Curbing the Impact of the Opioid Epidemic: Arm Yourselves with the Latest Tools and Strategies to Manage Opioid Use Disorder (OUD)

Mark S. Gold, MD
ASAM's Annual Lifetime Achievement John P. McGovern Award & Prize Winner
Adjunct Professor of Psychiatry
Washington University School of Medicine
St. Louis, MO
17th University of Florida Distinguished Alumni Professor
Gainesville, FL

Mark S. Gold, MD
Disclosures

- ***Consultant:*** ADAPT Pharma (Dublin, Ireland)

Learning Objective 1

Analyze the latest clinical evidence on the use of MOUD, and its various formulations and routes of delivery, to promote long-term recovery and relapse prevention.

Learning Objective 2

Apply collaborative care strategies to optimize the management of OUD in patients with comorbid psychiatric illness.

Opioid Use Disorder

- It is estimated that 2.1 million American adults have an opioid use disorder (OUD)
- OUD is a chronic, lifelong and relapsing disease, currently without a cure
- Its destructive forces have resulted in death, strained families and personal relationships, loss of employment, and an increase in infectious diseases such as hepatitis A, B, C and HIV[1]
- Approximately 46-68% of individuals with OUD have experienced at least 1 overdose[2-4]

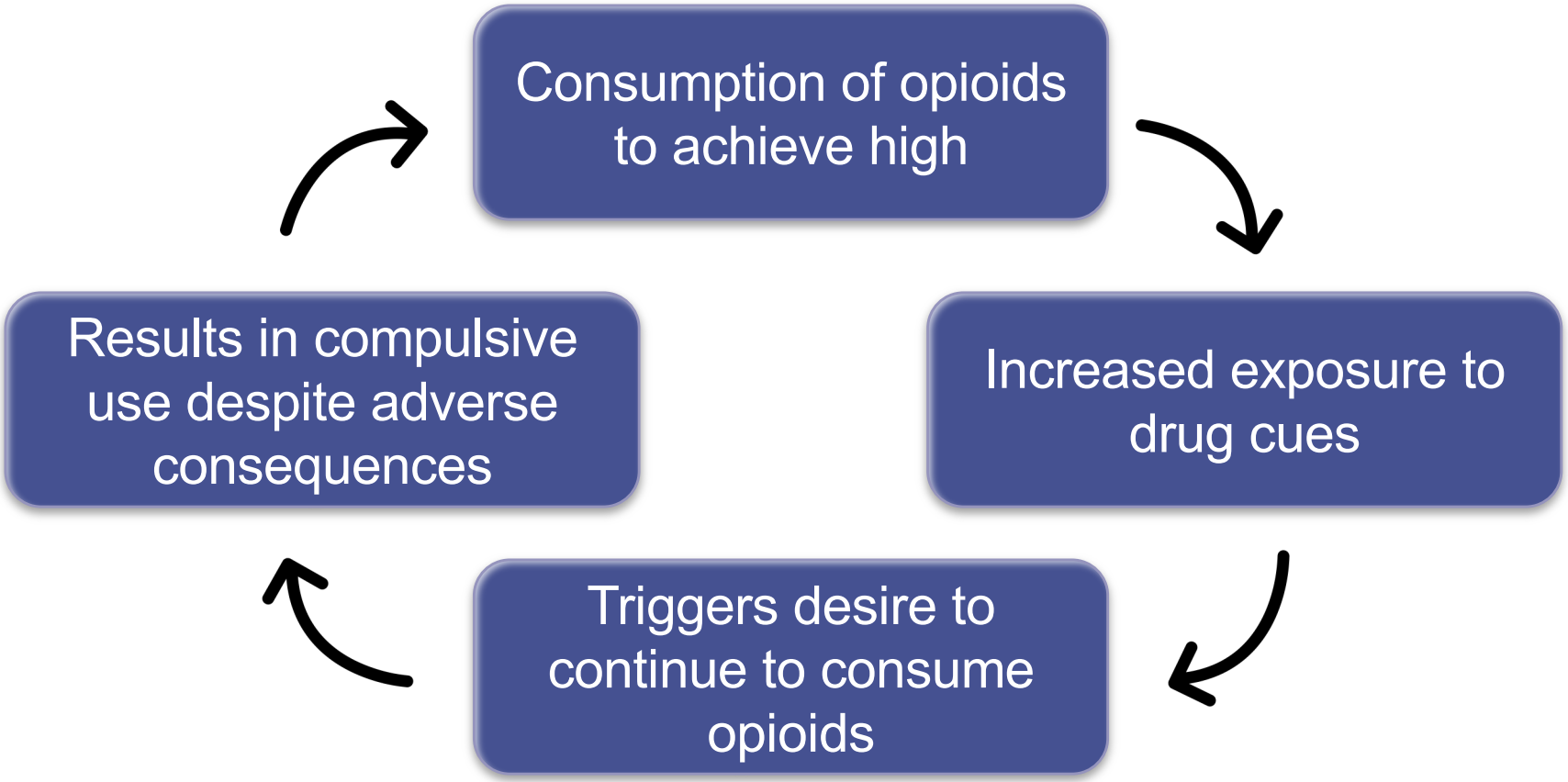
1. Kolla BP, Oesterle T, Gold MS, Southwick F, Rummans T. *J Neurol Sci*. 2020;411:116719.; 2. Katzman JG, et al. *JAMA Network Open*. 2020;3(2):e200117.; 3. Strang J, et al. *Addiction*. 2008;103(10);1648-1657.; Green TC, et al. *Addiction.* 2008;103(6):979-989.

