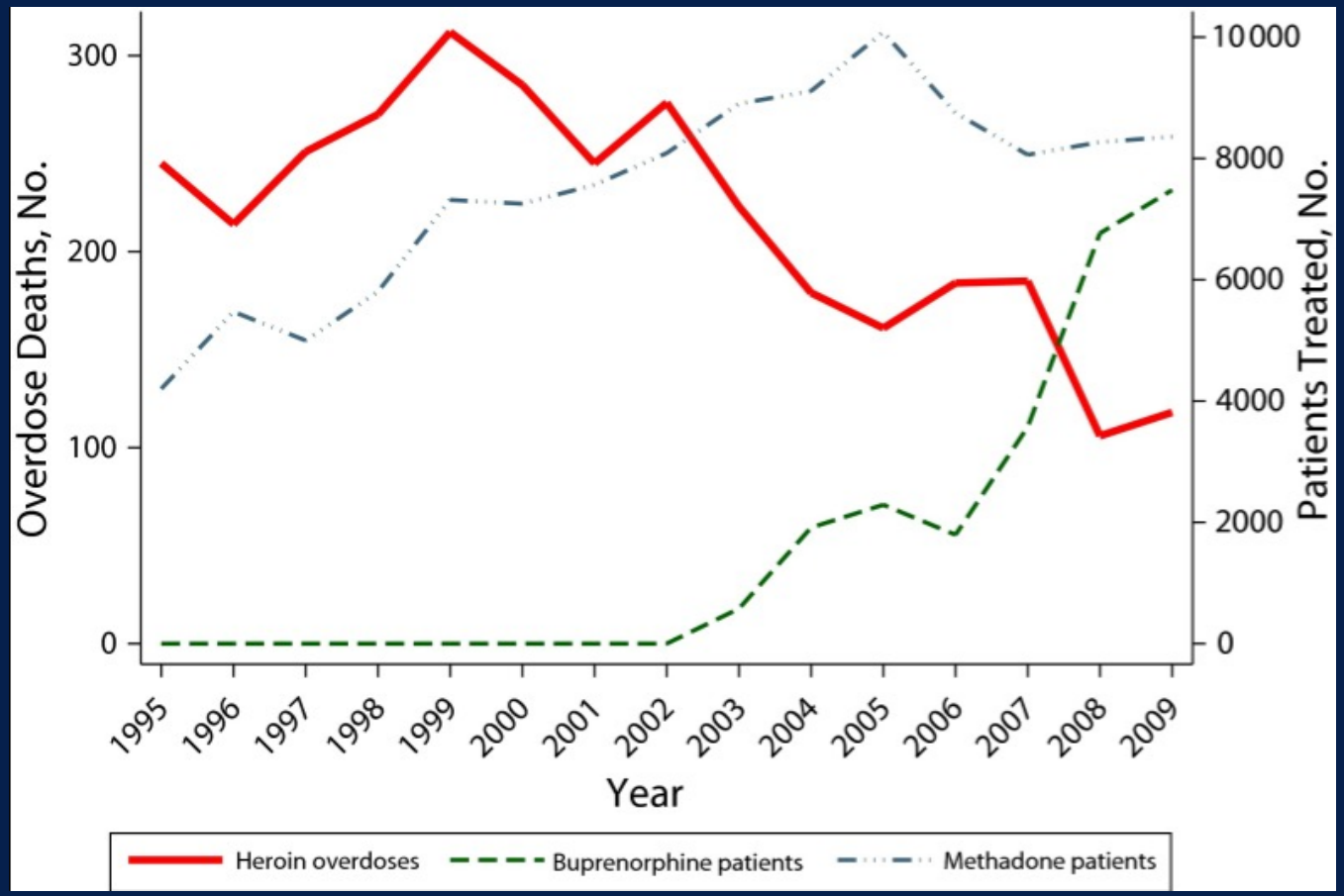
** One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates*
*** Effective dose 16-24mgs equal to 60 to 80 mg/d or possibly greater of methadone.*
**** 6 month treatment with extended release naltrexone*

