Medications for Opioid Use Disorder: Which Option is Best for My Patient?

Clement Chen, PharmD, BCPS
Clinical Pharmacist/Academic Detailer
Northern NJ MAT Center of Excellence
Rutgers New Jersey Medical School

Date 03.04.22

Disclosures

The following session leader has no relevant financial relationships with ineligible companies to disclose:

- Clement Chen, PharmD

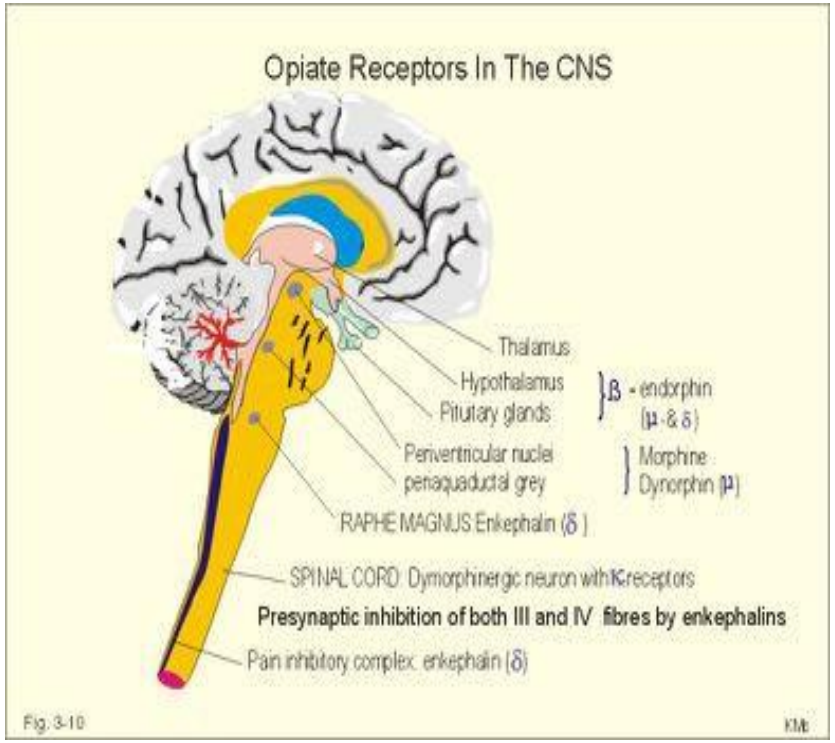
- I may discuss non-FDA approved, exploratory uses for buprenorphine beyond the package insert
- Resolution of Conflicts of Interest:
  - I will support my presentation and clinical recommendations with the “best available evidence” from the medical literature
  - I will refrain from making recommendations regarding products that are not FDA-approved
  - I submitted my presentation in advance to allow for adequate peer review

Learning Objectives

- Justify the rationale for medication treatment in opioid use disorder
- Identify and compare the medications for opioid use disorder (MOUD)
- Summarize recent literature on the use of MOUD available in the community-based setting
- Demonstrate how to approach the management of MOUD in patients with varying goals

Understanding Opioid Use Disorder

- **Chronic, relapsing (recurring) disease** involving brain reward, motivation, and related circuitry characterized by **compulsive drug seeking and use despite harmful consequences**[1,2]



Slide credit: clinicaloptions.com

1. American Society of Addiction Medicine. Definition of addiction. Adopted April 12, 2011. 2. NIDA. Drugs, brains, and behavior: the science of addiction. Updated July 2014.

Opioid Withdrawal

- Nausea/vomiting
- Muscle aches
- Lacrimation
- Rhinorrhea
- Pupil dilation
- Piloerection
- Sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

Lasts 7-14 days

Post-Acute Withdrawal Syndrome (PAWS)

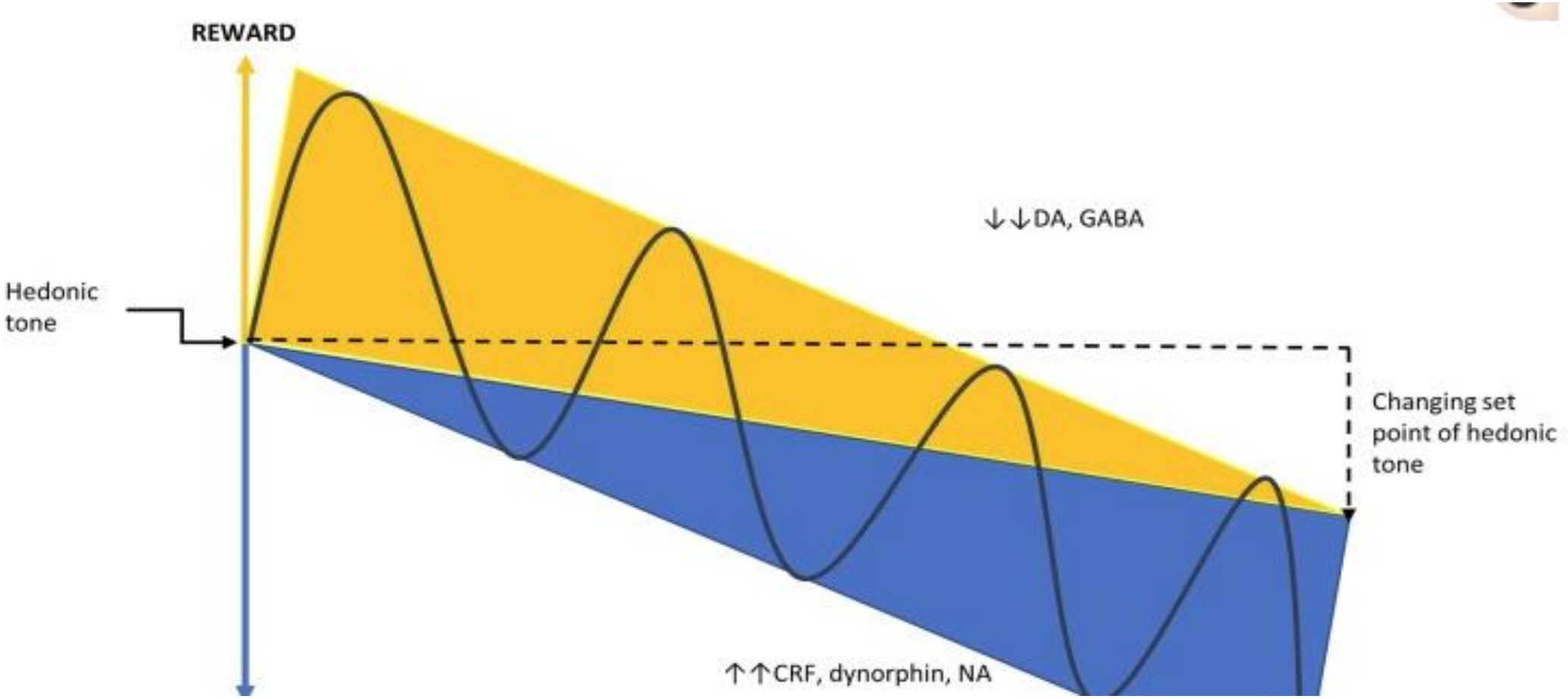
- **Presence of a dysphoric state or depression**
- **Irritability**
- **Anxiety**
- **Decreased ability to feel pleasure (anhedonia)**
- **Reduced control of executive functions**
- **Physical problems, such as pain, that may not be attributable to a specific cause and more "painful" than the original cause**
- Trouble sleeping
- Decreased libido
- Chronic and lasting fatigue

Leads to poorer physical/functional status, medical, and psychiatric instability that can lead to recurrence of SUD, and harmful behaviors such as suicide and violence

Due to homeostatic changes and can last for years

Manhapra A, et al. *Subst Abuse.* 2018; 39(2):152-61.

Changing of the Homeostatic Set Point

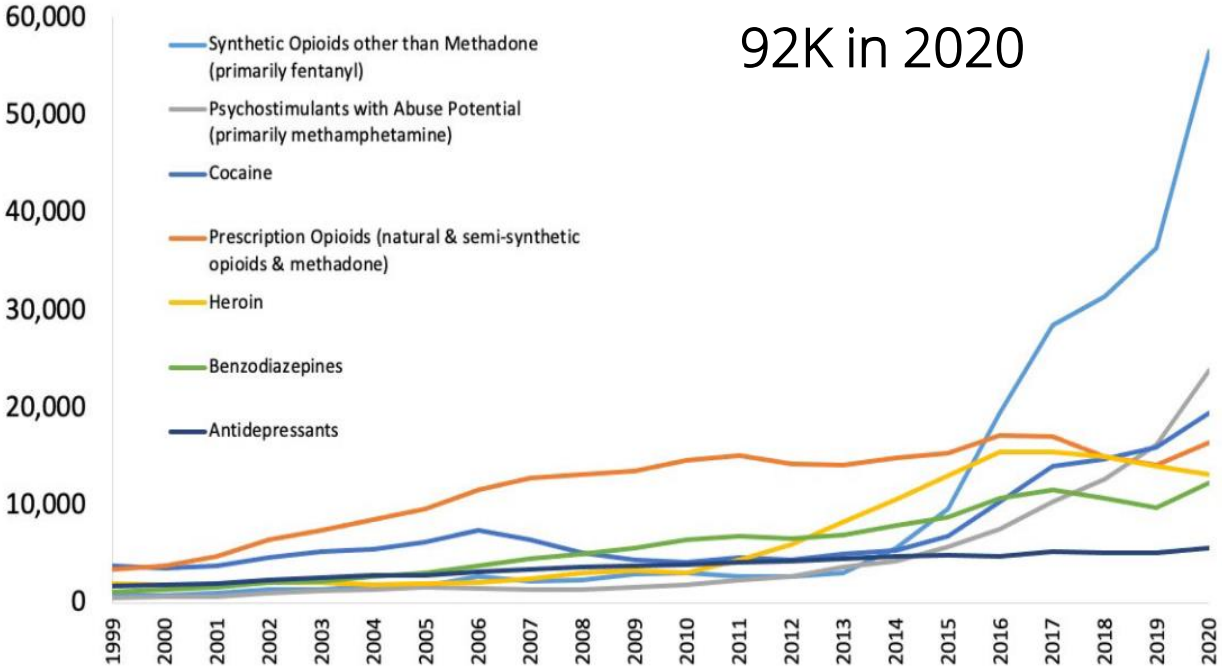


Presence of a negative feedback system usually occurs until overpowered through neuroadaptations due to addiction

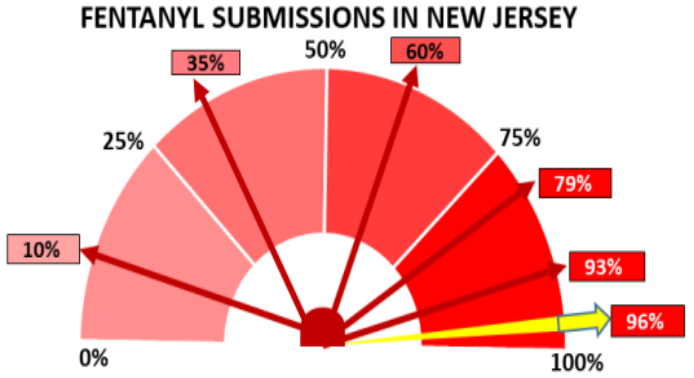
Kakko J, et al. *Front Psychiatry.* 2019 Aug 30:10:592.