Clinician Attitudes and Behaviors Regarding Treating OUD

- Only 1 in 10 emergency medicine (EM) professionals found caring for patients with OUD satisfying
- Less than 50% of EM and family medicine (FM)/internal medicine (IM) professionals believed that OUD is treatable
- 1 in 4 EM or FM/IM professionals feel treating OUD will attract undesirable patients to their practice
- 38% of EM professionals believe methadone treatment for OUD **is** substituting one addiction for another — twice as many as any other specialty
- 2 in 5 EM or FM/IM professionals feel treating patients with OUD takes away time and resources from other patients
- Less than 1/3 of EM, OB/GYN, or pediatric professionals feel very prepared to screen, diagnose, provide brief intervention for, or discuss treatment for OUD

Davidson C, et al. 2019. Available at https://www.acponline.org/sites/default/files/documents/about_acp/chapters/ma/ge-rize-shatterproof-white-paper_final.pdf.

OUD: A Repetitive Cycle of Harm, Stimulating Continued Use



Volkow ND, Morales M. *Cell*. 2015;162(4):712-725.

Symptoms of OUD

- Taking more of an opioid than intended
- Failed attempts to cut down or stop the opioid
- Excessive time spent obtaining the opioid
- Cravings for opioids
- Failure to fulfill obligations at school, work, or home
- Repetitive interpersonal conflicts because of use
- Giving up important things for the opioids
- Using opioids in hazardous situations
- Using opioids despite knowing the substance is causing significant emotional, or physical consequences, tolerance, and withdrawal

American Psychiatry Association. *Diagnostic and Statistical Manual of Mental Disorders. 5th Edition (DSM-5)*. American Psychiatric Publishing. Washington, DC, 2013.

Severity of OUD Determined by Number of Symptoms

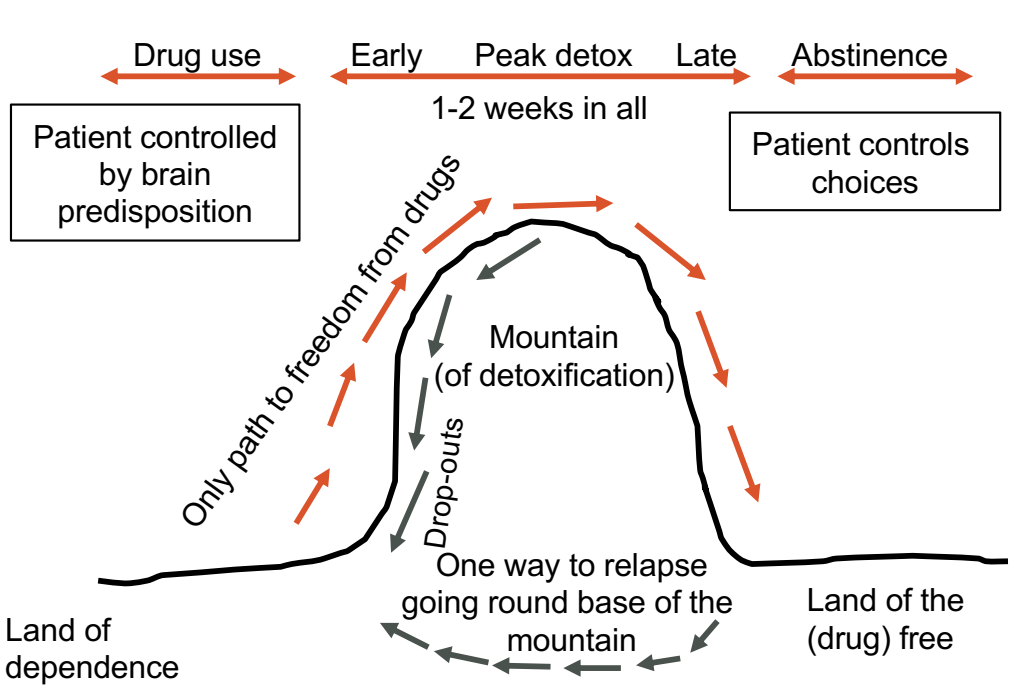
- Mild: Display 2-3 symptoms
- Moderate: Display 4-5 symptoms
- Severe: Display 6 or more symptoms

American Psychiatry Association. *Diagnostic and Statistical Manual of Mental Disorders. 5th Edition (DSM-5)*. American Psychiatric Publishing. Washington, DC, 2013.

