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How to Save a Life: Evidence and Misconceptions About Medications for Opioid Use Disorder

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- Phone consultation for clinical questions provided by expert addiction medicine specialists
- Education and training opportunities related to substance use disorders and chronic pain management
- Assistance in the identification of substance use and behavioral health resources and referrals that meet the needs of the patients in your community

Funding for DACS is provided by The District of Columbia Government, DC Health, Health Regulation and Licensing Administration (HRLA), Pharmaceutical Control Division (PCD). DACS is administered by the University of Maryland School of Medicine staff and faculty.

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Financial Disclosure

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Learning Objectives

Through this activity, participants will learn about:

1. Medications currently available for the treatment of opioid use disorder
2. Evidence-base for medications for opioid use disorder (MOUD)
3. Common misconceptions about MOUD

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- Current state of the opioid epidemic
- Overdose deaths
- MOUD treatment options
- Evidence
- Misconceptions about MOUD

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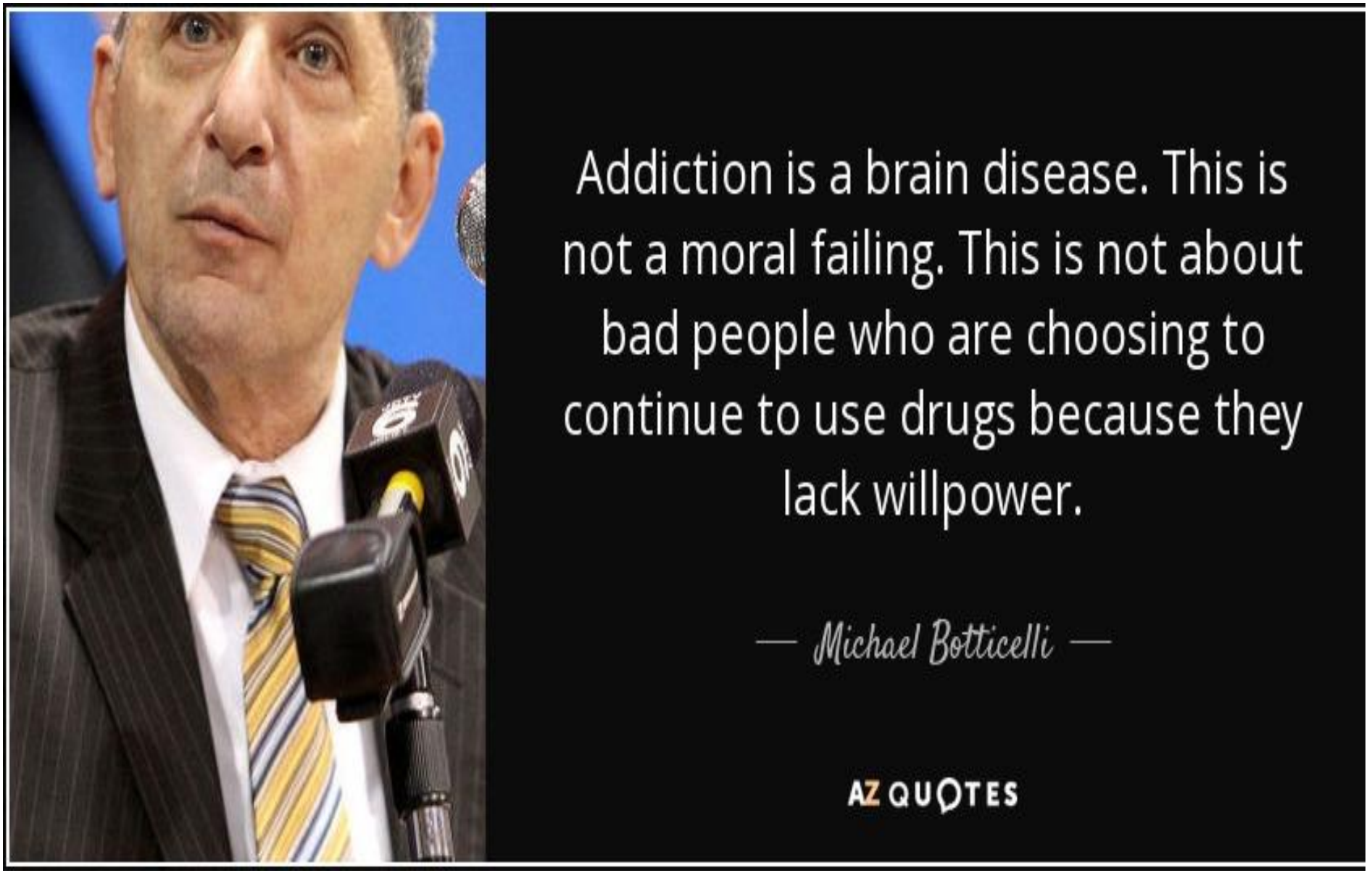

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- **Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry**. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

- Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. **Like other chronic diseases, addiction often involves cycles of relapse and remission**. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

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Addiction is Similar to Other Chronic Illnesses Because:

- It has biological and behavioral components, both of which must be addressed during treatment.
- Recovery from it--protracted abstinence and restored functioning--is often a long-term process requiring repeated episodes of treatment.
- Relapses can occur during or after treatment, and signal a need for treatment adjustment or reinstatement.
- Participation in support programs during and following treatment can be helpful in sustaining long-term recovery

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- Craving for the drug
- Obsessive thinking about the drug
- Decrease in inhibitory control in efforts to not use the drug
- Compulsive behavior in regard to drug taking
- Persistent changes in the brain's structure and function in the reward, inhibitory, and emotional circuits of the brain

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SAMHSA: Definition of Recovery