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

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

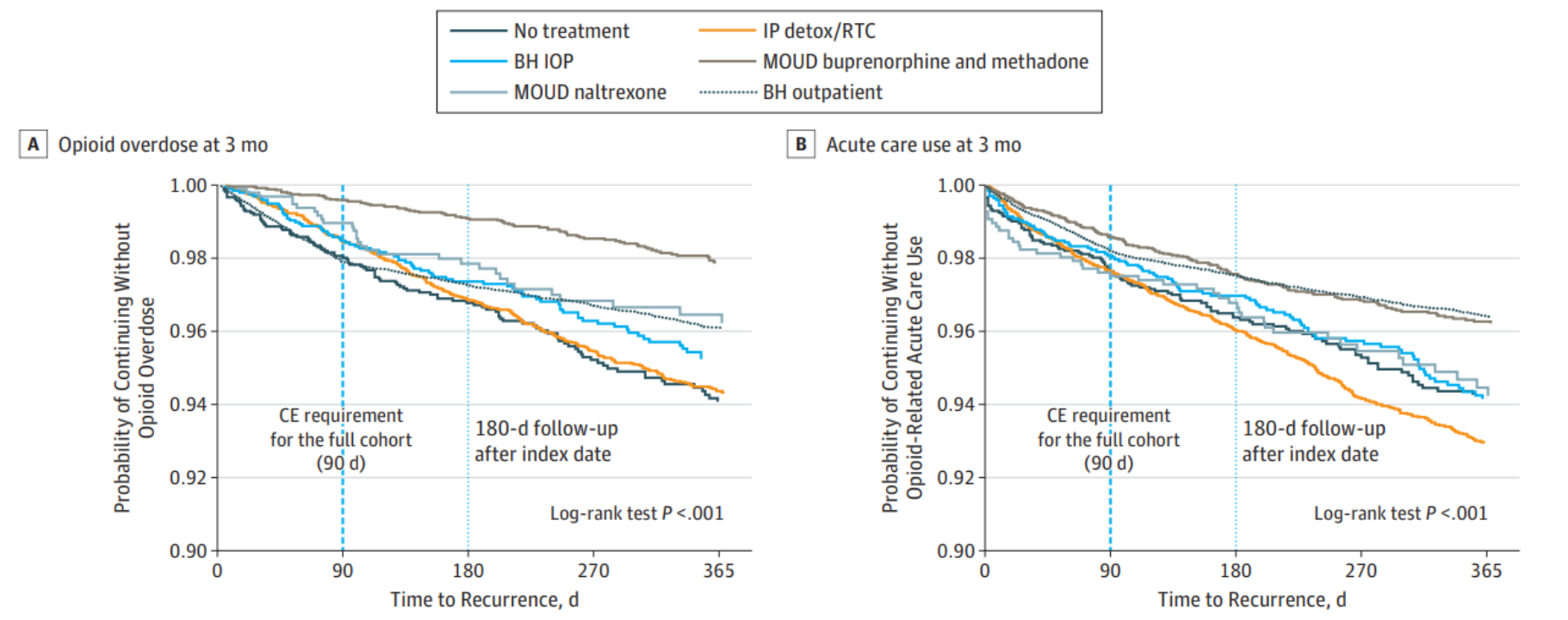
Kreek 1996, 2001, 2003, 2006, Krupitsky 2011, Fudala 2003, Weiss 2011, Woody 2008, Mattick 2009, Lee 2016+2017, CSAT