Overdose Deaths – An Update

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020



92K in 2020

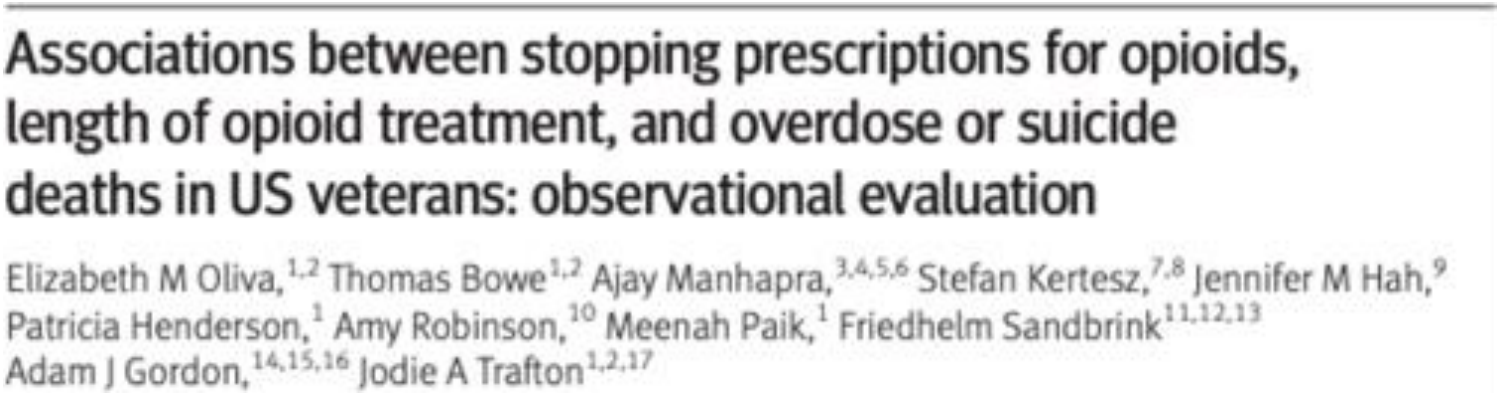


Submissions containing fentanyl or fentanyl analogs have steadily increased. 96% of suspected heroin submissions during the 3rd quarter of 2021 contained fentanyl, compared to 93% during the 3rd quarter of 2020, 79% (2019), 60% (2018), 35% (2017), and 10% (2016).

*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates; NJ Office of Drug Montoring and Analysis 2021 Third Quarter Report

Not Just Overdose Deaths…



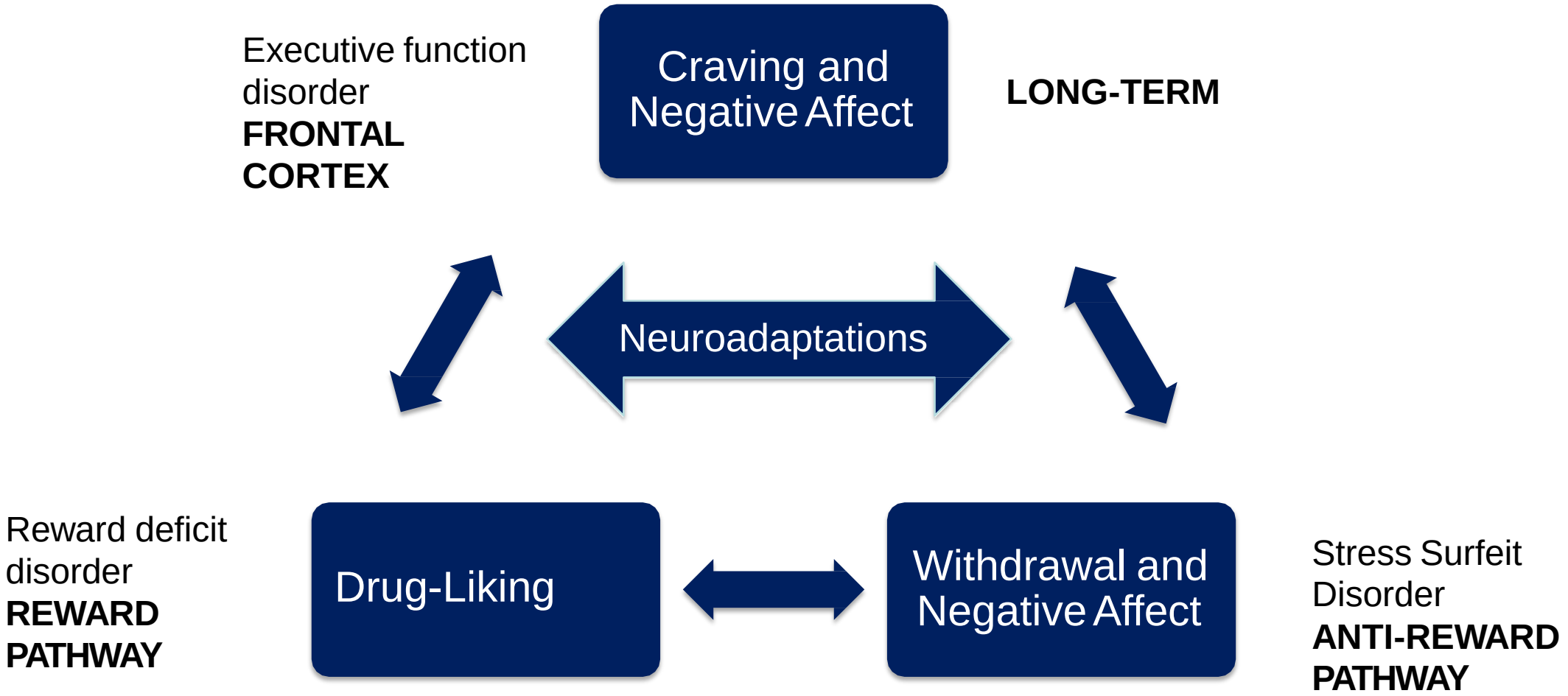
Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation

Elizabeth M Oliva,[1,2] Thomas Bowe[1,2] Ajay Manhapra,[3,4,5,6] Stefan Kertesz,[7,8] Jennifer M Hah,[9] Patricia Henderson,[1] Amy Robinson,[10] Meenah Paik,[1] Friedhelm Sandbrink[11,12,13] Adam J Gordon,[14,15,16] Jodie A Trafton[1,2,17]

- The longer the patient was on opioid therapy and stopped, the higher the risk of suicide:
  - <30 days: ~2x
  - 31-90 days: ~3.5x
  - 91-400 days: ~5x
  - >400 days: ~8x

Oliva EM, et al. *BMJ*. 2020 Mar 4;368:m283.

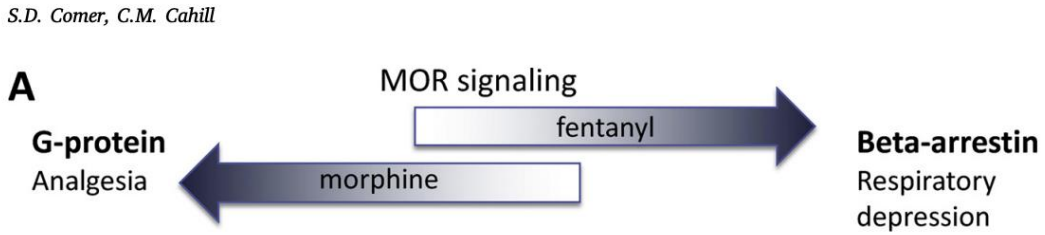
Addiction Neuroadaptation



Kakko J, et al. *Front Psychiatry.* 2019 Aug 30:10:592.