A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential

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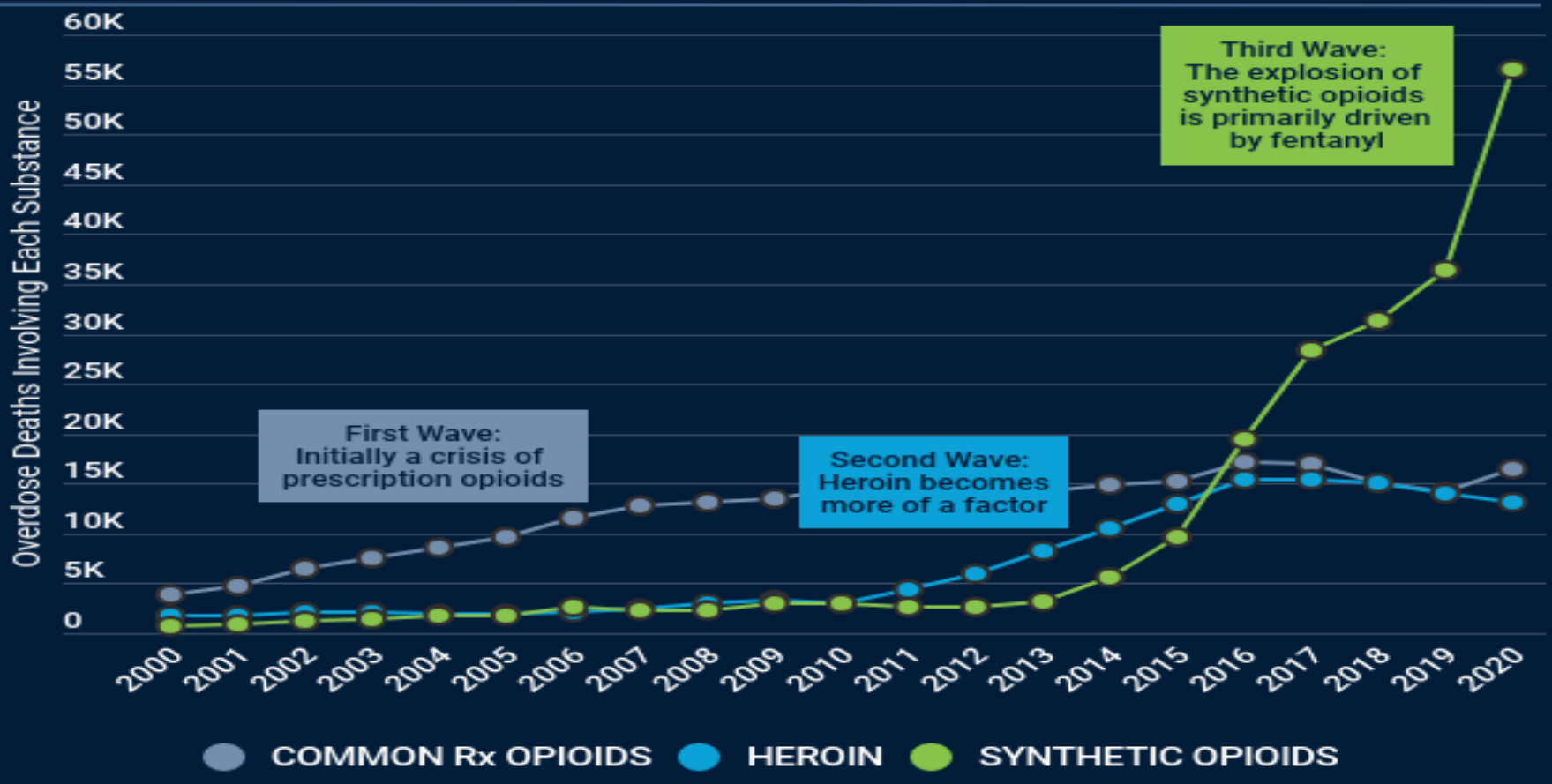
- Opioid overdose deaths have increased six-fold since 1999
- 2020 overdose deaths increased by 29.4% from 2019 to a total of 93,331 (over 107,000 in 2021)
- Opioid overdose deaths increased from 50, 963 in 2019 to 69,710 in 2020 (over 75,000 in 2021)
- Approximately 200 deaths per day from an opioid overdose

Third wave still going strong:

Synthetic opioid deaths climbing rapidly; uptick in deaths from common Rx Opioids in 2020



Categories not mutually exclusive; a single death may involve multiple substances.

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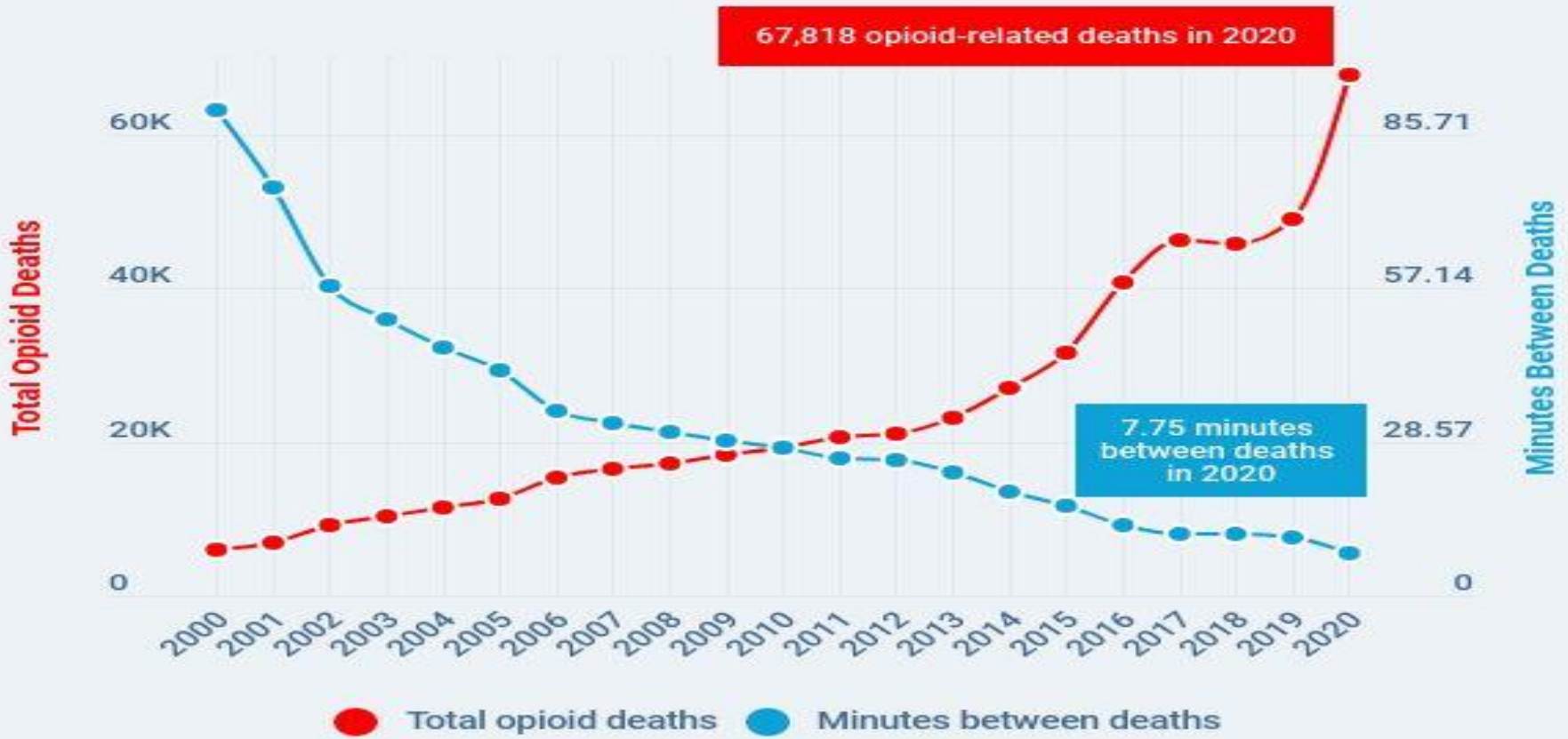
Total opioid-related deaths rose again in 2020, one person dying every 7.75 minutes