Access to Treatment



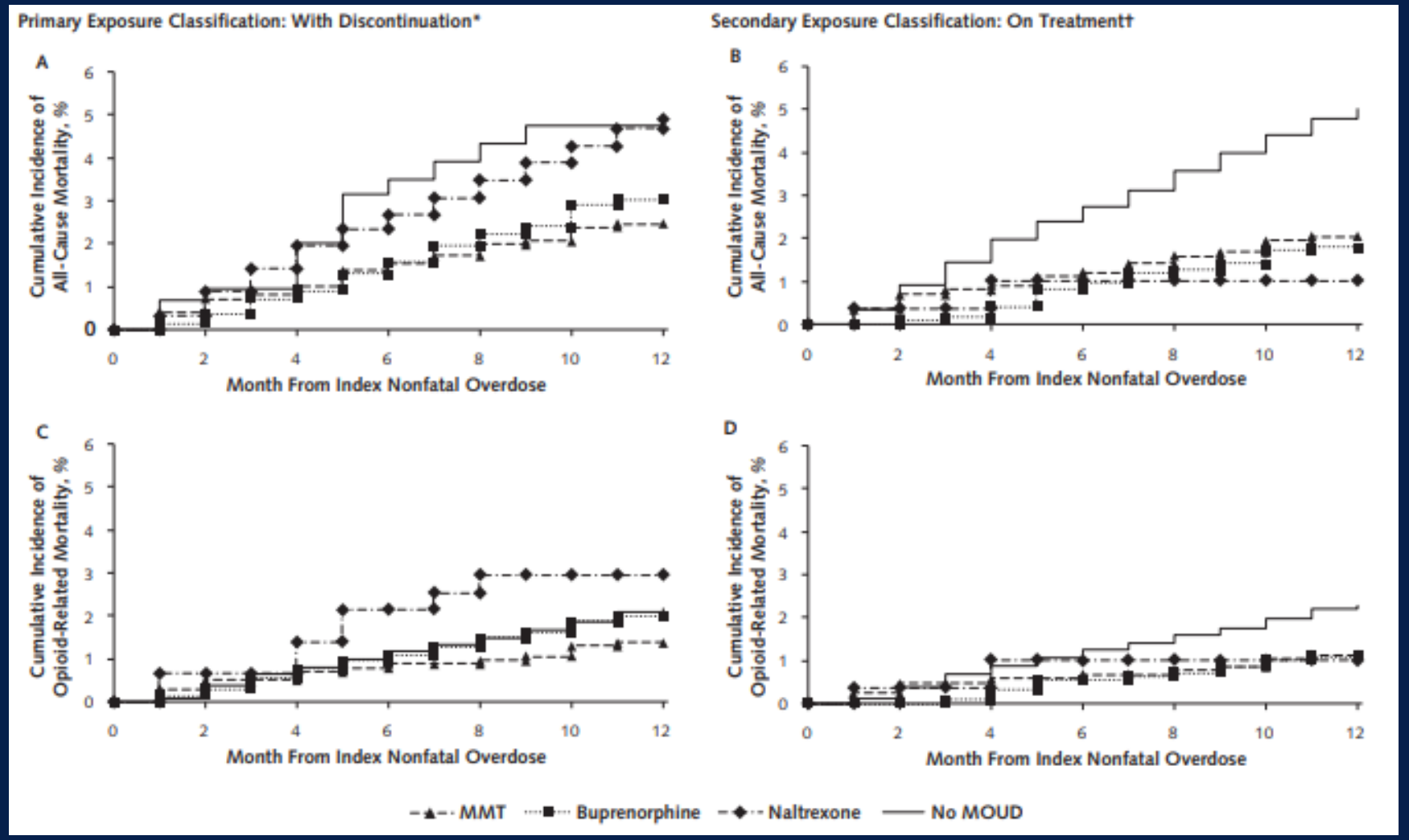
Schwartz RP. Am J Public Health 2013

Access to Treatment



Wakeman et al. JAMA 2020

Access to Treatment

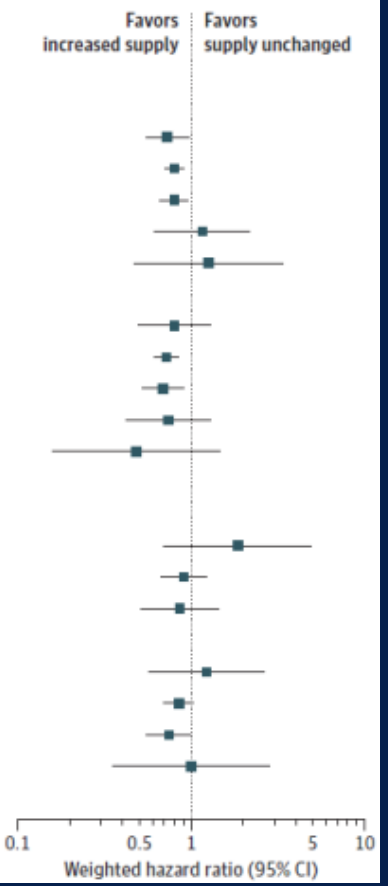


Larochelle et al. Annals of Internal Medicine 2018

COVID and OUD Treatment Outcomes

Figure 3. Six-Month Outcomes Among People Treated With Opioid Agonist Therapy Prior to the COVID-19 Pandemic, Weighted on Propensity Score