Opioid Use Disorder Today

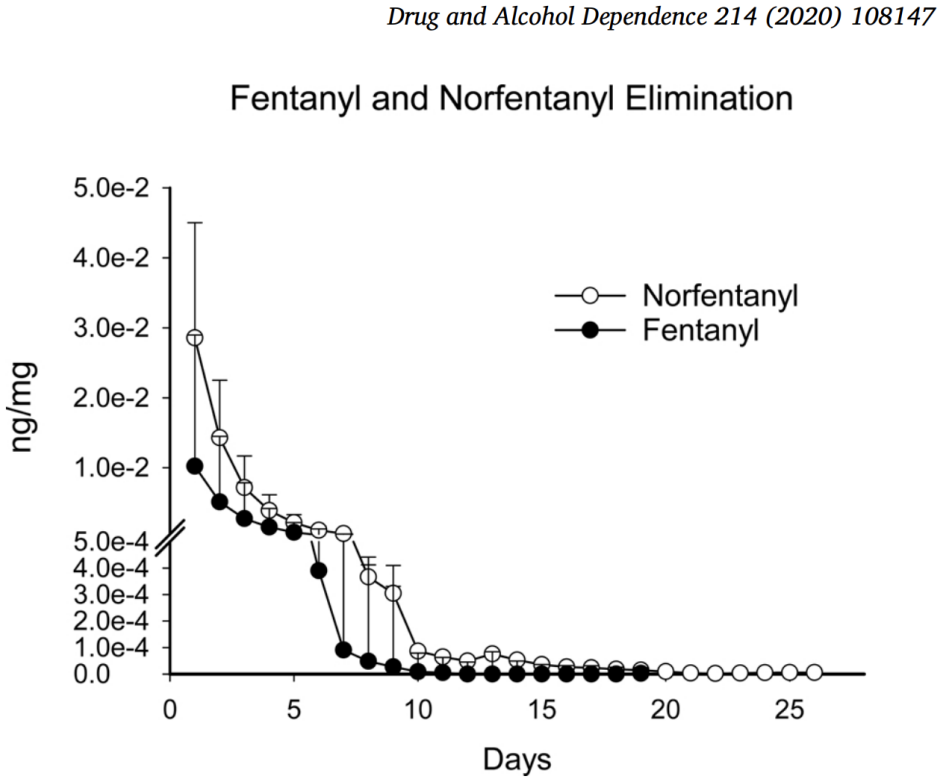
Age of Highly Potent Synthetic Opioids (HPSOs) - Fentanyl



Morphine	Fentanyl
Less lipophilic	More lipophilic
Slow CNS entry	Rapid CNS entry

Fentanyl and analogs account for >70% of opioid overdose deaths

Illicit fentanyl is illegally synthesized, forming many different analogs that may be more potent than the parent compound



Comer SD, et al. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Sep 1;214:108147.

.

What are the Implications of all this?

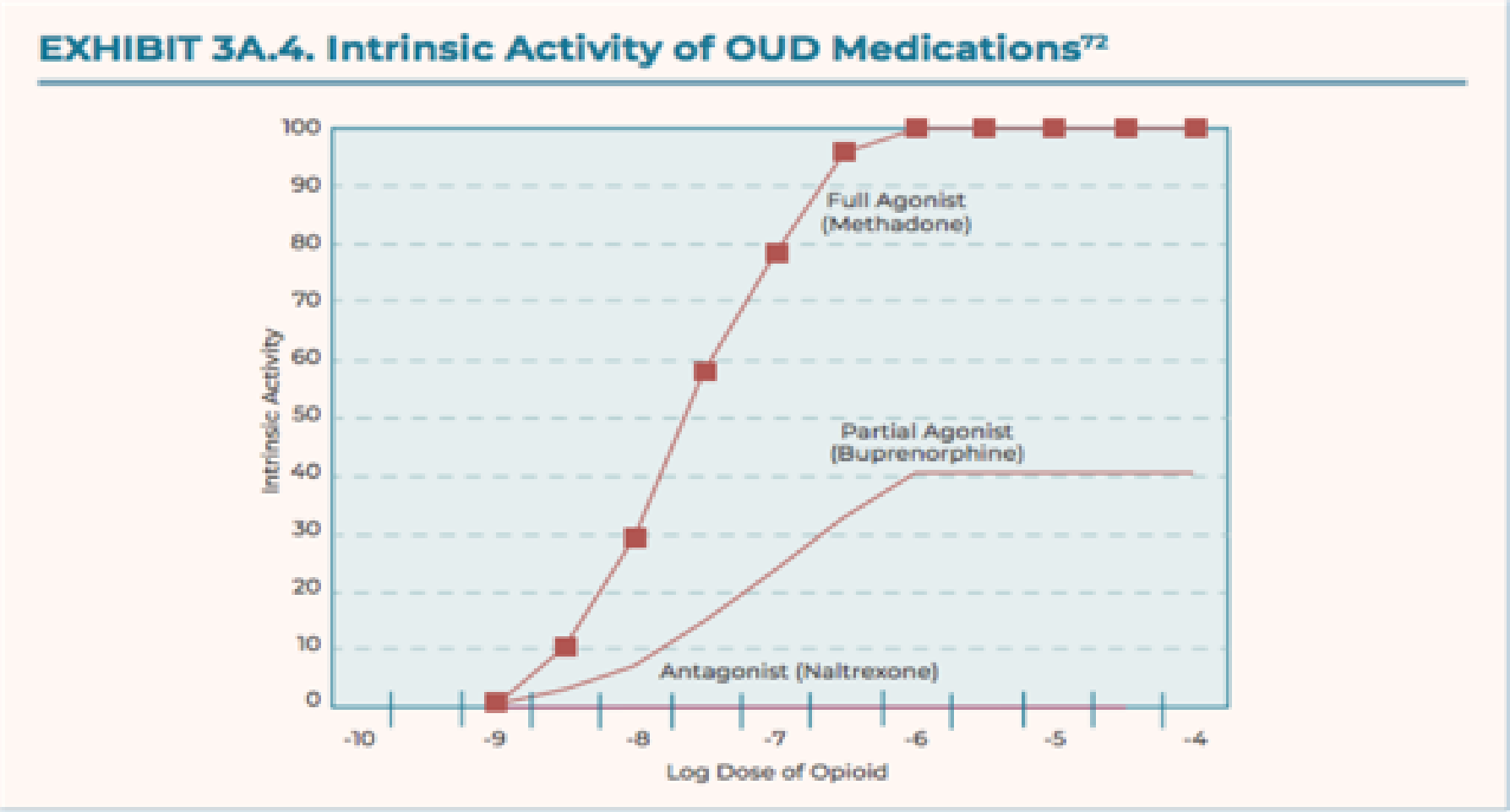
- Fentanyl, its analogs, and synthetic opioids have properties that are much different than opiates like heroin and morphine
- Many illicit drugs are contaminated with fentanyl, which plays a major part in deaths due to drug use
- Our treatment for and ability to save-lives is essentially a race to get everyone treated before future synthesized drugs are able to overcome current therapies

Medications for Opioid Use Disorder (MOUD)

- Methadone
- Buprenorphine
- XR-Naltrexone

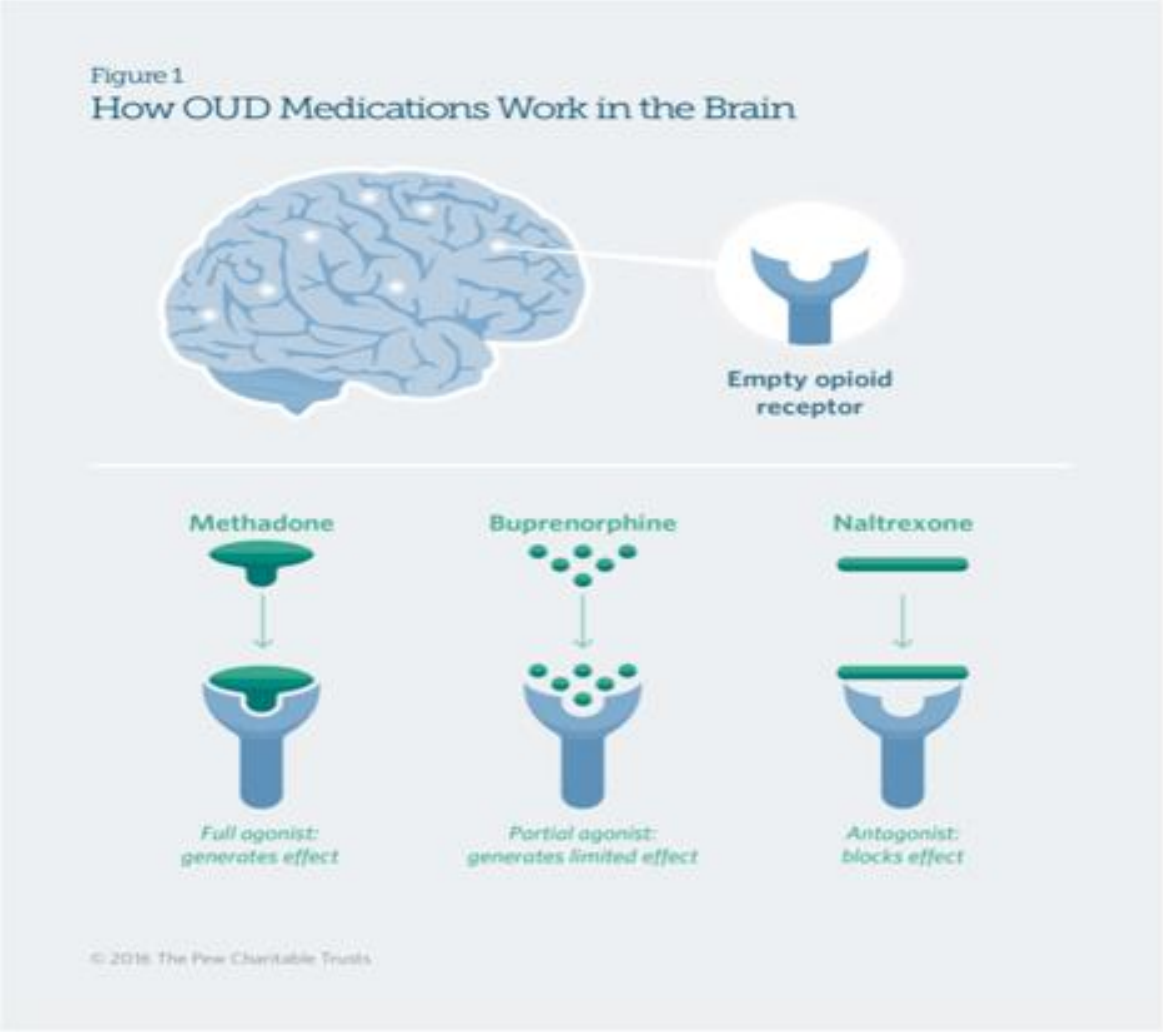
MOUD

Comparison of Agonist Activity Among MOUD



Sordo, et al. *BMJ.* 2017 Apr 26;357:j1550.