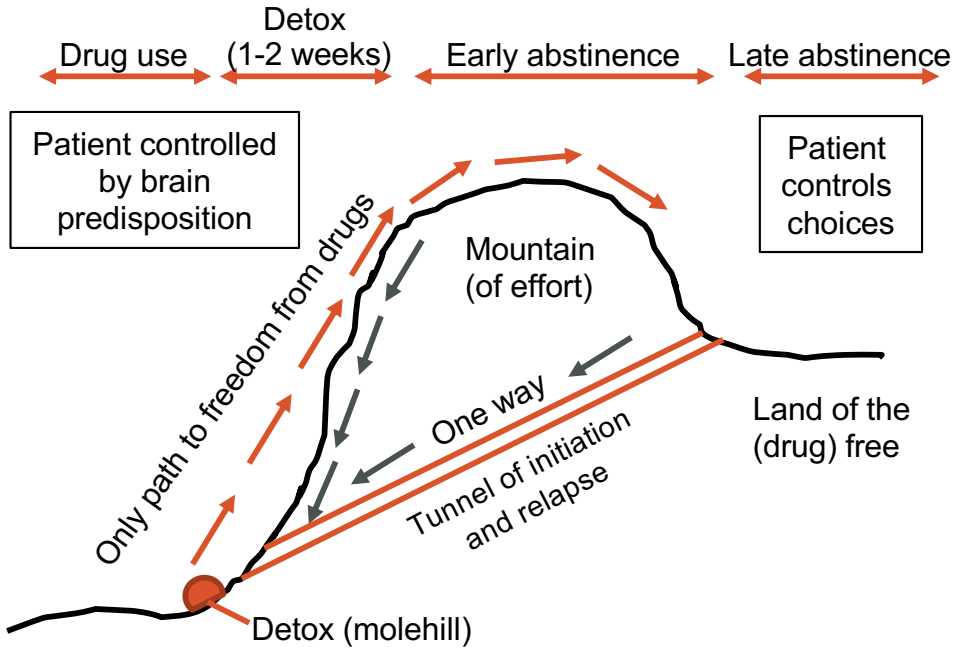
The Road to Abstinence

Fantasy vs. Reality

The Fantasy



The Reality



Adapted from Diaper AM, et al. *Br J Clin Pharmacol*. 2014;77(2):302-314.

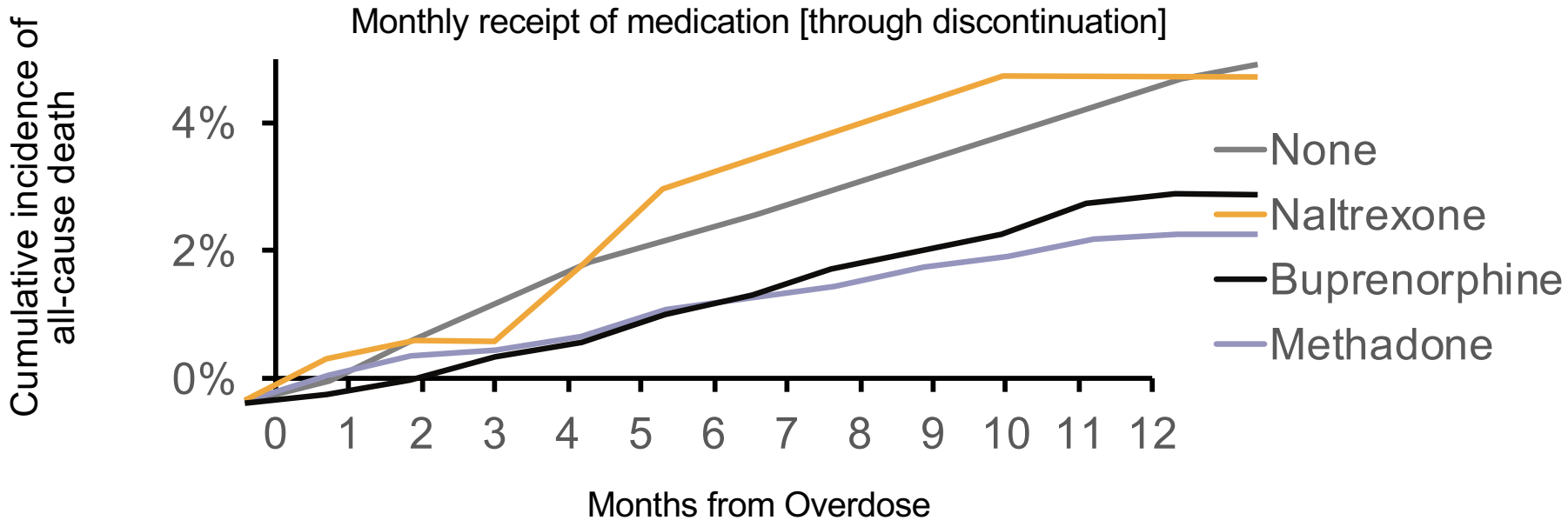
Rationale for Medication for OUD (MOUD)

- Patients engaged in MOUD have higher odds of positive outcomes compared to those with abstinence-based treatment
- Relapse rates are ≥ 90% with just detoxification combined with psychosocial treatment
- Higher treatment retention with maintenance MOUD (66%) compared to tapering off MOUD (11%)
- Among 48,274 adults with primary diagnosis of OUD between 2015-2016, periods on treatment were protective against overdose

Weiss RD, et al. *Drug Alcohol Depend*. 2015;173(Suppl 1):S48-S54; Gossop M, et al. *Addiction*. 2003;98(3):291-303; Weiss RD, et al. *Arch Gen Psychiatry*. 2011;68(12):1238-1246; Mattick RP, et al. *Cochrane Database Syst Rev*. 2009;(3):CD002209. Nielsen S, et al. *Cochrane Database Syst Rev*. 2016;(5):CD011117. Fiellin DA, et al. *JAMA Intern Med*. 2014;174(12):1947-1954.; Krawczyk N, et al. *Addiction*. 2020 Feb 24. doi: 10.1111/add.14991. [Epub ahead of print}.