	No. (%) of events/person-year		Hazard ratio (95% CI)	
	Increased dose	Unchanged dose	Unweighted	Weighted
Methadone-treated individuals				
Received daily dispensed dose	2865	2987		
Opioid overdose	87 (6.9)	150 (9.5)	0.60 (0.46-0.78)	0.73 (0.56-0.96)
Discontinuation of therapy	574 (51.0)	806 (63.6)	0.71 (0.63-0.79)	0.80 (0.72-0.90)
Interruption in therapy	215 (19.0)	332 (23.9)	0.66 (0.56-0.78)	0.80 (0.67-0.95)
All-cause mortality	20 (1.5)	21 (1.3)	0.99 (0.54-1.83)	1.16 (0.62-2.16)
Opioid-related death	9 (0.6)	8 (0.5)	1.17 (0.45-3.04)	1.26 (0.48-3.33)
Received 5-6 take-home doses	5758	5252		
Opioid overdose	35 (1.4)	51 (1.8)	0.63 (0.41-0.96)	0.80 (0.50-1.28)
Discontinuation of therapy	370 (14.1)	456 (19.6)	0.73 (0.63-0.83)	0.72 (0.62-0.84)
Interruption in therapy	133 (5.1)	165 (7.4)	0.73 (0.58-0.92)	0.69 (0.53-0.90)
All-cause mortality	27 (0.8)	28 (1.1)	0.88 (0.52-1.49)	0.74 (0.43-1.27)
Opioid-related death	≤5	9 (0.3)	0.51 (0.17-1.51)	0.48 (0.16-1.45)
Buprenorphine/naloxone-treated individuals				
Received daily dispensed dose[a]	230	432		
Opioid overdose	9 (6.5)	8 (3.5)	2.13 (0.82-5.51)	1.86 (0.70-4.92)
Discontinuation of therapy	74 (85.1)	151 (93.2)	0.91 (0.69-1.20)	0.91 (0.68-1.22)
Interruption in therapy	25 (25.3)	54 (29.3)	0.86 (0.53-1.38)	0.86 (0.52-1.41)
Received 5-6 take-home doses	2138	1635		
Opioid overdose	17 (1.7)	12 (1.4)	1.08 (0.52-2.27)	1.23 (0.58-2.63)
Discontinuation of therapy	255 (26.0)	230 (30.8)	0.83 (0.70-1.00)	0.85 (0.70-1.01)
Interruption in therapy	93 (9.5)	101 (12.9)	0.69 (0.52-0.92)	0.74 (0.56-0.99)
All-cause mortality	8 (0.8)	7 (0.8)	0.87 (0.32-2.41)	1.00 (0.36-2.81)