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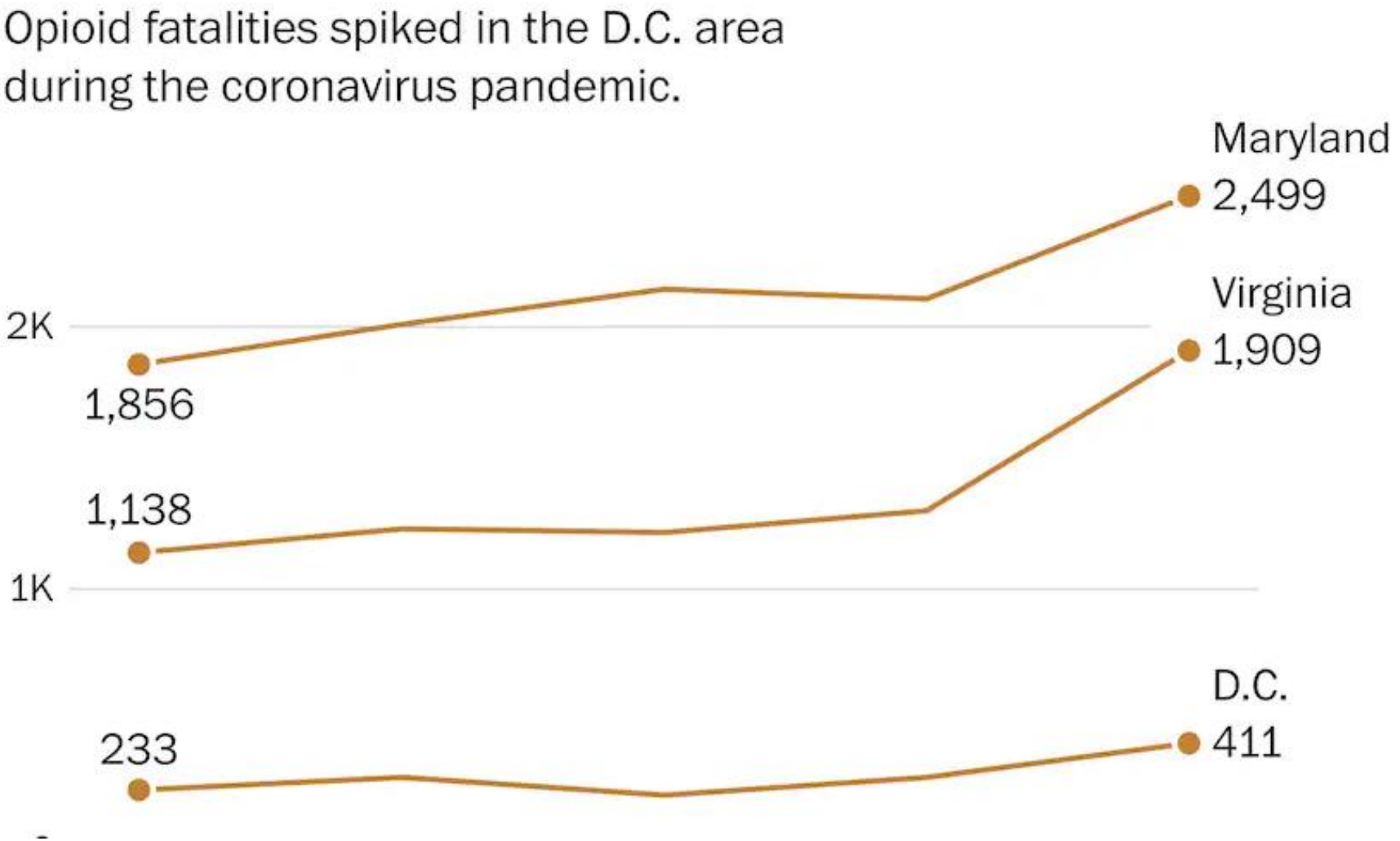

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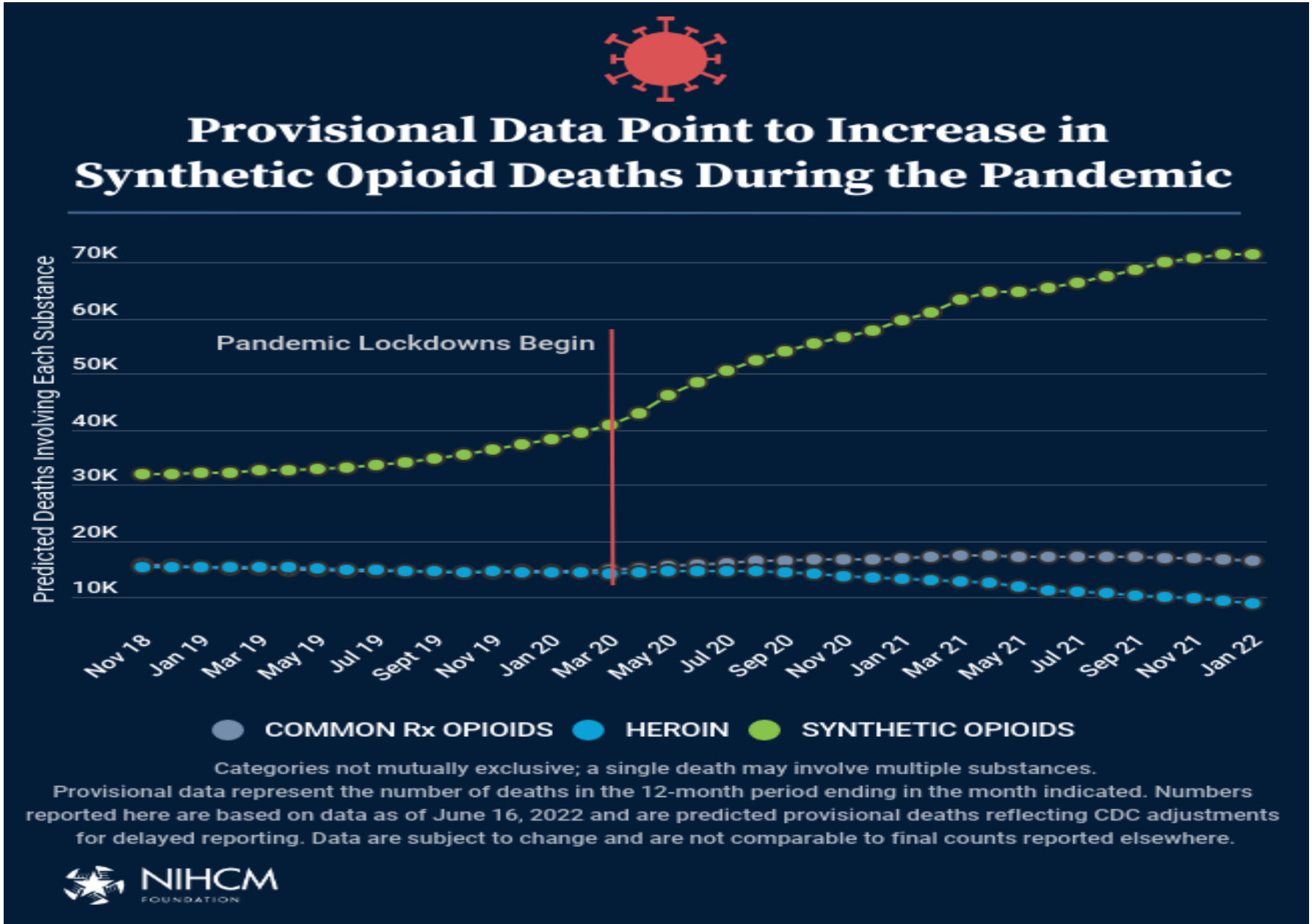

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“Access to medication-assisted treatment can mean [the] difference between life or death.”