MOUD Improves Survival in Overdose Survivals

- Overdose survivors who receive medications have better survival
  - Cohort of 17,755 overdose survivors in MA, 2012-2014

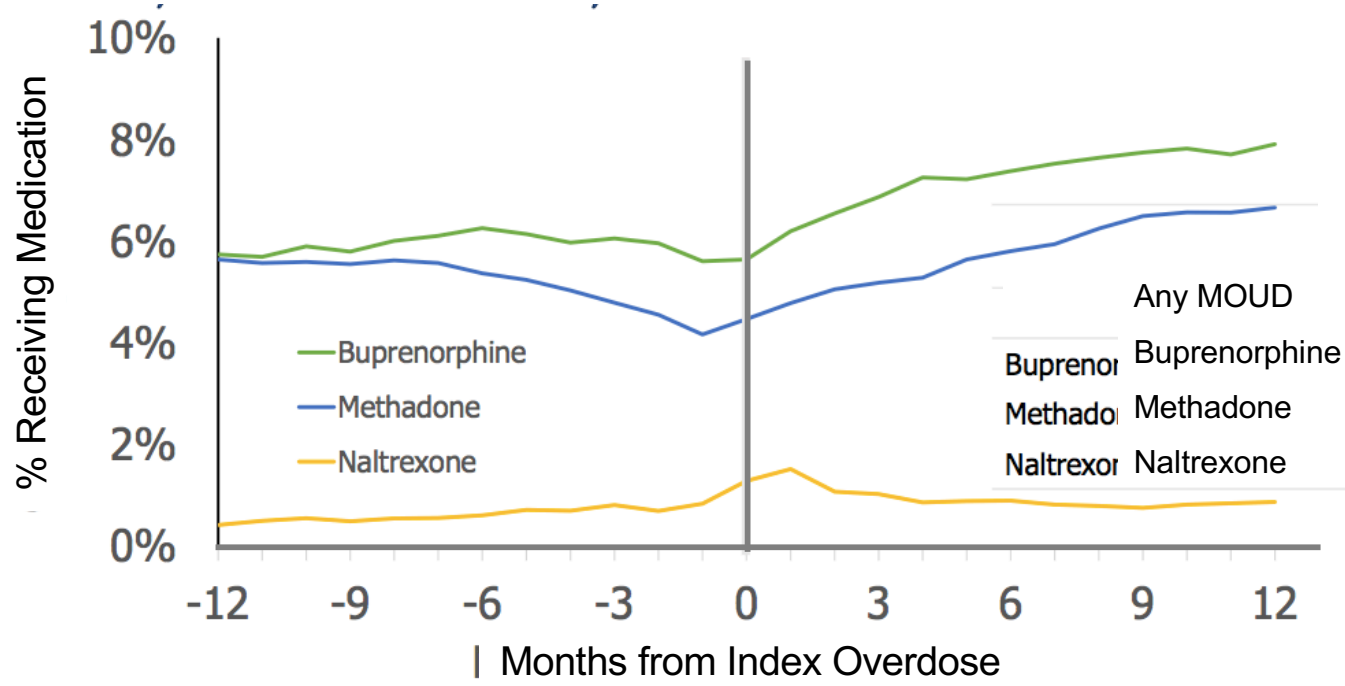


MA = Massachusetts.

Larochelle MR, et al. *Ann Intern Med*. 2018;169(3):137-145.

BUT, After Overdose Few Survivors Receive MOUD

Cohort of 17,755 Overdose Survivors in Massachusetts, 2012-2014



	Number Treated	%	Months Received (Median [IQR])
Any MOUD	5,273	30%	
Buprenorphine	2,228	17%	4 [2,8]
Methadone	1,416	12%	5 [2,9]
Naltrexone	772	6%	1 [1,2]

IQR = interquartile range; MOUD = medications for opioid use disorder.

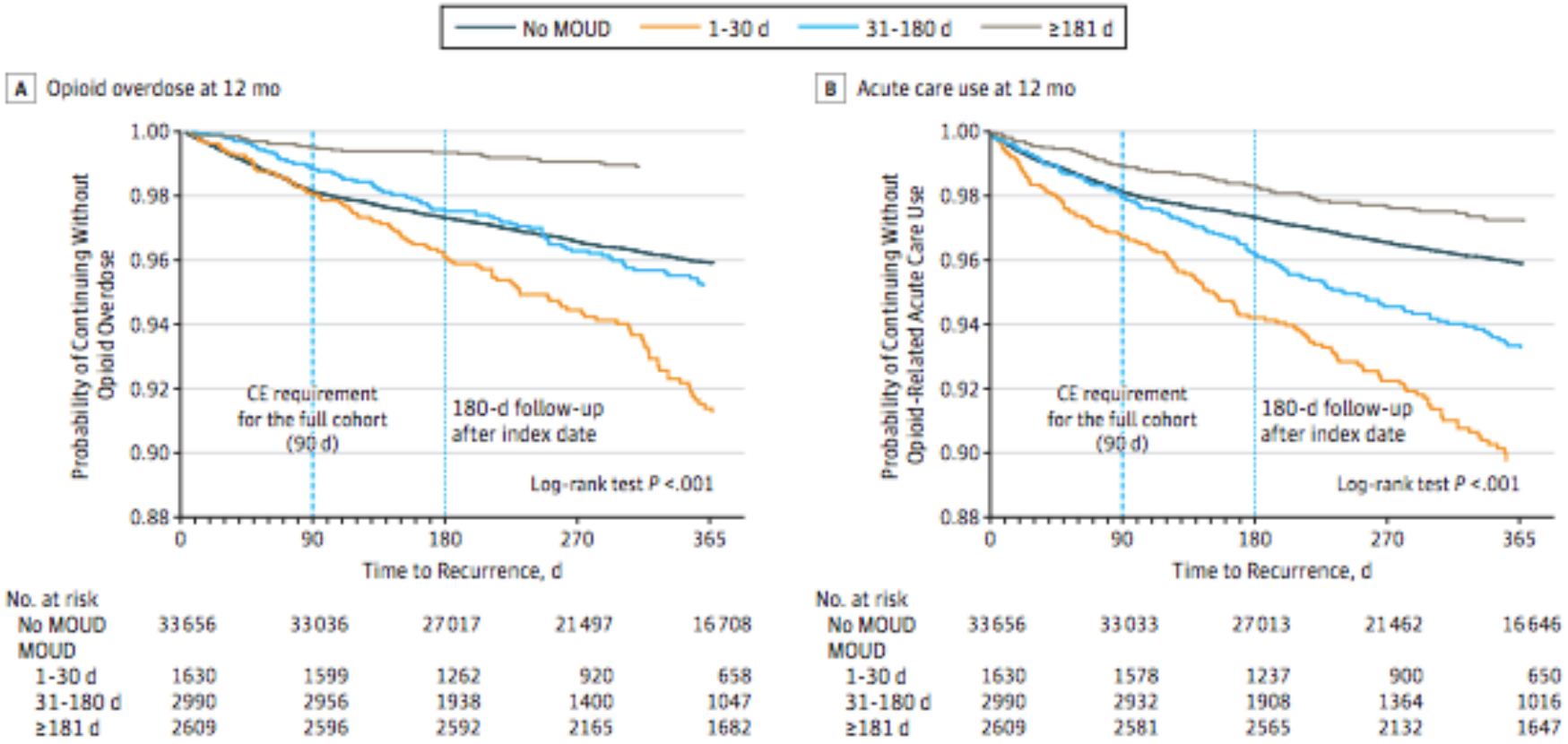
Larochelle MR, et al. *Ann Intern Med*. 2018;169(3):137-145.