No statistically significant increases in opioid-related overdoses over 6 months

Gomes et al. JAMA 2022

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

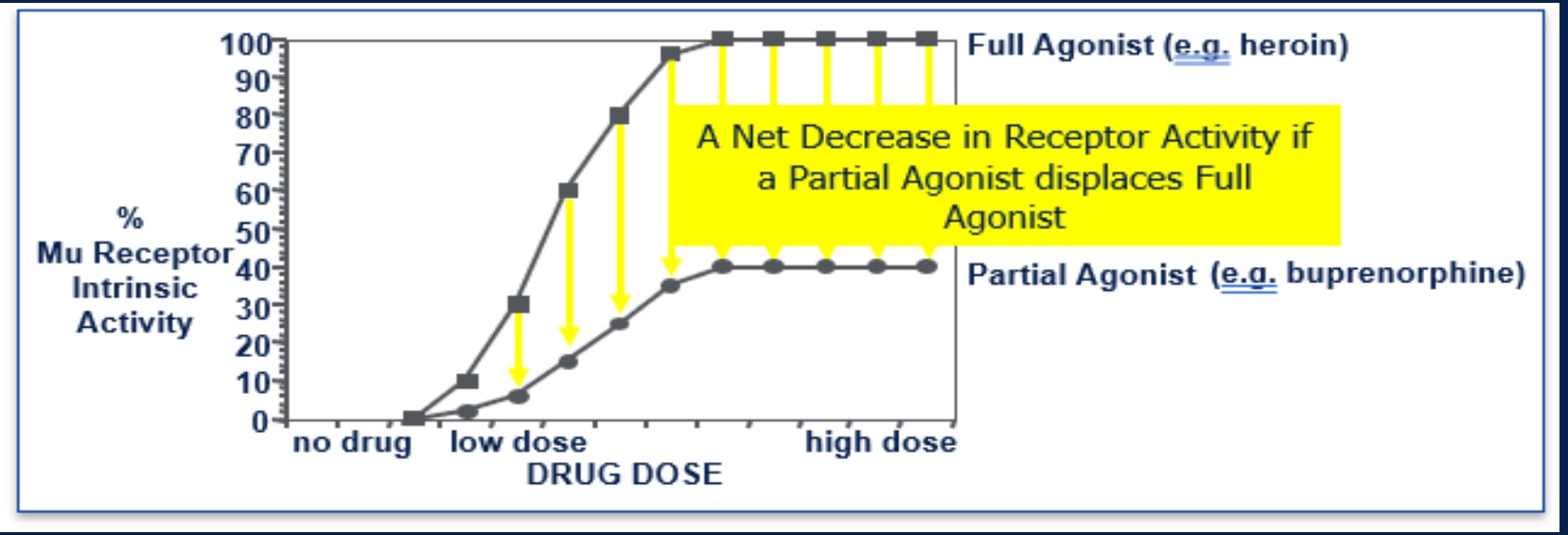
Pregnancy

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

Buprenorphine

Multiple FDA Approved Formulations for OUD: SL film or tablet, monthly SQ, 6-month implant

- 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; at high doses or in patients dependent on high doses of chronic opioids, it has the ability to act as an antagonist.



Induction

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 significant 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

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

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 injectable formulation (naltrexone-XR), 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.
  - *Given high dropout rates and known OD risk of interrupted antagonist treatment, rigorous evaluation and reporting of fatal/nonfatal ODs remains needed*. Jarvis 2018

When Treating Fentanyl OUD

	Methadone	Buprenorphine	Naltrexone-XR
Initiation	Same day	1-3 days, to minimize risk of precipitated withdrawal	7-14 days for opioid detoxification
Induction withdrawal risk	Low Residual withdrawal may persist during dose titration	Moderate Precipitated withdrawal may last 1-2 days during the induction	Moderate Precipitated withdrawal if given before completion of detoxification Protracted withdrawal may persist 1-2 wks post-induction
Time to full therapeutic dose	2-3 weeks, or longer	2-3 days, or longer	1-day post-administration
Potential to decrease craving	High Dose-related full agonist effect	Moderate Ceiling on the agonist effect (usually at 24-32 mg/d dose)	Variable Mechanism of anti-craving effect poorly understood
Blocking potential	Low	Moderate	High

Abuse and Overdose Potential

Buprenorphine has limited abuse potential (epidemiological, human laboratory studies show)

- Relatively low compared to other opioids

Diversion and illicit use of analgesic form (by injection)

Overdose risk low

- Partial μ-OR agonist results in limited CNS and respiratory depression in those with physical dependence
- Risk higher with combined abuse of other sedatives e.g., benzodiazepine
- Deaths more associated with mono formulations dissolved and injected with concurrent benzodiazepine use

Induction

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
- Toxicology testing:

	Minutes	Hours	Days	Weeks	Months
Blood					
Breath					
Oral Fluid					
Urine					
Sweat					
Hair					

Induction

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 2-4 hrs later if OWS persist
- Total Day 1 dose 8-12 mg

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

- Consider additional 2-4mg increase for ongoing symptoms
- Eval 2-4 hours later and consider additional 2-4 mg for ongoing symptoms
- Total Day 2 dose 16 mg

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

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

Induction Continued

- Typically initiated for outpatients at-home with physician instructions and availability, and during hospitalizations or ED assessments.

- May be carried out using either Bup/Nal or Bup mono, dependent upon the physician's judgment.
  - Bup/Nal commonly utilized but may consider bup mono formulation for those pregnant, severe liver disease, allergic rxn.