Michael Botticelli, October 23, 2014 Director, White House Office of National Drug Control Policy

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Medication Based Treatment: FDA Approved

Methadone (**Methadose**; Dolophine; generic)

Buprenorphine (Suboxone; Subutex; Bunavail; Zubsolv; generics)

Naltrexone (Trexan; Vivitrol; generic)

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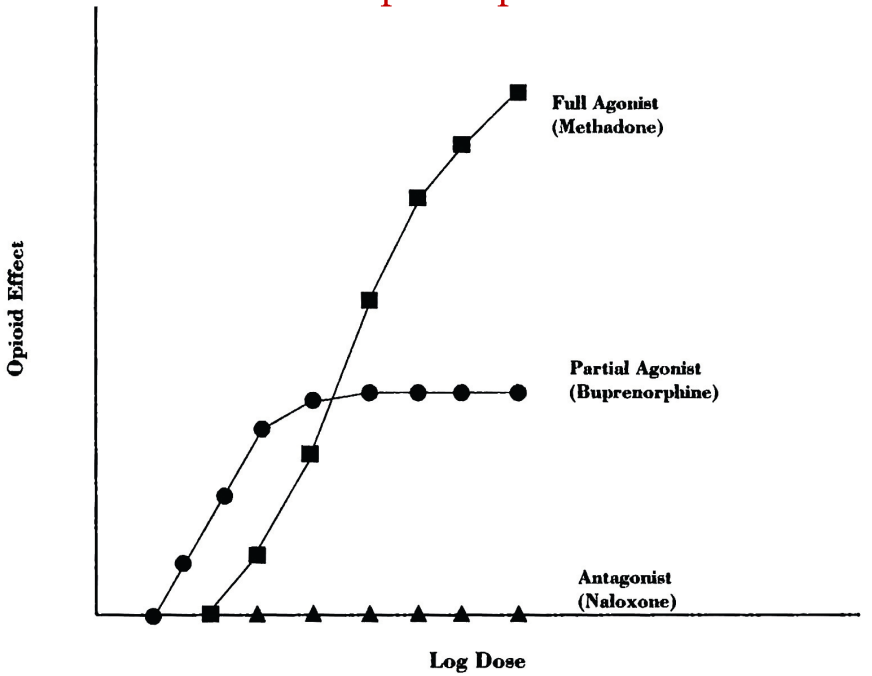
How do Buprenorphine and Naloxone/ Naltrexone Differ from Methadone?

The Buprenorphine Effect



SAMHSA chart shows how buprenorphine works to ease withdrawal while producing less euphoric opioid effects

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Medication Based Treatment

- Increases retention in treatment
- Decreases illicit opioid use
- Decreases rate of overdoses by up to 50%
- Improves social functioning
- Decreases transmission of infectious diseases
- Decreases criminal activity

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Partial Mu Opioid receptor Agonist
Kappa Opioid Receptor Antagonist

BUPRENORPHINE

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Buprenorphine Safety

- Highly safe medication
- Primary side effects: like other mu agonist opioids but may be less severe
- No evidence of significant disruption in cognitive or psychomotor performance
- No evidence of organ damage with chronic dosing
- Possible mild increase in LFTs for patients with hepatitis

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Buprenorphine/Naloxone Pharmacology

If taken under tongue, predominant buprenorphine effect

If opioid dependent person dissolves and injects, predominant naloxone effect (and precipitated withdrawal)

Naloxone will block buprenorphine's effects by the IV but not the sublingual route

Sublingual absorption:

buprenorphine @ 70%

naloxone @ 10%

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Precipitated Withdrawal

- Because of its high affinity for mu opioid receptors, buprenorphine can displace other agonists (such as heroin, methadone) that are already present and occupying the receptors

- The sudden change from full-agonist to partial-agonist activation of opioid receptors can cause sudden and severe withdrawal symptoms, a condition known as precipitated withdrawal

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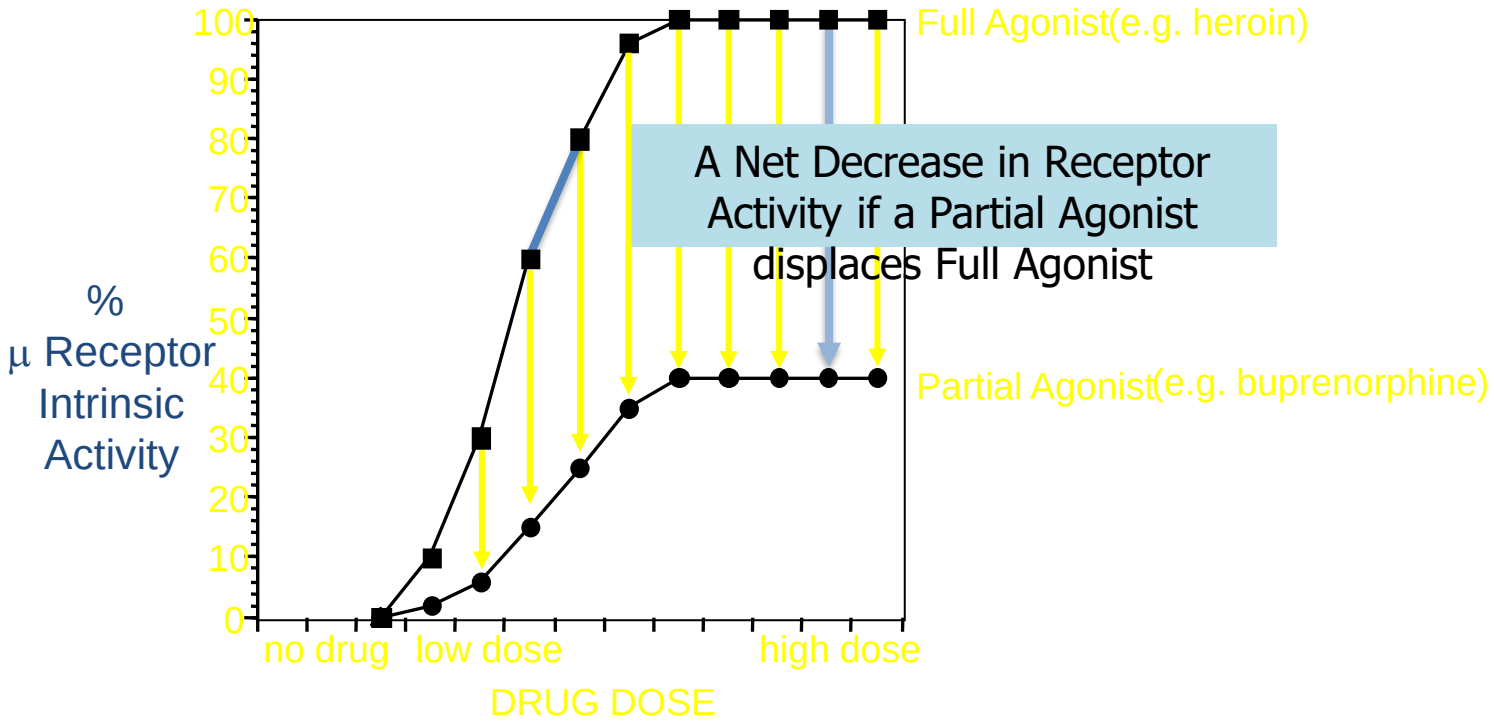
Precipitated Withdrawal