Comparative Effectiveness of Different Treatment Pathways for OUD

- In a national cohort of 40,885 individuals with OUD between 2015-2017, treatment with buprenorphine or methadone was associated
  - 76% reduction in overdose at 3 months
  - 59% reduction in overdose at 12 months
  - 32% relative reduction in serious opioid-related acute care at 3 months and 25% reduction at 12 months compared to no treatment
- Despite the known benefit, only 12.5% initiated treatment
- Retention in care in patients on buprenorphine or methadone for longer than 6 months experienced less overdose and opioid-related acute care

Wakeman SE, et al. *JAMA Netw Open.* 2020;3(2):e1920622.

Probability of an Opioid Overdose and Acute Care Use During the 12-Month Period



Wakeman SE, et al. *JAMA Netw Open.* 2020;3(2):e1920622.

FDA-Approved Medications to Treat OUD

Medication	Receptor Pharmacology	Formulation	Dosing Frequency
Methadone	Full mu opioid agonist	• Oral solution, liquid concentrate, tablet/diskette, powder	• Daily
Buprenorphine	Partial mu opioid agonist	• Sublingual tablet	• Daily
		• Implant	• Every 6 months
		• Extended-release injection for subcutaneous use	• Monthly
		• Extended-release injection*	• Weekly and monthly
Buprenorphine-naloxone	Partial mu opioid agonist - mu antagonist	• Sublingual film • Buccal film • Sublingual tablet	• Daily
Naltrexone	Mu opioid antagonist	• Extended-release injectable suspension	• Every 4 weeks or once a month

*Tentative FDA approval.

[Package Insert]. Drugs@FDA Website.

Methadone Maintenance Treatment (MMT): Successes and Challenges

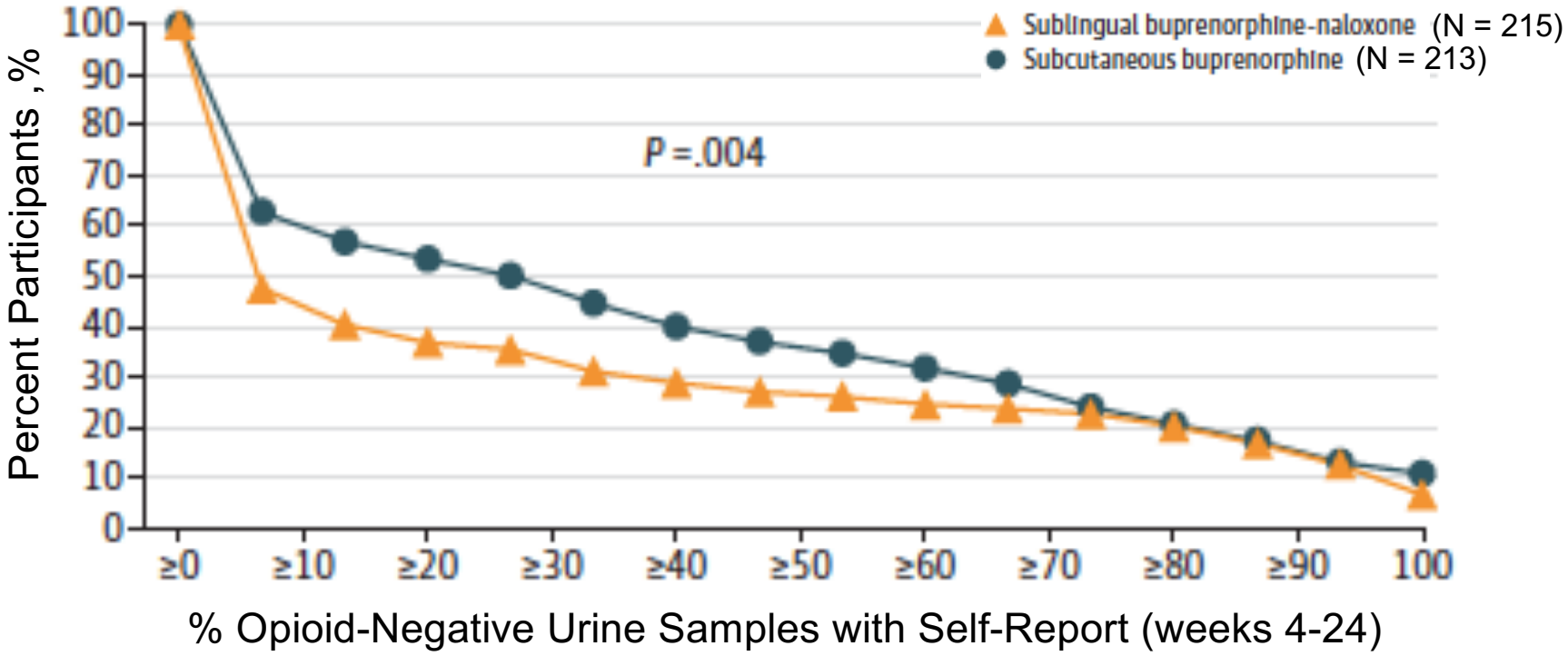
- MMT is the gold standard for MOUD with positive 5-year outcomes
- Patients in MMT had a 1-year mortality rate of 1% compared to 8% of those who discontinue treatment
- Suggested that 2-years is minimum duration before attempting withdrawal