Types of MOUD – Preventing Overdose/Respiratory Depression

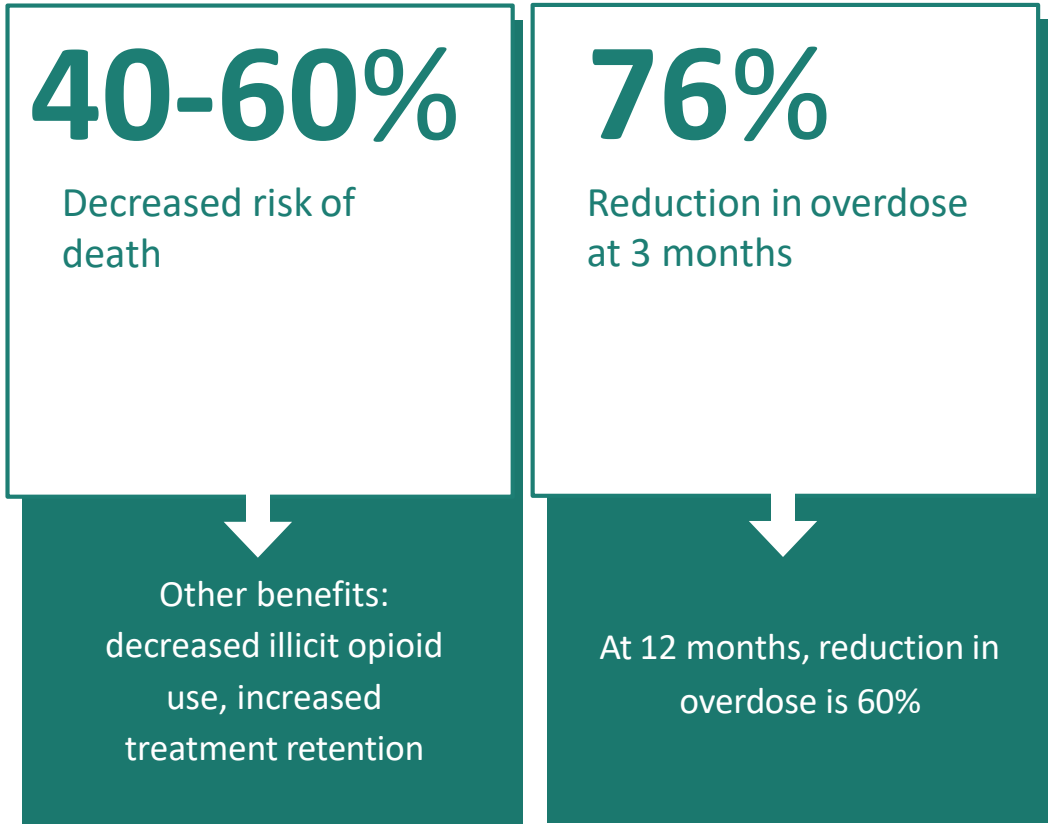


- Methadone = raises opioid tolerance levels
- Buprenorphine and Naltrexone = provide a mu-opioid receptor blockade effect

Image Credit: The Pew Charitable Trusts

Benefits of MOUD

- Reduced opioid use
- Increased physical and mental health quality of life
- Reduced criminal behavior and incarceration
- Reduced emergency department use
- Increased employment
- Improved management of comorbid conditions



Less than 1/3 of OUD patients ever receive MOUD

Sordo, et al. *BMJ.* 2017 Apr 26;357:j1550.
Liebschutz JM, et al. *JAMA Intern Med.* 2014 Aug;174(8):1369-76. D'Onofrio G, et al. *JAMA* Apr 28;313(16):1636-44.
Larochelle MR, et al. *Ann Intern Med*. 2018;169:137-145
Wakeman SE, et al. *JAMA Network Open*. 2020;3:e1920622

MOUD Reduces Mortality

Annals of Internal Medicine ORIGINAL RESEARCH

Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality

A Cohort Study

Marc R. Larochelle, MD, MPH; Dana Bernson, MPH; Thomas Land, PhD; Thomas J. Stopka, PhD, MHS; Na Wang, MA; Ziming Xuan, ScD, SM; Sarah M. Bagley, MD, MSc; Jane M. Liebschutz, MD, MPH; and Alexander Y. Walley, MD, MSc

RETROSPECTIVE COHORT, MASSACHUSETTS PUBLIC HEALTH DATASET, 2012-2014

17,568 opioid overdose survivors
with ambulance or hospital encounter

Only 3 in 10 receive MOUD*
over 12 months of follow-up

*Medication for Opioid Use Disorder

Mortality at 12 months:
4.7 deaths / 100 person-yrs

Association of MOUD* with mortality:

Methadone	↓ 53%
Buprenorphine	↓ 37%
Naltrexone**	↔

** *limited by small sample*

Larochelle et al. *Annals of Internal Medicine*. 2018.

BOSTON MEDICAL CENTER

Grayken Center for Addiction
Boston Medical Center

CARE

BOSTON UNIVERSITY SCHOOL of Medicine

Methadone

- Full opioid agonist
  - Metabolized via N-demethylation via CYP to inactive metabolites
    - Drug interactions: SSRIs, antiseizure and HIV medications
  - t1/2 = 24-36 hours

- Steady state may take 5 days
  - Peak 2-4 hours after dose
  - Initiated at 20-30mg daily; maintenance 80-120mg daily

- Risk for QTc prolongation and mortality when dose exceeds tolerance
  - No ceiling effect

- Requires enrollment in opioid treatment program (OTP)

- Role in age of fentanyl?

Methadone. Lexicomp online. Wolters Kluwer Health, Inc.

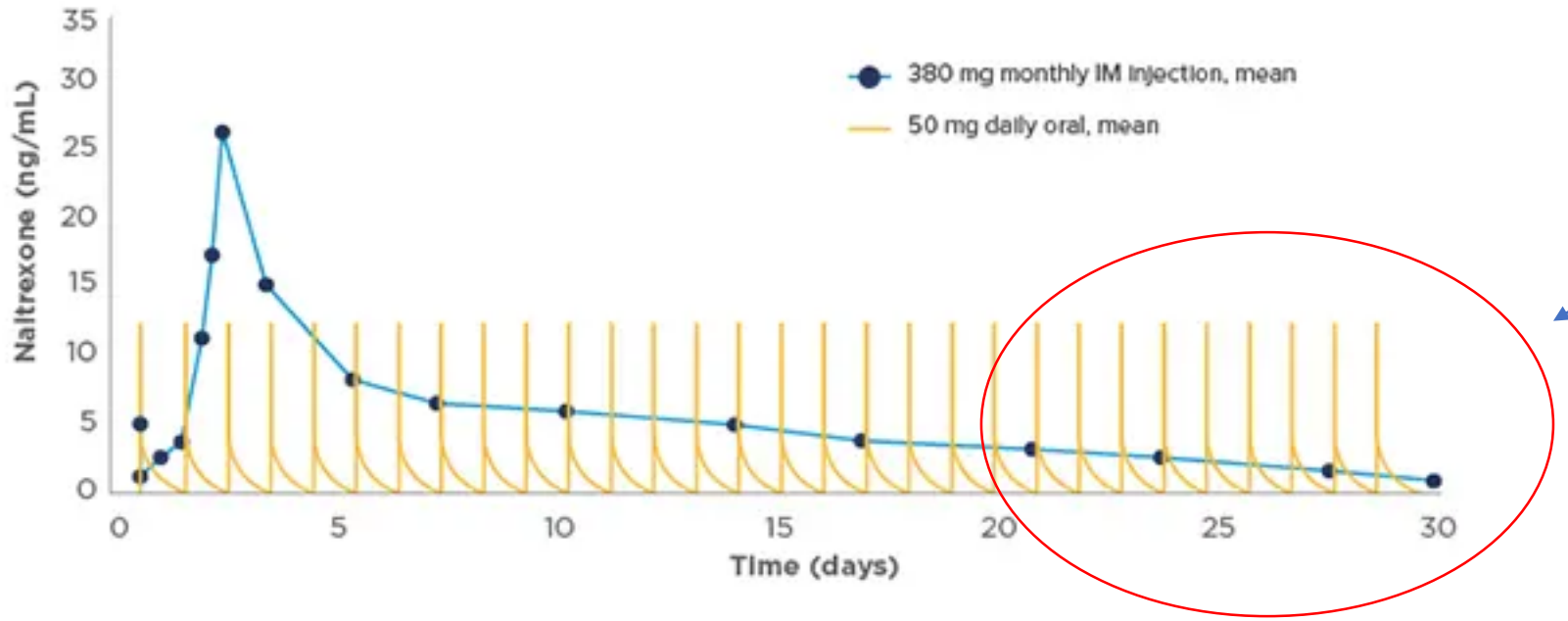
Naltrexone ER Injection

- Full μ-opioid antagonist with high affinity for the opioid receptor
  - Not metabolized by CYP enzymes
  - Some kappa-antagonist activity <<< mu-agonist activity
- Intramuscular depot formulation to prevent relapse dosed at 380mg monthly
  - Vs. Oral Naltrexone
- **Requires 7-10 days of opioid-free state**
- Shown to reduce return to illicit opioid use, increased treatment retention, and craving vs. placebo
  - Mortality?
- **Risk of lower tolerance** → fatal overdose?
- Population that may benefit most from naltrexone ER
  - After a period of withdrawal management
  - Fully motivated
- Role in age of fentanyl?

Substance Abuse and Mental Health Services Administration (2012). Accessed from: https://store.samhsa.gov/system/files/sma14-4892r.pdf

Naltrexone ER vs. Oral Naltrexone by Concentration

Plasma naltrexone concentration[2,3*]



Concern?

*Data for oral naltrexone beyond Day 5 have been extrapolated from a study of normal healthy volunteers (n=14) given oral naltrexone 50 mg daily for 5 days. Plasma concentrations do not necessarily correlate with clinical efficacy.