ED Initiated Buprenorphine Treatment

- Similar to other routine ED-based interventions for medical conditions
  - Buprenorphine induction acutely stabilizes and serves to initiate treatment of OUD
  - Facilitate linkage to community-based providers of OBAT
- From 2009 and 2013, 329 randomized to Screening + Referral, SBIRT, or SBIRT + bup induction in ED and appt for OBAT within 72hrs.
  - At 30 days
    - Increased engagement in addiction treatment: 37%, 45%, 78% (p<.001)
    - Decreased illicit opioid use in past 7 days: 2.3 days, 2.4 days, 0.9 days (p<.001)
  - At 2 months
    - Increased engagement in addiction treatment: 43%, 47%, 74% (p<.001)
    - Decreased illicit opioid use in past 7 days: 1.8 days, 2.0 days, 1.1 days (p=.04)

D'Onofrio 2015, 2017

Buprenorphine

- Extended-release monthly injection, FDA approved 2017, available 2018
  - Monthly subcutaneous (initial 300mg x 2, followed by maintenance 100mg).
  - Pt initially inducted onto once daily buprenorphine of 8-24mg for 7-10 days.
  - Compared to placebo, increased opi neg tox or self-reported opi use and higher proportion without any evidence of illicit opioid use. (FDA report 2017)

Transdermal and parenteral analgesic formulations not approved for OUD, only pain

Buprenorphine

- Long-acting subdermal implant, FDA approved 2016
  - Low, steady state dose for 6 months
  - Intended for use only after clinical stability on a daily dose of 8mg or less.
  - 4 approx. 1-inch-long implants requiring a minor surgical procedure for both insertion and removal.
  - Requires completion of in-person training.
  - Non-inferior percentage of urine samples negative for opioids, with favorable findings complete abstinence and time to first use of illicit opioids at 24 weeks compared to SL buprenorphine of 8mg or less.

Naltrexone

- Long-acting, competitive, non-selective opioid-antagonist with highest 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, no known hepatic toxicity at standard doses

Naltrexone

- Oral formulation FDA approved 1984
  - Once daily, 3xweek alternative
  - Low adherence limits use to highly motivated populations (Cornish 1997, Roth 1997)
- Completion of withdrawal treatment must precede naltrexone treatment for those with current physical dependence
- POC toxicology
- Consider induction protocol prior to naltrexone initiation (Sigmon 2012)

Naltrexone

Long-acting injectable formulation (naltrexone-XR), FDA approved for OUD in 2010

- 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
- While the number of reported OD in studies to date is low, most studies did not report clearly how overdose events were measured, particularly in those lost to follow-up.
  - Given high dropout rates and known OD risk of interrupted/stopping treatment, rigorous evaluation and reporting of fatal/nonfatal ODs remains needed. Jarvis 2018

Naltrexone - XR

Initial Readiness Assessment

- Vital signs, urine toxicology (screen for all opioids including, buprenorphine, oxycodone and methadone), recent opioid use history, pregnancy test, assess for contraindications, e.g., active pain requiring opioids

Last Opioid Use ≥14 days

- IF: Good evidence of opioid abstinence in past 2 weeks, no withdrawal symptoms, and opioid-negative toxicology.
- THEN: Proceed with the XR-naltrexone injection.

Naltrexone - XR

Last Opioid Use 8-13 days ago, evaluate for withdrawal using COWS

- If COWS >4 treat withdrawal with adjunctive medication and reevaluate in 1-2 days.
- If COWS ≤4 AND opioid-negative toxicology, perform naloxone challenge. If negative, proceed with the XR-naltrexone injection. If positive, adjunctive medication and reevaluate in 1-2 days.

Last Opioid Use ≤7 days

- Patient may still be physically dependent even with opioid-negative toxicology.
- Treat withdrawal with adjunctive medication and postpone evaluation until at least 7 days of no opioid use (See USE within 8-13 days).
- In case of daily opioid use, recommend cessation and conduct buprenorphine-assisted withdrawal management.

Naltrexone / Naltrexone Challenge Test

Naloxone (IM) Challenge Procedure

- Obtain baseline COWS, if 4 or less proceed with the challenge
- Administer naloxone 0.4 mg (1 cc) IM to deltoid and observe for 20 minutes.
- If no change in COWS administer additional 0.8 mg (2 cc) to the other deltoid and monitor for

  additional 20 minutes
- Test is considered positive if there is a COWS increase of 2 or more from the pre-injection score

Naltrexone (PO) Challenge Procedure

- Obtain baseline COWS; if 4 or less proceed with the challenge
- Administer naltrexone 25 mg p.o. and observe for 90 minutes
- Test is considered positive if there is a COWS increase of 2 or more