Displaces full agonist off μ receptors



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Buprenorphine Formulations

Buprenex-for pain only

Butrans/Belbuca-for pain only

Subutex-for opioid addiction only

Suboxone-for opioid addiction only

combination pill/film/buccal "patch" w/ naloxone

Probuphine- 6 month sc implant

Sublocade- monthly sc injection


2 mg/0.5 mg
Suboxone
4 mg/1 mg
Suboxone
8 mg/2 mg
Suboxone
Suboxone


Bunavail
(buprenorphine and naloxone) buccal film
2.1 mg / 0.3 mg
Bunavail
(buprenorphine and naloxone) buccal film
4.2 mg / 0.7 mg
Bunavail
(buprenorphine and naloxone) buccal film
6.3 mg / 1 mg


Belbuca
(buprenorphine hydrochloride)
buccal film
75 mcg
Belbuca
(buprenorphine hydrochloride)
buccal film
150 mcg
Belbuca
(buprenorphine hydrochloride)
buccal film
300 mcg
Belbuca
(buprenorphine hydrochloride)
buccal film
450 mcg
Belbuca
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600 mcg
Belbuca
(buprenorphine hydrochloride)
buccal film
750 mcg
Belbuca
(buprenorphine hydrochloride)
buccal film
900 mcg


A 14
2mg/0.5mg
AN 415
8mg/2mg


1·4
1.4mg/0.36mg
5·7
5.7mg/1.4mg


zubsolv
1.4 mg/0.36 mg
zubsolv
5.7 mg/1.4 mg


Sublocade
100 mg
WARNING: SERIOUS HARM OR DEATH
COULD RESULT IF INJECTED INTRAVENOUSLY

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Maintenance Treatment Using Buprenorphine

- Numerous outpatient clinical trials comparing efficacy of daily buprenorphine to placebo, and to methadone
- Consistently find:
  - Buprenorphine more effective than placebo in increasing retention in treatment and decreasing illicit opioid use
  - Buprenorphine equally effective as moderate doses of methadone (e.g., 60 mg per day)

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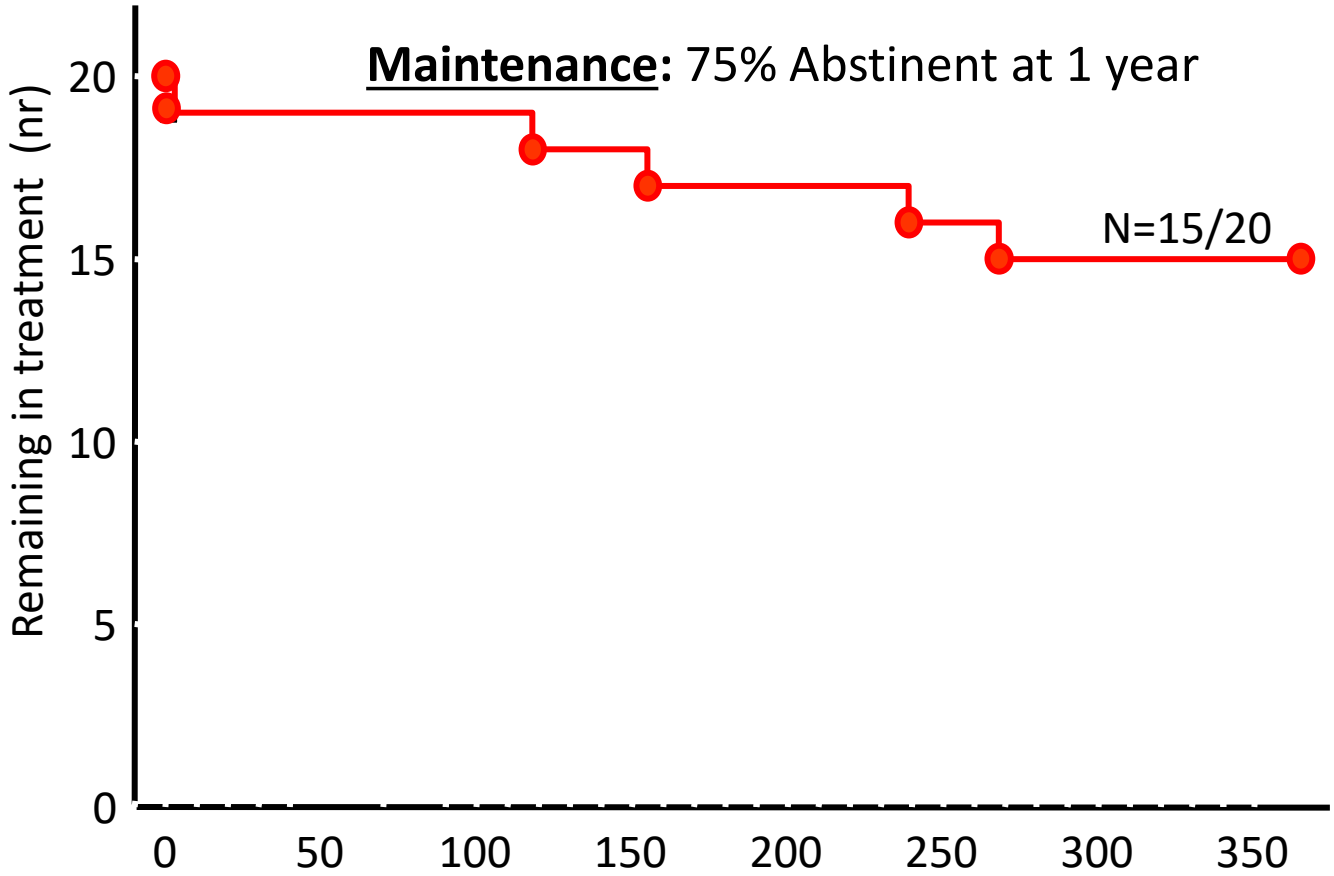
Treatment Retention: Buprenorphine Detox vs. Maintenance