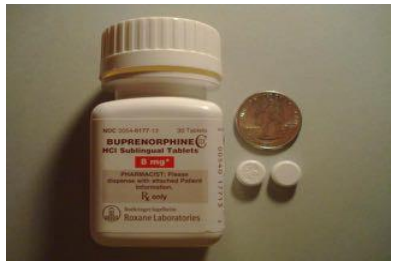
https://www.vivitrolhcp.com/dosing-and-administration

Buprenorphine

- Partial μ-receptor agonist of 40% intrinsic activity with more defined pharmacokinetics – t1/2 = 24-69 hours
  - Inhibited by 3A4 primarily – no major clinically significant interactions
  - Also has significant kappa-receptor antagonist activity

- Ceiling effect that reduces risk of respiratory depression and euphoria

- Initiate when patient develops period of moderate withdrawal symptoms*



Buprenorphine. Lexicomp online. Wolters Kluwer Health, Inc.
Thomas CP, et al. *Psychiatr Serv.* 2014 Feb 1;65(2):158-70.

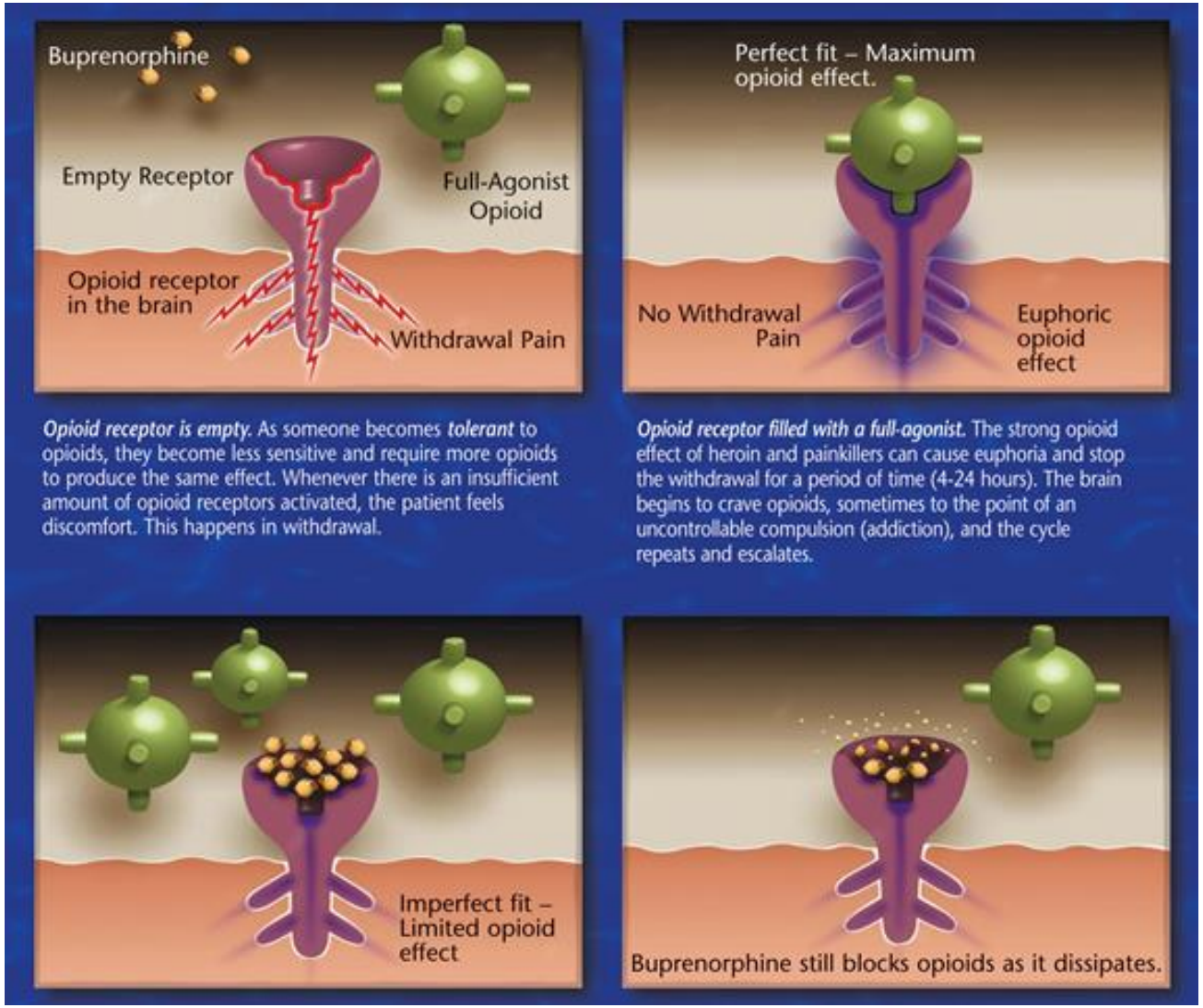
Types of Buprenorphine Approved for OUD

- **Buprenorphine tablets (Subutex®)**
- **Buprenorphine/Naloxone tablets and films (Suboxone® and Zubsolv®)**
- **Extended-release injection (Sublocade®)**
  - Once-monthly formulation moderate-severe OUD
  - Need initiation with mucosal formulation of buprenorphine for at least a week and stable on doses of 8-24mg/day
  - Need to enroll in REMS program
- **Intradermal implant (Probuphine®)**
  - 4 implants for 6 months of treatment
  - Indicated for those with daily doses of buprenorphine of ≤ 8mg
  - Need to enroll in REMS program

Buprenorphine. Lexicomp online. Wolters Kluwer Health, Inc.
Buprenorphine/Naloxone. Lexicomp online. Wolters Kluwer Health, Inc.

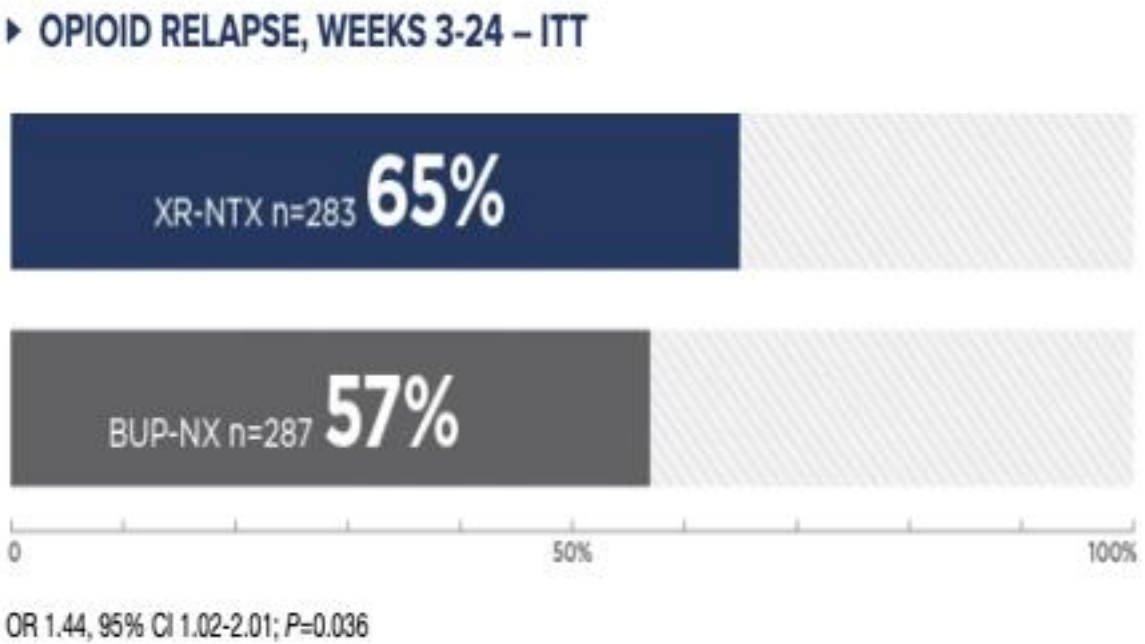
Buprenorphine:

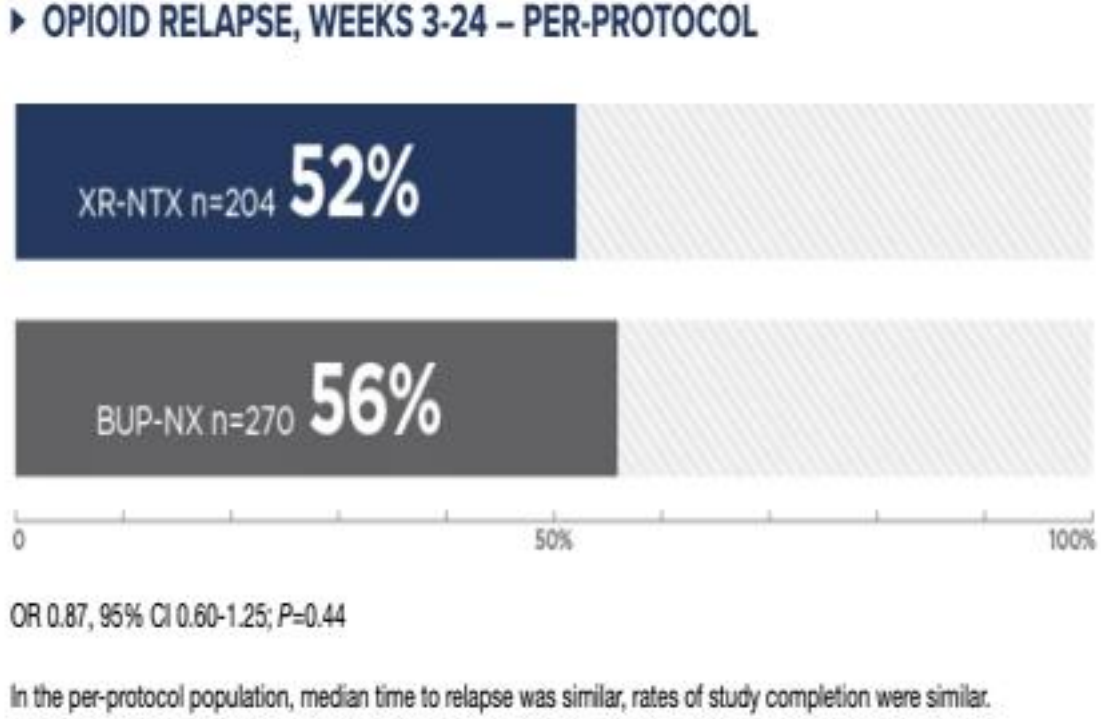
- ✓ Partial agonist = 40% activation
- ✓ Virtually no overdose risk in adults
- ✓ High affinity to / slow dissociation from the mu-opioid receptor
- ✓ Precipitated withdrawal is a risk