Challenges

- Daily dosing in a licensed clinic
- Lack of psychiatric and psychological services

1. Kleber HD. *JAMA.* 2008;300(19):2303-2305. 2. Harris KA, et al. *J Subst Abuse Treat.* 2006;31(4):433-438.

Subcutaneous Buprenorphine vs. Sublingual Buprenorphine-Naloxone: Percentage Opioid-Negative Urine Samples Over 24 Weeks



Weeks 1-12: Weekly injections; Weeks 12-24: Monthly injection

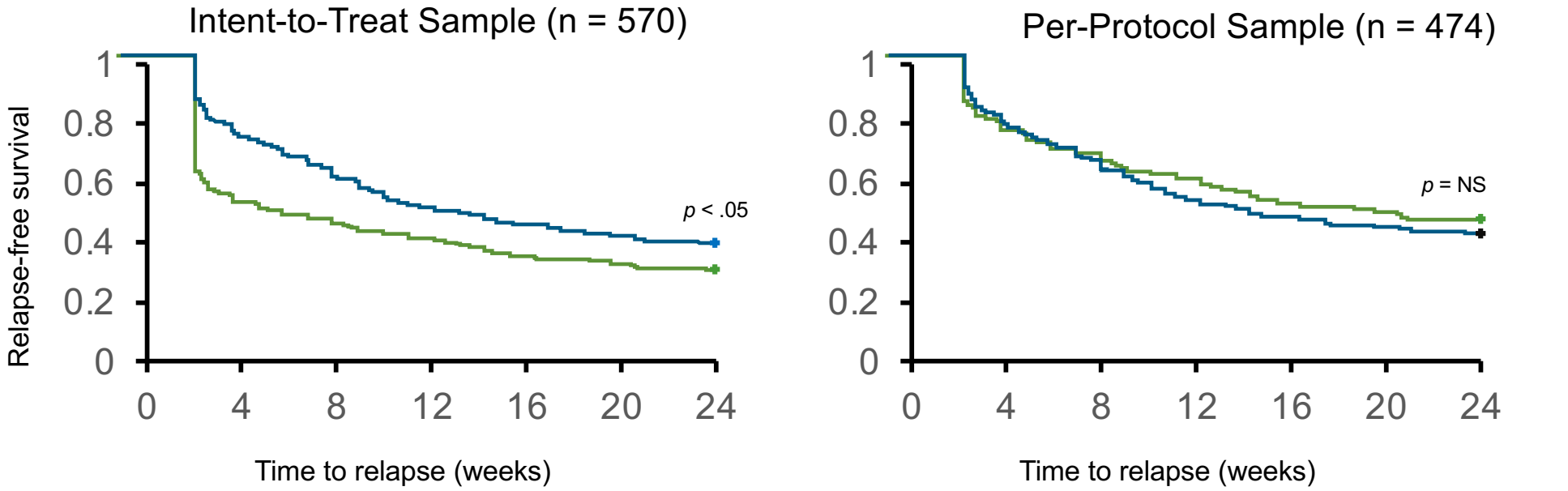
Lofwall MR, et al. *JAMA Intern Med*. 2018;178(6):764-773.

Comparative Effectiveness of Extended-Release Naltrexone vs Sublingual Buprenorphine for Opioid Relapse Prevention (X:BOT)

- 24 wk, open-label, randomized controlled, comparative effectiveness trial in outpatients after inpatient induction
  - Monthly extended-release naltrexone injections (XR-NTX) vs. daily sublingual buprenorphine (BUP-NX) film
  - Fewer participants successfully initiated XR-NTX than BUP-NX: 72% VS 94%; $p < .0001$
    - At 24 wks, among participants that were successfully initiated, both medications were equally safe and effective
    - Study treatment retention for 24 wks was between 43% and 47%
  - During treatment outcomes were better for BUP-NX than XR-NTX

Lee JD, et al. *Lancet* 2018;391(10118):309-318.

Comparative Effectiveness of XR-NTX vs. BUP-NX for Opioid Relapse Prevention (X:BOT): Relapse-Free Survival



Number at risk (censored)														
BUP-NX	287	229	100	155	140	130	0 (124)	270	222	184	149	134	126	0 (120)
XR-NTX	283	165	142	125	109	103	0 (98)	204	164	141	124	109	103	0 (98)

BUP-NX = buprenorphine/naloxone.