Kakko, Lancet 2003

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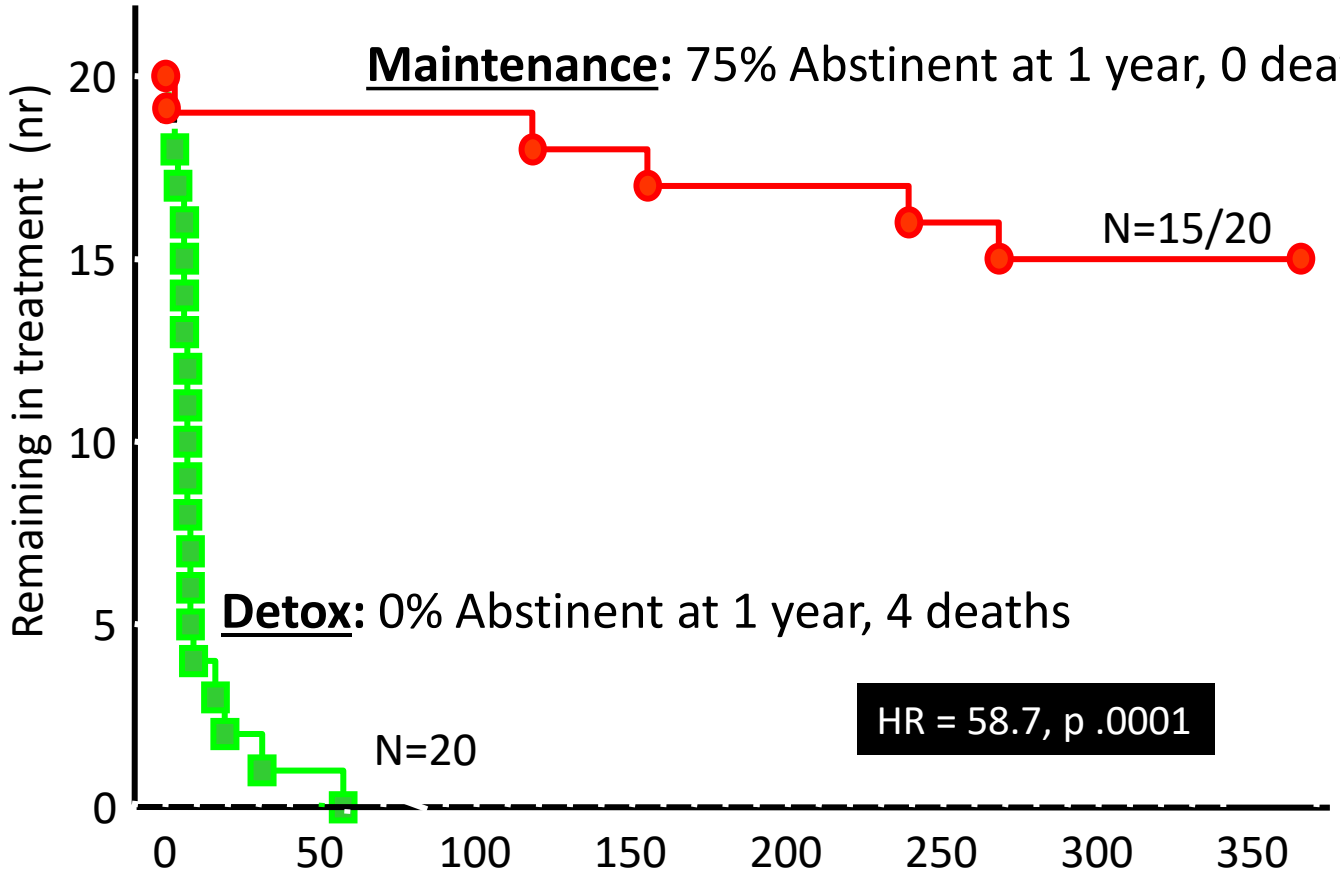
Treatment Retention: Buprenorphine-assisted Detox vs. Maintenance



Kakko, Lancet 2003

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METHADONE

Full Mu Opioid Receptor Agonist

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Methadone

- Orally administered
- Gradual onset of action
- Long half-life
- Long duration of action
- **Wider dose range: allows titration to** high doses if needed for **blockade of extraneous opioids**
- **Minimal** adverse effects with chronic use

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Methadone Disadvantages

- Some misuse liability & street value (diversion mostly for "self-treatment")
- Strict regulation: necessitates "take home" doses
- Pharmacologically complex; overdose potential in non-tolerant people
- Taper from blocking dose may be difficult
- Stigma and lower public acceptability
- Difficult to expand treatment capacity

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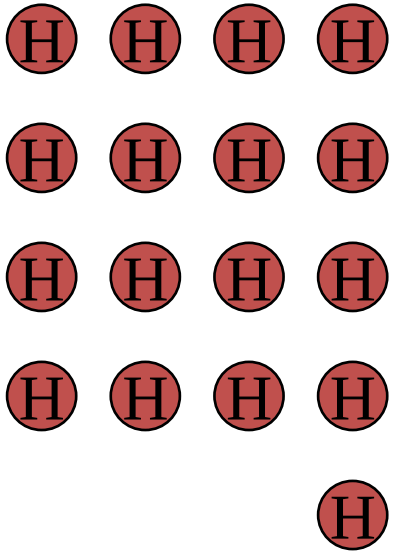
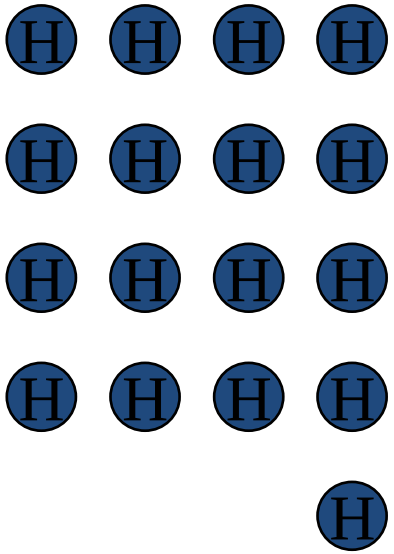
Methadone Effectiveness

Baseline

Methadone



Regular Outpatient Tx



Gunne LM, Grönbladh L. The Swedish methadone maintenance program: a controlled study. Drug Alcohol Depend. 1981 Jun;7(3):249-56. doi: 10.1016/0376-8716(81)90096-x. PMID: 7261900.