The National Alliance of Advocates for Buprenorphine Treatment. How Buprenorphine Works. Available from: https://www.naabt.org/collateral/How_Bupe_Works.pdf

X:BOT Study – Comparing Buprenorphine/Naloxone SL Daily and XR-Naltrexone





- **Open-label, RCT of 570 highly-motivated patients (some were randomized within 72 hours of opioid use; others > 72 hours)**
- **~ 25% (204/283 successful) of patients dropped-out from the XR-naltrexone arm**
- **Nearly 95% (270/287) of patients successfully initiated on buprenorphine/naloxone**

Lee JD, et al. *Lancet.* 2018 Jan 27;391(10018):309-18.
https://www.vivitrolhcp.com/xbot-clinical-study

X:BOT Study – Comparing Buprenorphine/Naloxone SL Daily and XR-Naltrexone

Intention-to-Treat

Per-Protocol

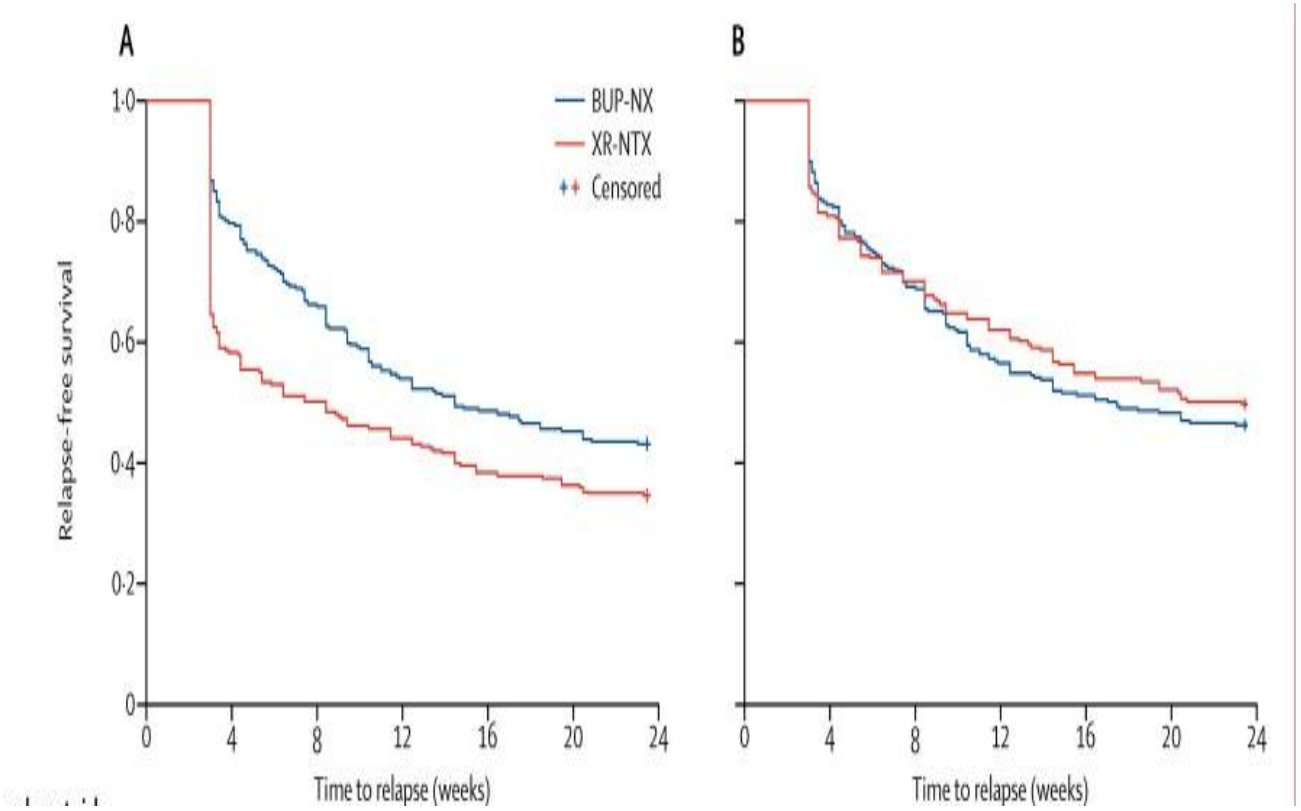
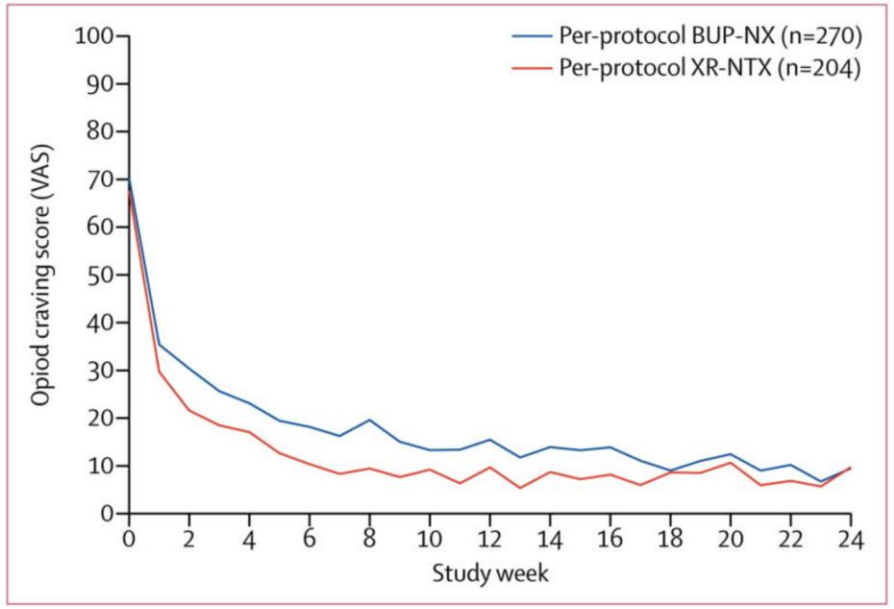


Figure 3

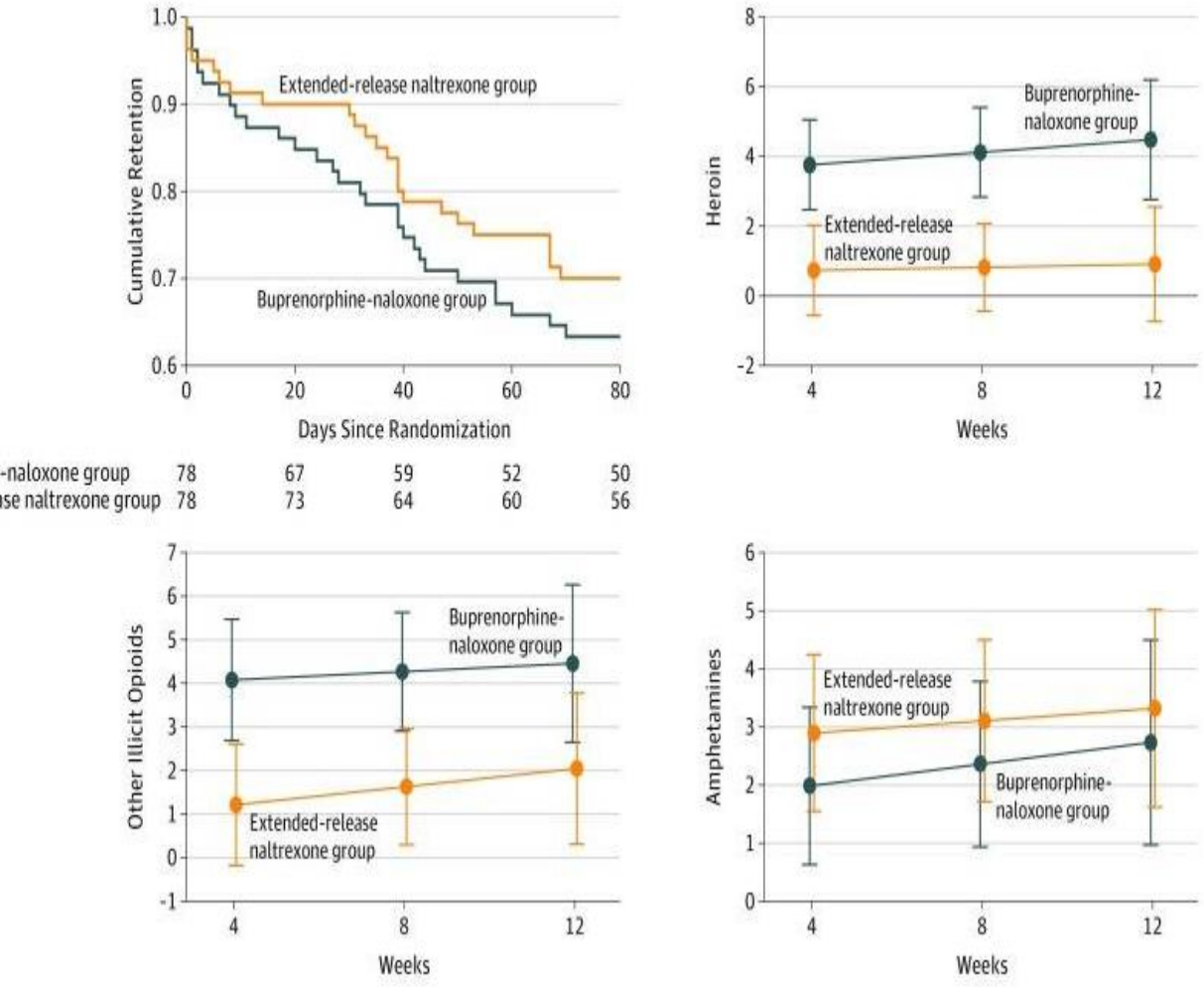


Opioid craving during the trial

Craving was self-reported with an opioid craving VAS, range 0–100. VAS=Visual Analogue Scale. XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone.