Lee JD, et al. *Lancet*. 2018;391(10118):309-318.

Success of Physician Health Programs (PHPs)

- 904 physicians admitted to 16 state PHPs were studied for 5 years or longer
  - Abstinence-based (alcohol or drugs of abuse)
  - Random testing to identify substance use with swift and significant consequences
- 78% of participants had no positive test for alcohol or substance use over 5 years
- 72% continued to practice medicine post-treatment
- PHP care management included close linkages to the 12-step programs of Alcoholics Anonymous and Narcotics Anonymous and the use of residential and outpatient treatment programs that were selected for their excellence

DuPont RL, McLellan AT, White WL, Merlo LJ, Gold MS. *J Subst Abuse Treat*. 2009;36(2):159-171.

Mandatory Naltrexone Treatment Prevent Opiate-Dependent Anesthesiologists

- Physicians are at risk for opiate abuse with anesthesiologists over-represented[1,2]
- Charts were reviewed for 11 anesthesiologists who underwent mandated pharmacotherapy with naltrexone, as well as 11 who were monitored[3]
  - 8 of 11 anesthesiologists who did **not** take naltrexone relapsed
  - Only 1 of 11 who took naltrexone relapse
  - 9 of 11 who took naltrexone returned to practice

1. Merlo LJ, Gold MS. *Harv Rev* Psychiatry. 2008;16(3):181-194.; 2. Hughes PH, et al. *J Addict Dis*. 1999;18(2):23-37.

More Providers of MOUD are Needed

- Objective of the study was to assess the accuracy of the SAMHSA database for patient to connect to providers
- Of the providers listed
  - 32.9% of providers could not be reached
  - 37.5% of the telephone numbers were incorrect
  - 27.7% of providers had available appointments
  - Wait times for appointments ranged from 1 to 120 days with an average of 16.8 for those that had a waitlist
  - 75.7% accepted insurance, 62.9% accepted Medicaid
  - Out-of-pocket costs averaged $231 (range: $90-$600)

Flavin L, et al. *J Psychiatry Pract*. 2020;26(1):17-22.

Geographic Breakdown of Buprenorphine Providers

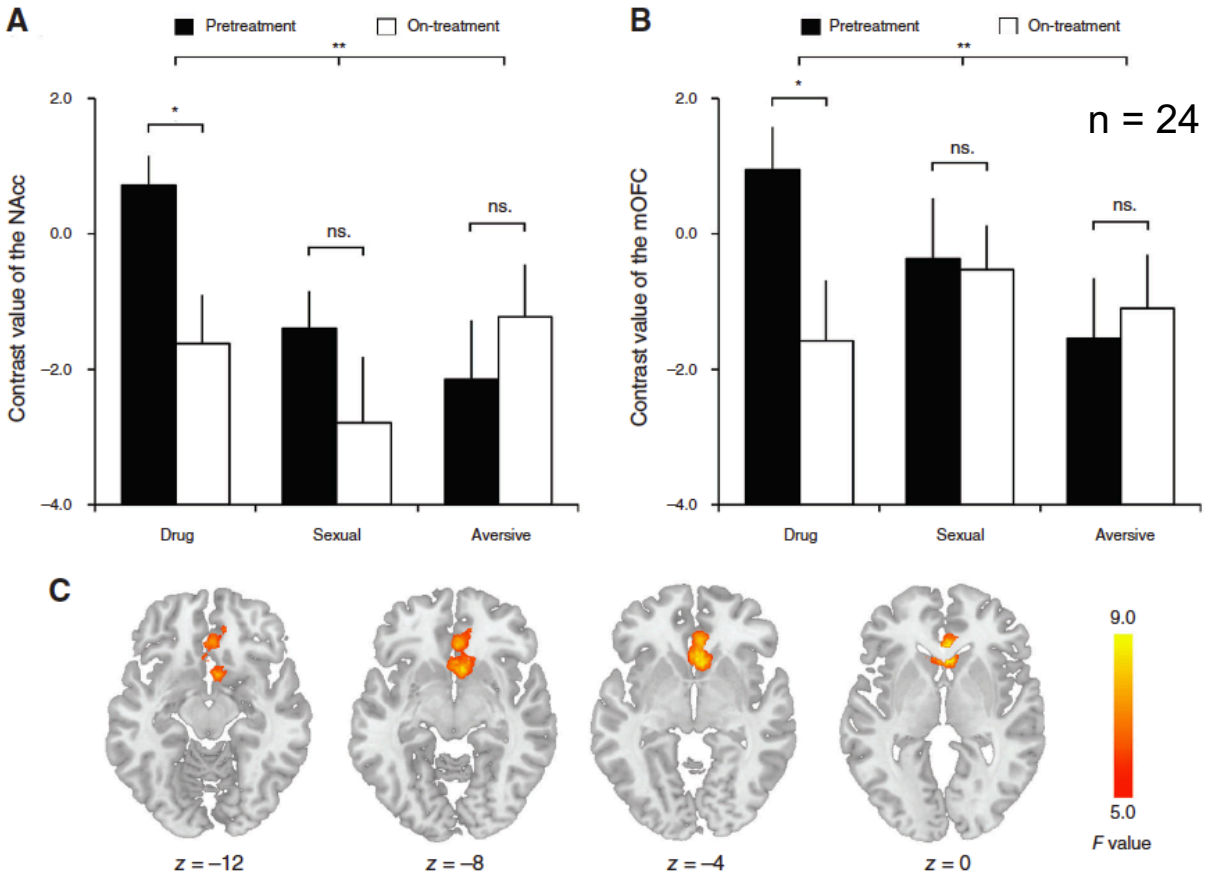
County	Population (2010 Census)	Opioid Overdose Death Rate*	#Providers per 100k People	#Confirmed Buprenorphine Providers	#Providers With Appointments	#Unlisted Buprenorphine Providers**
Benton, TN	16,489	57.7	42	2	2	8
Carbon, UT	21,403	23.1	37	4	3	3
McDowell, WV	22,113	93.2	18	2	0	1
Bell County, KY	28,691	72.3	49	3	3	2
Coos, NH	33,055	31.6	12	2	0	4
Rio Arriba, NM	40,246	82.1	2	0	0	6
Cambria, PA	143,679	34.7	24	15	12	23
Kent, RI	166,158	27.7	93	59	34	2
Montgomery, OH	535,153	46.3	21	35	26	89
Bristol, MA	548,285	28.1	30	73	60	4