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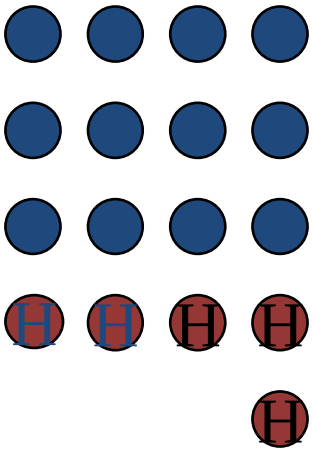
Methadone Effectiveness

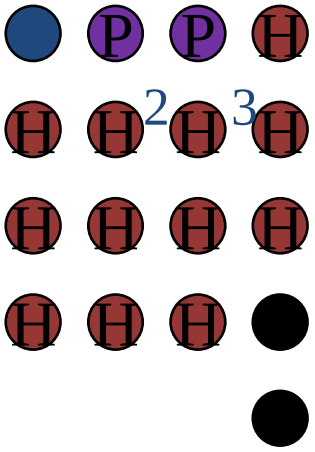
After 2 Years

Methadone



12 abstinent,
employed
5 non-abstinent

No Methadone



1 abstinent,
employed
12 non-abstinent
2 incarcerated
2 deaths

1- Sepsis & endocarditis
2- Leg amputation
3- Sepsis

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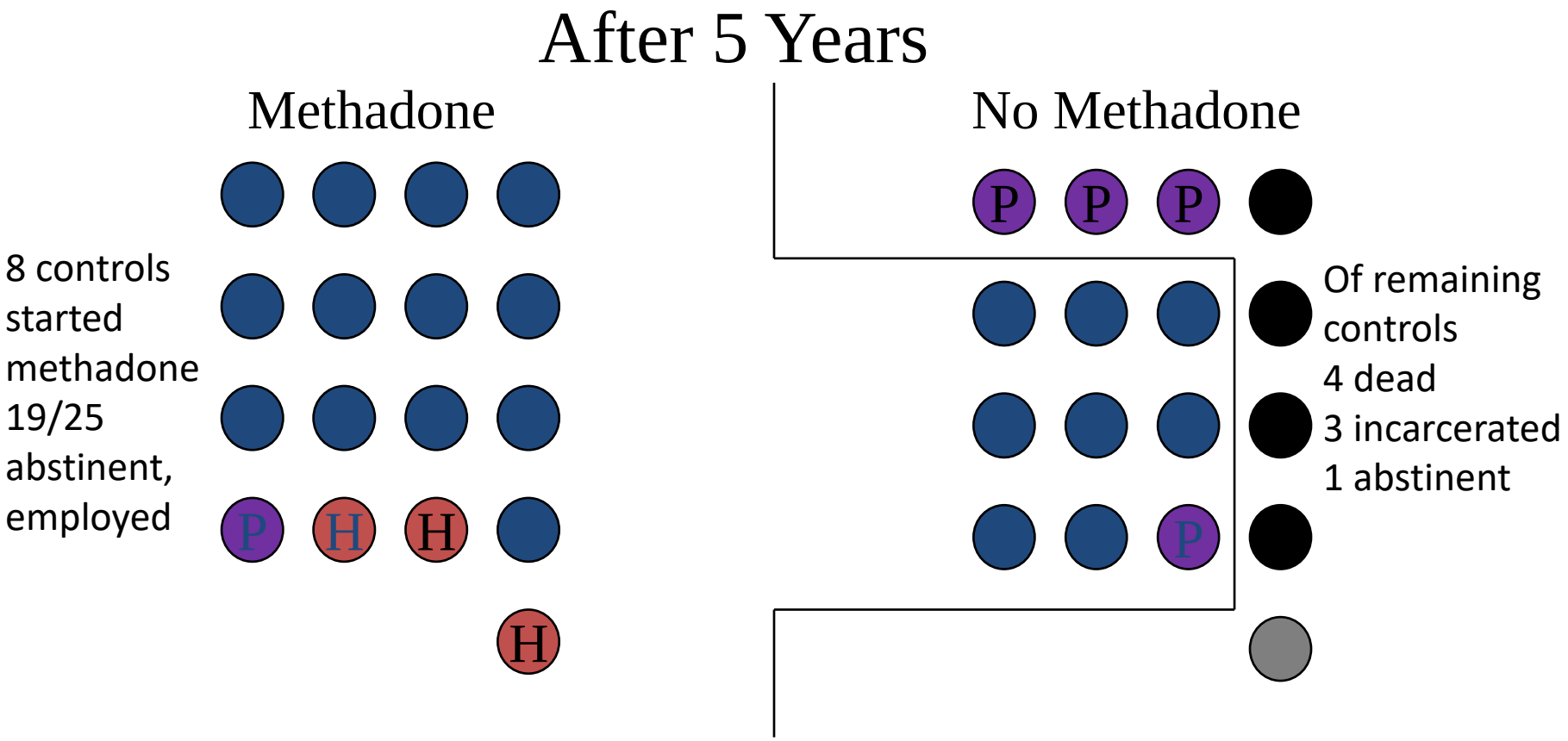
Methadone Effectiveness



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Methadone vs Buprenorphine

	Methadone	Buprenorphine	Comments
Opioid receptor activity	Mu agonist	Mu partial agonist*; kappa antagonist	*But very high receptor affinity
Duration of action	Long	Longer*	*Long receptor occupancy allows alternate day dosing
Efficacy	Small advantage at higher doses*	Small disadvantage compared to high dose methadone	*Equal at low to moderate doses
Adverse effects	More common	Less common	
Risk of respiratory depression	Higher	Lower (“ceiling effect”)*	*Unless combined with other CNS depressants
Effect on QTc interval	Dose-related prolongation	Minimal effect	
Metabolism	CYP 450 3A4, 2D6, 2B6	3A4	
Risk of drug interactions	Higher*	Lower	*Clinically significant interactions with anticonvulsants, anti-HIV, antituberculosis, and CNS depressant medications

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Methadone vs Buprenorphine

	Methadone	Buprenorphine	Comments
Withdrawal	Difficult, protracted	Milder, less prolonged	
Schedule	II	III	
Pregnancy risk	Fetal harm: low NOWS: ++ Breastfeeding: low	Fetal harm: low NOWS: + Breastfeeding: low	Much more experience with use of methadone in pregnancy
Physician training and DEA waiver to prescribe	Currently not required	Required for higher level waiver (100/275 pts)	
Treatment setting	Licensed programs	Physicians' offices or licensed programs	
Cost of medication	Very low	Higher*	* Cheaper generics available
Cost of ancillary treatments	High	Variable*	*No mandatory requirement, but recommended

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MOUDs Impact on Overdose Deaths

- Compared to patients receiving MOUD, untreated patients with OUD have at 1 year:
  - >2.5 X all-cause mortality
  - > 8 X overdose mortality

Source: Ma J, Bao YP, Wang RJ, et al. **Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis.** *Mol Psychiatry*. 2018 Jun 22. doi: 10.1038/s41380-018-0094-5.