Lee JD, et al. *Lancet.* 2018 Jan 27;391(10018):309-18.

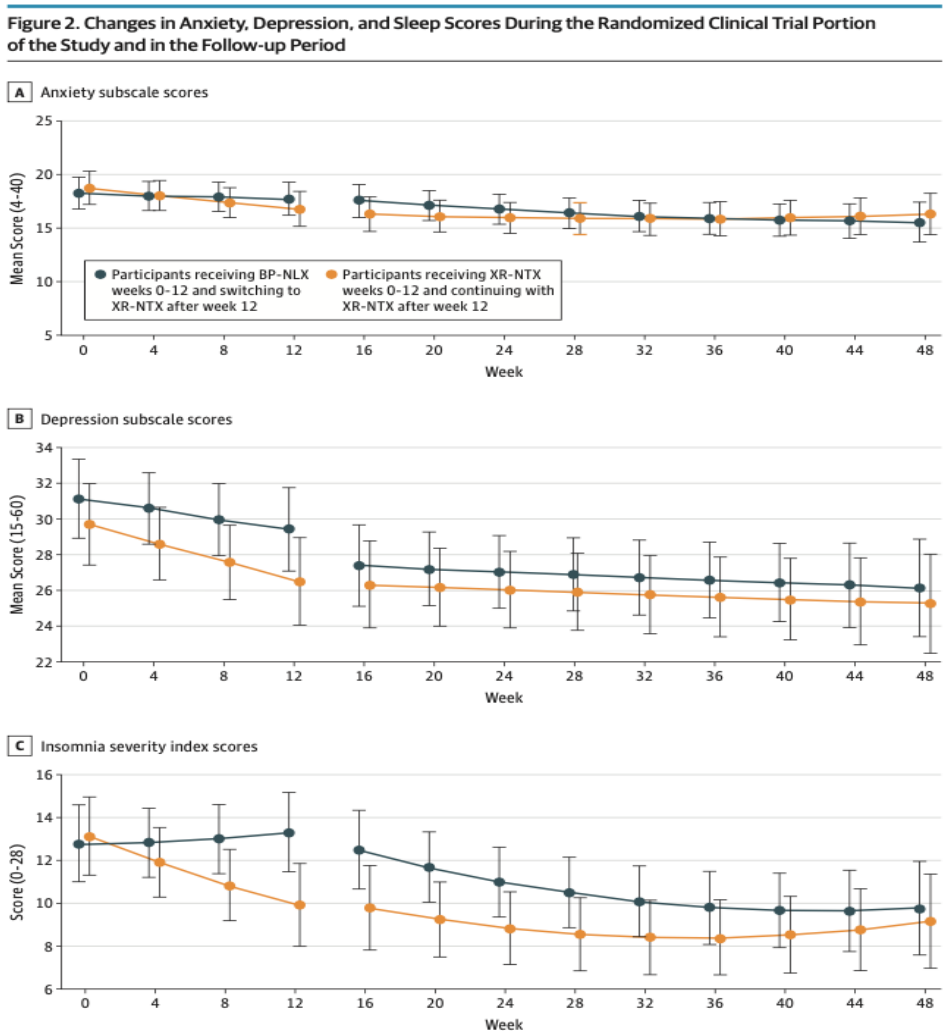
XR-Naltrexone vs. Daily Buprenorphine/Naloxone: An Noninferiority RCT on Retention and Illicit Drug Use



- 12-week, multicenter, outpatient, open-label RCT at 5 urban addiction clinics in Norway (2012-2015)
- 159 participants (80:79) followed for 12 weeks
  - 56/80 completed 12-week of XR-NTX
  - 49/79 completed 12-week of BP-NLX
- Non-inferiority analysis
  - Proportion of retained patients
  - Proportion of total # of opioid-negative tests
  - Use of heroin
  - Other illicit opioids
- BUT, superiority analysis showed lower use of heroin (through 12 weeks) and other illicit opioids in XR-naltrexone group (through 8 weeks)

Tanum L, t al. JAMA Psychiatry. 2017;74(12):1197-1205.

XR-Naltrexone vs. Buprenorphine/Naloxone: An RCT on Anxiety, Depression, and Insomnia



- RCT of 159 for opioid use disorder to 12 weeks of treatment (80:79) followed by 9-month study with treatment of choice (2012-2015) in Norway
- XR-naltrexone 380mg monthly or buprenorphine (4-24mg; 16mg target) of daily SL bupe
- 117/122 preferred XR-NTX to bupe
  - 56 from the original XR-NTX group → 29/56
  - 61 from the original BP-NLX group → 29/61
- No significant difference in treatment effect on anxiety or depression; insomnia significantly lower in XR-NTX group in the 12-week trial period vs. bupe
- During the follow-up period, no differences in all 3 between those continuing on XR-NTX or switching to XR-NTX

Latif Z, et al. *JAMA Psychiatry*. 2019 Feb 1;76(2):127-34.

Buprenorphine on Reducing Risk of Fentanyl-Respiratory Depression

- Single-center, cross-over study of 14 healthy volunteers and 8 opioid-tolerant patients taking at least 90 MME
- Received continuous IV buprenorphine or placebo for 360 minutes, targeting concentrations of 0.2-0.5 ng/mL in healthy volunteers and **<u>1,2, or 5.0 ng/mL</u>** in opioid-tolerant patients
- Fentanyl given IV at escalating doses after achieving goal bupe [] with outcome of change in minute ventilation (Ve)
- Changes in Ve were smaller at higher bupe [] and risk of experiencing apnea following fentanyl boluses was lower with bupe than with placebo.

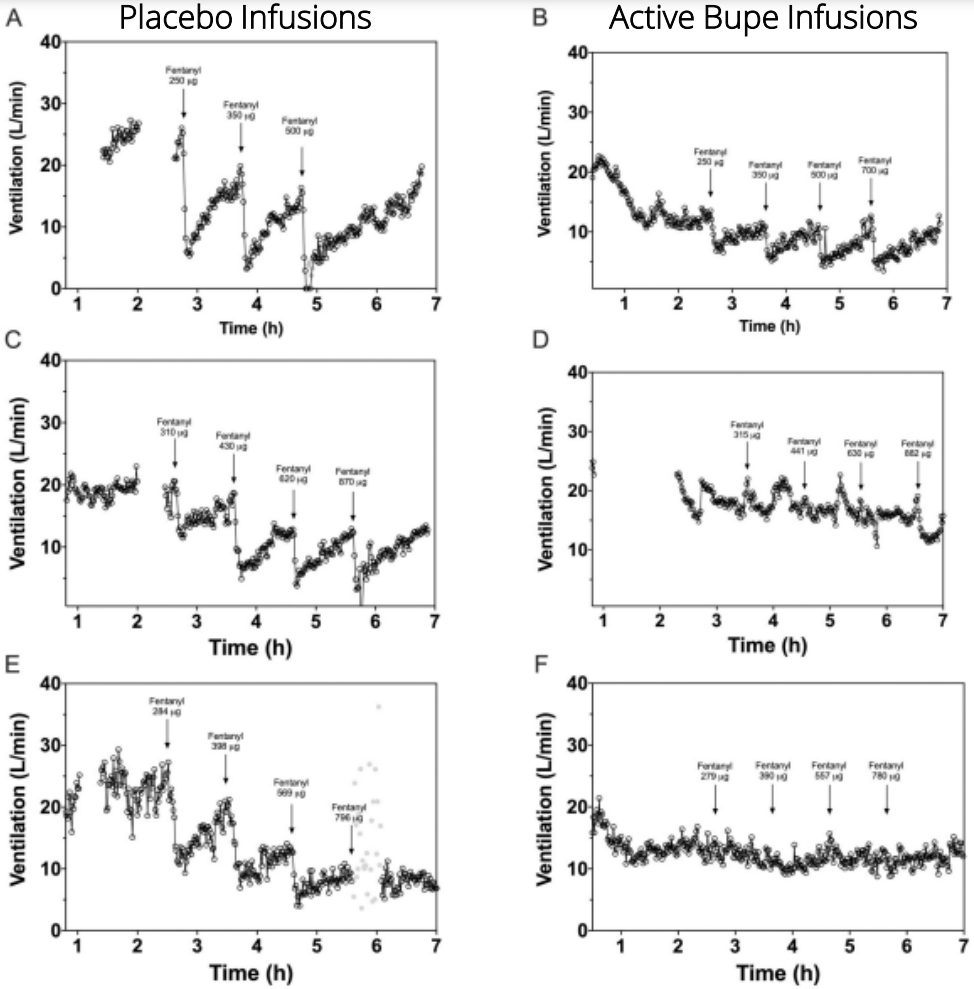
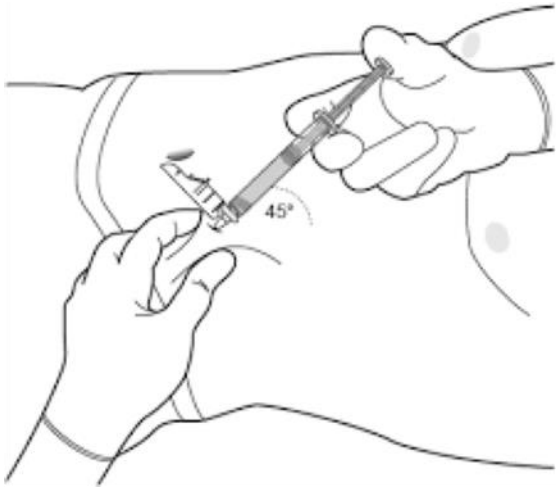


Fig 4. Example graphs showing the effect of fentanyl on minute ventilation in three opioid-tolerant patients during placebo infusion and buprenorphine infusion. (1) Placebo infusion (A, C and E) and buprenorphine infusion (B, D, F) at target plasma concentrations of 1 ng/mL (top row), 2 ng/mL (middle row) and 5 ng/mL (lower row). (2) Open spaces in the beginning of graphs A, C, D and E relate to concurrent clinical events such as temporary removal of the facemask. (3) Grey dots are stimulated breaths in case of an apnea episode. (4) The time on the x-axis in the graphs is related to the start time of the ventilation experiment, not the timing of the buprenorphine/placebo infusion and fentanyl injections.