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

Naltrexone - XR

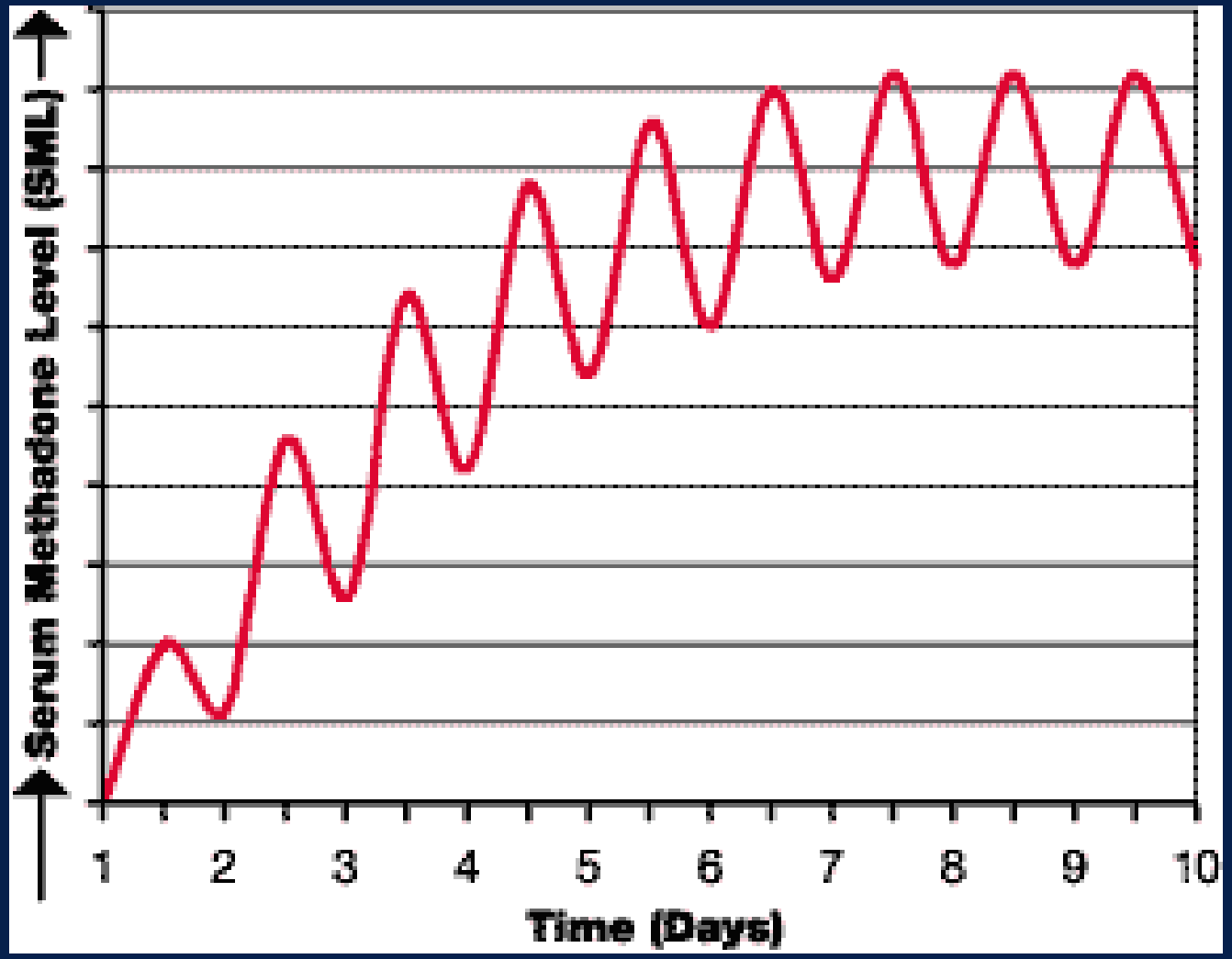
Buprenorphine-assisted Withdrawal Management for Naltrexone-XR Initiation

- Wait until the patient is in withdrawal (COWS > 8) and administer buprenorphine (4 mg bid on Day 1)
- Administer adjunctive medications as needed to alleviate residual withdrawal
- Continue adjunctive medication for at least 7 days after the last day of buprenorphine
- Perform naloxone/naltrexone challenge before administering XR-naltrexone

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

Steady State



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 (not routinely recommended to exceed 30mg in first 24 hours)
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
- Broadening of MAT options from methadone to incorporation of buprenorphine, etc.
- Attendance schedule for medication dispensing
- Guest Medication
- Confidentiality, 42 CFR Part 2
- Regulatory Oversight

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

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