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NALTREXONE

Mu Opioid Receptor Antagonist

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Common Opioid Antagonists And Their Uses

Centrally acting:

- Naltrexone (OUD, AUD, obesity; shortening withdrawal)
- Naloxone (overdose reversal, preventing opioid misuse; ultra-rapid withdrawal)
- Nalmefene (overdose reversal, AUD)
- Samidorphan (weight gain prevention with olanzapine)

Peripherally acting:

- Methylnaltrexone (OIC)
- Naloxegol (OIC)
- Alvimopan (post-op ileus)

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Antagonist Maintenance

Advantages	No physical dependence/addiction
	No risk of diversion
	Not a controlled medication
Disadvantages	Less strong evidence of effectiveness vs agonist maintenance
	Lower patient acceptability and adherence
	Need for abstinence from opioids before initiation
	Greater risk of overdose after drop-out
	High cost of injectable extended-release naltrexone

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Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

Findings Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90·0% (95% CI 69·9–92·4) in the XR-NTX group compared with 35·0% (11·4–63·8) in the placebo group (p=0·0002). Patients in the XR-NTX group self-reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004). The mean change in craving was –10·1 (95% CI –12·3 to –7·8) in the XR-NTX group compared with 0·7 (–3·1 to 4·4) in the placebo group (p<0·0001). Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0·0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0·0001). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.

Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011 Apr 30;377(9776):1506-13. doi: 10.1016/S0140-6736(11)60358-9. PMID: 21529928.

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Main Findings

	XR-NTX N=126	Placebo N=124
Median weeks of confirmed abstinence	90%	35%
Median self-reported opioid-free days	99.2%	60.4%
Mean change in craving	-10.1	0.7
Median retention in days	168	96

1 year open label extension (N=114): 62.3% completed, 50.9% abstinent, no safety concerns, no deaths, no overdoses*

*Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. Addiction. 2013 Sep;108(9):1628-37. doi: 10.1111/add.12208. Epub 2013 May 24. PMID: 23701526.

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Extended-release Naltrexone vs Buprenorphine (X:BOT Study)

- 570 participants randomized to receive XR-NTX (n=283) or BUP-NX (n=287)
- **Fewer participants successfully initiated XR-NTX (204/283 [72%]) than BUP-NX (270/287 [94%]; p<0·0001)**
- In the intention-to-treat population (n=570) 24-week relapse events were greater for XR-NTX (185/283 [65%]) than for BUP-NX (163/287 [57%]; HR 1·36)
- Among participants successfully inducted (per-protocol population, n=474), 24-week relapse events were similar across study groups (p=0·44)
- Opioid-negative urine samples (p<0·0001) and opioid-abstinent days (p<0·0001) favored BUP-NX among the intention-to-treat population, but were similar across study groups among the per-protocol population
- Treatment-emergent adverse events including overdose did not differ between treatment groups. 5 fatal overdoses occurred (2 in the XR-NTX group and 3 in the BUP-NX group)

*Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2018 Jan 27;391(10118):309-318. doi: 10.1016/S0140-6736(17)32812-X. Epub 2017 Nov 14. PMID: 29150198; PMCID: PMC5806119.

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Antagonists: Bottomline

- 2nd line option for most patients
- May be useful in specific situations:
  - Patients refusing agonist treatments
  - Younger patients with short/intermittent opioid use history
  - Medical contraindication for methadone- e.g., long QTc
  - Comorbid heavy alcohol/sedative misuse
  - Patients leaving controlled environments (IM-XR)

MISCONCEPTIONS ABOUT MOUD

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"Detox And Rehab Are The Ideal Treatments For OUD"

Withdrawal management (preferred term for "detox") typically results in very high rates of relapse within a short time: >90% within a month

It also leads to lower opioid tolerance, which places the patient at a high risk of fatal/non-fatal overdose when they return to using

However, it is a prerequisite to initiate opioid antagonist treatment (naltrexone/Vivitrol)

Rehab without MOUD also results in high relapse rates and increased risk of overdose after completion

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"The Goal of MOUD Should Be To Taper Off As Soon As Possible"

This is often a reflection of stigma associated with MOUD, esp methadone/buprenorphine

OUD is a chronic, relapsing, disease and longevity in treatment is the best predictor of positive outcomes

Prematurely tapering MOUD may lead to relapse

Studies have shown a high rate of relapse (>80% within 6 months in some studies), resulting in elevated overdose risk

Think of MOUD as analogous to insulin/oral agents for DMII

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"It's Not Real Recovery"/"It Replaces One Addiction With Another"

- Again, a reflection of stigma or perception that these are not legitimate treatments
- Misses the distinction between physiologic dependence on opioids vs addiction
- Hallmark of addiction is compulsive seeking and use of a substance
- Most people on MOUD do not have a desire to use non-prescribed opioids and many are able to return to a relatively normal life

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"Patients With OUD Take Methadone/Buprenorphine to Get High"

- These medications are rarely used for their reinforcing effects

- Neither has the typical pharmacological profile of a substance that people would choose to get high: a rapid action on brain receptors producing a high, coupled with a short duration of action that quickly wears off leaving the individual in withdrawal, driving a cycle of craving-use-withdrawal-craving

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"Methadone/ Buprenorphine Dose Should Never Exceed X Mg"

Effective dose ranges for both vary widely, and have gone up since the advent of fentanyl

Doses should be individualized; any arbitrary limit on the dose is inappropriate (though buprenorphine above 32mg is unlikely to produce incremental benefit)

Inadequate dose is often the cause of early drop-out or continued use

Typically, at an adequate dose of buprenorphine/methadone, patient will not have any opioid withdrawal/cravings and will not experience a "high" from using extraneous opioids

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"Methadone Damages Your Health"

Properly managed, opioids tend to be quite safe even over long-term use

Weighed against uncontrolled use of non-prescribed opioids, MOUD are vastly safer

When patients start MOUD, their health tends to improve as they take better care of themselves and seek treatment for health problems they have thus far neglected

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"Counseling Is Real Treatment, Medications Are An Adjunct"

Counseling, while potentially helpful, and a regulatory requirement with methadone, is not a requisite for MOUD to be effective

Many studies have shown that MOUD are highly efficacious even in the absence of counseling

The term "Medication Assisted Treatment" is being challenged as a misnomer and replaced by "MOUD"

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"Prescribing Naloxone Encourages Patients To Use More Opioids"

Prescribing naloxone (Narcan) can be life-saving, with minimal risk

People with OUD often associate with others who use non-prescribed opioids

Increasingly, even patients who use other substances are also at risk for exposure to fentanyl and accidental overdose

Many of our patients have reversed multiple overdoses in others around them

Always prescribe naloxone to a patient being prescribed opioids, or known to use non-rx opioids

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Honor Overdose Awareness Day:
GET WAIVERED!

Join DACS on 9/27/22 from 12-2pm
to learn about screening, diagnosing, and treating OUD, including harm reduction tools.

Get waivered to prescribe buprenorphine. Find out more and register here: https://bit.ly/3B07BHs