Moss LM, et al. *PLoS One.* 2022 Jan 27;17(1):e0256572.

Extended-Release Injectable Buprenorphine

- Prefilled 19-gauge syringe that is refrigerated
- Depot injection
- Dose: Given monthly
  - First 2 months: 300mg SC
    - Peak after 24 hours
  - Subsequent months: 100mg or 300mg SC*
    - Steady state after 4-6 months
  - Average concentration: **3-6 ng/mL >> 2-3 ng/mL**
- Adverse drug reactions:
  - Nausea, vomiting, diarrhea, injection site reactions



Haight BR, et al. *Lancet.* 2019 Feb 23;393(10173):778-790.

Extended-Release Buprenorphine Pharmacokinetics

Table 6. Comparison of Buprenorphine Mean Pharmacokinetic Parameters Between SUBUTEX and SUBLOCADE

Pharmacokinetic parameters	SUBUTEX daily stabilization		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/mL)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/mL)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/mL)	0.81	1.54	1.42†	2.48	5.01

#Exposure after 1 injection of 300 mg SUBLOCADE following 24 mg SUBUTEX stabilization

†Mean plasma concentration of 1.86 ng/mL was observed on last day of the dosing interval (Day 29)

*Steady-state exposure after 4 injections of 100 mg or 300 mg SUBLOCADE, following 2 injections of 300 mg SUBLOCADE

Potential Place in Therapy

- **Reduce:**
  - Diversion
  - Need for daily dosing
- **What about patients at risk for non-adherence and misuse?**
  - Approved for patients who are stabilized on buprenorphine 8-24mg/day
  - Mariani, et al.
    - May be feasible to start sooner than 1 week on sublingual buprenorphine
    - May be a good option for treatment failures on sublingual buprenorphine
    - May be a good option for those using HPSOs
  - Maintain appropriate levels (less variation) of buprenorphine on mu-receptors
- **Overall:** In a real-world outcomes retrospective case series, XR-bup was feasible and well-tolerated
  - 65% had opioid negative toxicology in this low-threshold clinic (mostly homeless, history of IV drug use, and concurrent nonopioid substance use)
  - 10 (25%) patients received SL bup for less than the seven recommended days prior to XR-bup
  - 22 patients (55%) required supplemental SL bup dosing.

Mariani JJ, et al. *Am J Addict.* 2020 Mar 13. doi:10.1111/ajad.13018. [Epub ahead of print].
Peckham AM, et al. *J Subst Abuse Treat.* 2021.

Summary of MOUD Therapy

	Buprenorphine	Methadone	Extended-Release Naltrexone
Pharmacology	Mu-opioid receptor partial agonist	Mu-opioid receptor full agonist	Mu-opioid receptor antagonist
Dosage Forms	Buprenorphine tablets (Subutex), intradermal implant (Probuphine), monthly subQ injection (Sublocade), buprenorphine/naloxone sublingual films and tablets (Suboxone, Zubsolv) and buccal film (Bunavail)	Daily oral administration as liquid	Monthly IM injection (Vivitrol®)
Prescribing	Physicians, nurse practitioners, and physician assistants require a waiver to prescribe	Can only be dispensed by federally certified opioid treatment programs	No special certification needed to prescribe
Clinical Pearls	Low risk of overdose and respiratory depression - "ceiling effect," patients must be in withdrawal to initiate treatment for traditional induction	Risk of overdose/sedation and respiratory depression - "start low, go slow"	Must be opioid-free for 7-10 days to reduce risk of precipitated withdrawal
Who may be a good candidate?	**Most patients receiving treatment in the community setting** **Those where you may be concerned about HPSO use** Concurrent chronic pain?	**Patients willing and desire treatment with methadone** Concurrent chronic pain?	**Patients who have undergone a period of detoxification; highly motivated and do no wish to be on an opioid** **Using prescription opioids vs. HPSOs**

Reference: SAMHSA Tip 63. Medications for Opioid Use Disorder

Consider the implications of fentanyl

The ASAM National Practice Guideline for the Treatment of OUD – 2020 Focused Update

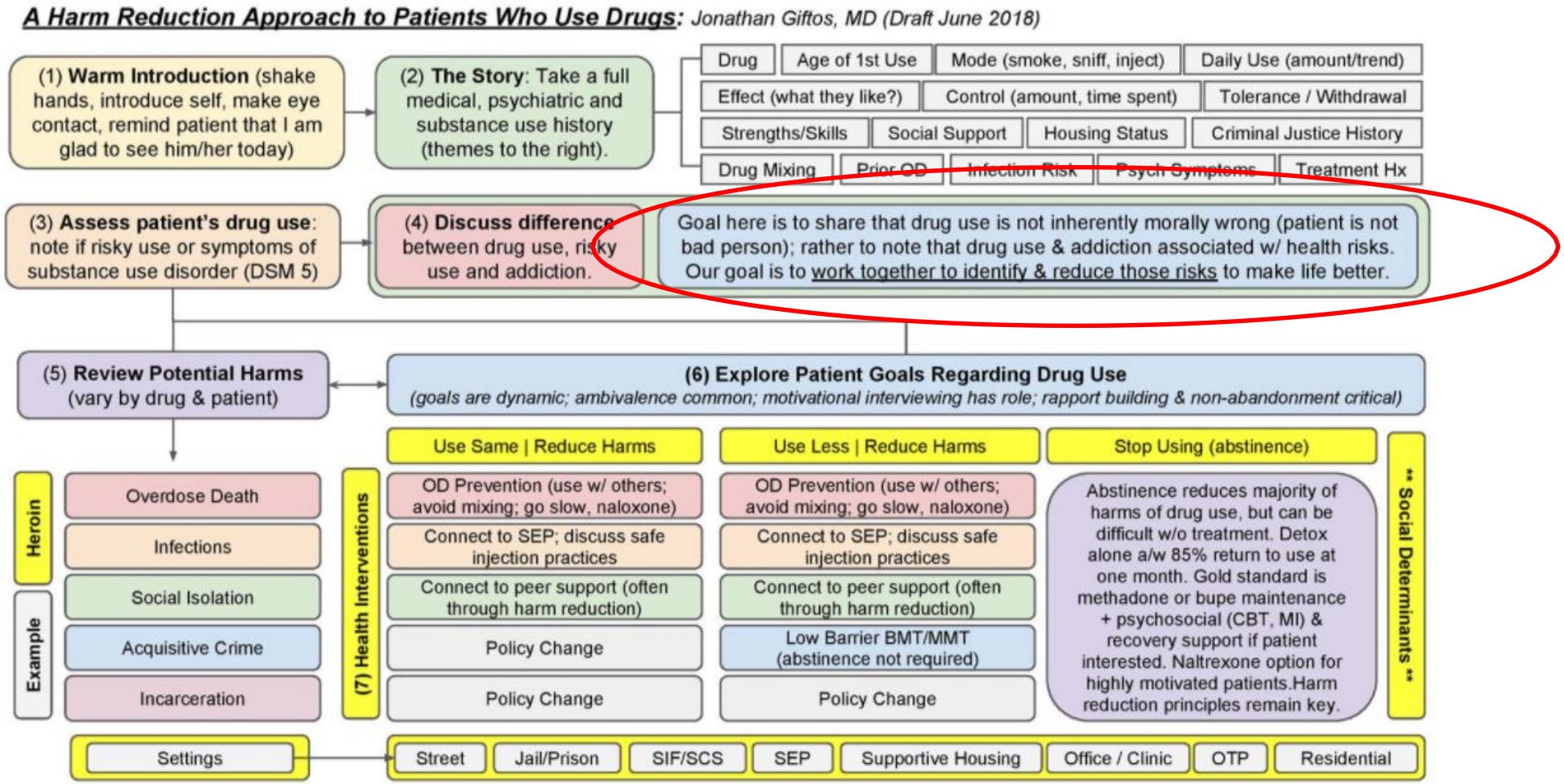
- Start patients on evidence-based medication as soon as possible:
  - Buprenorphine
  - Methadone
  - Naltrexone ER

MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacotherapy, with appropriate medication management.

NEW Comprehensive assessment of the patient is critical for treatment planning. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed soon thereafter.

J Addict Med. Mar/Apr 2020;14(2S Suppl 1):1-91.

Approaching Patients Who Use Drugs



https://www.grepmed.com/images/4692/harmreduction-addiction-algorithm-drugabuse-patients-approach-drugs

Summary

- Amongst the available MOUD in the community-based setting, buprenorphine may be the treatment-of-choice especially for those using HPSOs
- Fentanyl is now a predominant contributor to opioid overdose deaths and methods to address this problem will need continued research
- Getting patients access to MOUD is paramount as that is what reduces mortality from opioid overdose
- A low-barrier approach to providing MOUD utilizing harm reduction is an effective, evidence-based method to starting patients on MOUD

Please Reach Out to US!

Clement Chen: clementc@njms.rutgers.edu

Northern NJ MAT Center of Excellence: coe@njms.rutgers.edu

COE Listserv: bit.ly/coe-listserv
COE Websites: bit.ly/mat-coe AND snjmatcoe.org

24/7 MAT Provider Hotline: 844-HELP OUD

Thank you!
Questions & Discussion