*Per 100k people.
**The total number of unlisted providers was obtained from the SAMHSA Office of Policy, Planning, and Innovation.
KY indicates Kentucky; MA, Massachusetts; NH, New Hampshire; NM, New Mexico; OH, Ohio; PA, Pennsylvania; RI, Rhode Island; SAMHSA, Substance Abuse and Mental Health Services Administration; TN, Tennessee; UT, Utah; WV, West Virginia.

Flavin L, et al. *J Psychiatry Pract.*. 2020;26(1):17-22.

Extended-Release Naltrexone Response to Opioid-Related Stimuli in Patients with OUD

- (A) The nucleus accumbens (NAcc) response to to cues during pretreatment and naltrexone on-treatment sessions.
- (B) The medial orbitofrontal cortex (mOFC) response cues during pre- and on-treatment sessions
- (C) Result of whole-brain analysis of variance showing significant session x stimulus interaction in the NAcc and mOFC.
- *p < 0.05; **p < 0.01



Shi Z et al. *J Psychiatry Neurosci.* 2018;43(4):254-261.

Time to Consider the Diagnosis of Treatment Resistant OUD?

- Like treatment resistant depression (TRD), there is a cohort of individuals who are not responsive to treatment
- But unlike TRD, the individual is blamed when relapses occur, not the treatment
- A review of the readmission data of 30 patients over the course of 4 years (2016-2019) found[1]
  - In July 2016, mean number of treatment attempts: 5.8 (0-27 attempts)
  - In July 2017, mean number of treatment attempts: 6.3 (0-32 attempts)
  - In July 2018, mean number of treatment attempts: 7.5 (0-34 attempts)
  - In July 2019, mean number of treatment attempts: 6.3 (0-24 attempts)
- Failure may have less to do with personal resistance and more to do with the disorder's resistance
- No one knows which treatment will work, need personalized medicine[2]

1. Patterson Silver Wolf D, Gold MS. *J Neurol Sci*. 2020;411:116718. doi: 10.1016/j.jns.2020.116718. [Epub ahead of print] Review. 2. Sanacora G. *JAMA Psychiatry*. Published online February 19, 2020. doi:10.1001/jamapsychiatry.2019.4764

Treatment Does Not Negate Risk of Overdose

Naloxone

- Not a “cure” but reverses the dangers of an opioid overdose allowing medical treatment and hopefully prevent death
- Ensuring ready access to naloxone is one of *SAMHSA’s Five Strategies to Prevent Overdose Deaths*
- All 50 states + DC have legislation increasing access
  - Allows naloxone distribution by pharmacists
  - Simplify the process of obtaining naloxone
  - Distribution beyond those at risk for overdose
- 46 states have Good Samaritan laws that protect bystanders and individuals from arrest or prosecution for administering naloxone in good faith

https://store.samhsa.gov/shin/content//SMA18-4742/SMA18-4742.pdf

Naloxone Saves Lives, But Only if Available When Overdose Occurs

- Overdose deaths have stabilized declining 4.1% in 2018[1]
- The number of naloxone prescriptions dispensed doubled between 2017-2018
- ***But*** only 1 naloxone prescription dispensed for every 69 high-dose opioid prescriptions[2]
- Rural counties are 3x more likely to be a low-dispensing county vs. metropolitan counties[2]
- Naloxone dispensing is 25x greater in the highest-dispensing counties vs. the lower dispensing counties[2]

1. Centers for Disease Control and Prevention. National Center for Health Statistics Data Briefs. Available at https://www.cdc.gov/nchs/products/databriefs.htm. Accessed January 30, 2020.; 2. Guy GP Jr., et al. *MMWR Morb Mortal Wkly Rep*. 2019;68:679-686.

Naloxone

- Not a “cure” but reverses the dangers of an opioid overdose allowing medical treatment and hopefully prevent death
- Three FDA-approved formulations[1]
  - Injectable
  - Autoinjectable
    - Prefilled autoinjection device
    - Once activated, device provides verbal instructions to the user
  - Prepackaged nasal spray, no assembly
    - Prefilled, needle-free device requiring
    - Sprayed into one nostril while patients back
- Access to naloxone is expanding
- SAMHSA Opioid Overdose Prevention Toolkit[2]

https://www.drugabuse.gov/related-topics/opioid-overdose-reversal-naloxone-narcan-evzio.; https://store.samhsa.gov/shin/content//SMA18-4742/SMA18-4742.pdf.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- OUD is a brain disease, not a moral failing
- Integrate MOUD into your practice
- Treatment failure/relapse may have less to do with personal resistance and more to do with treatment resistant OUD
- OUD puts patients at risk for overdose, be sure they have naloxone in the home

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.