NORTHERN NJ
MAT CENTER OF EXCELLENCE
Coe@njms.rutgers.edu

RUTGERS
New Jersey Medical School

SOUTHERN NJ
MAT CENTER OF EXCELLENCE
Southernnjcoe@rowan.edu

Cooper
University Health Care

RowanMedicine

Rutgers ECHO Series: The Evidence-Based Treatment for Opioid Use Disorder

Friday, October 2nd, 2020

Rutgers ECHO

Clement Chen, PharmD, BCPS

RUTGERS
Robert Wood Johnson
Medical School

State of New Jersey
DHS
Department of
Human
Services

RUTGERS
New Jersey Medical School

Project
ECHO®

Disclosures

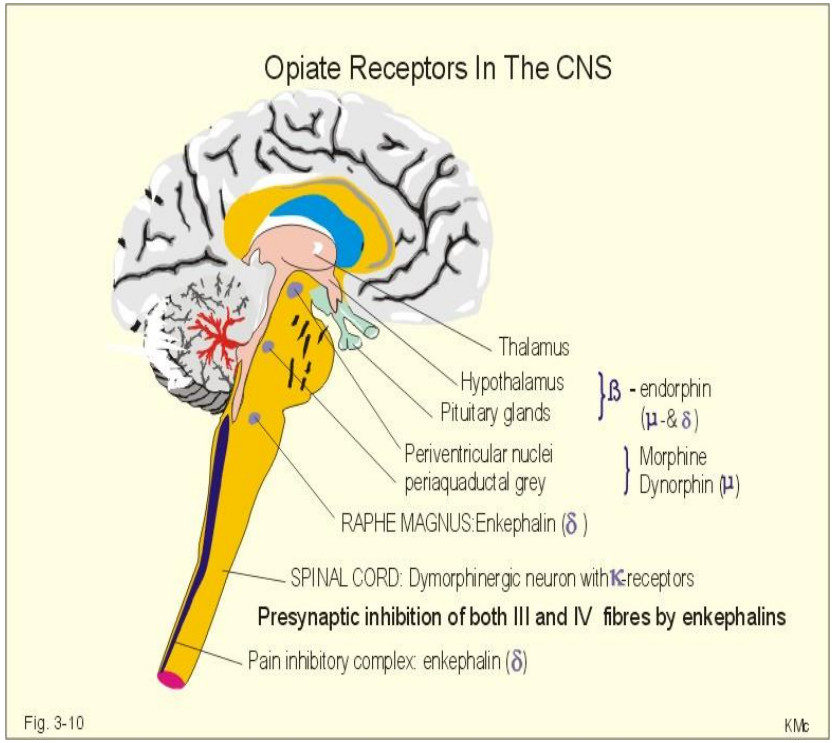
No financial disclosures to report

Objectives

- Review the benefits of medication-assisted treatment (MAT)
- Compare and contrast the types of MAT
- Identify recent evidence in the treatment of opioid use disorder (OUD) with buprenorphine
- Understand what the treatment duration for opioid use disorder should be

Understanding Opioid Use Disorder

- **Chronic, relapsing 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.

- Methadone
- Buprenorphine
- XR-Naltrexone

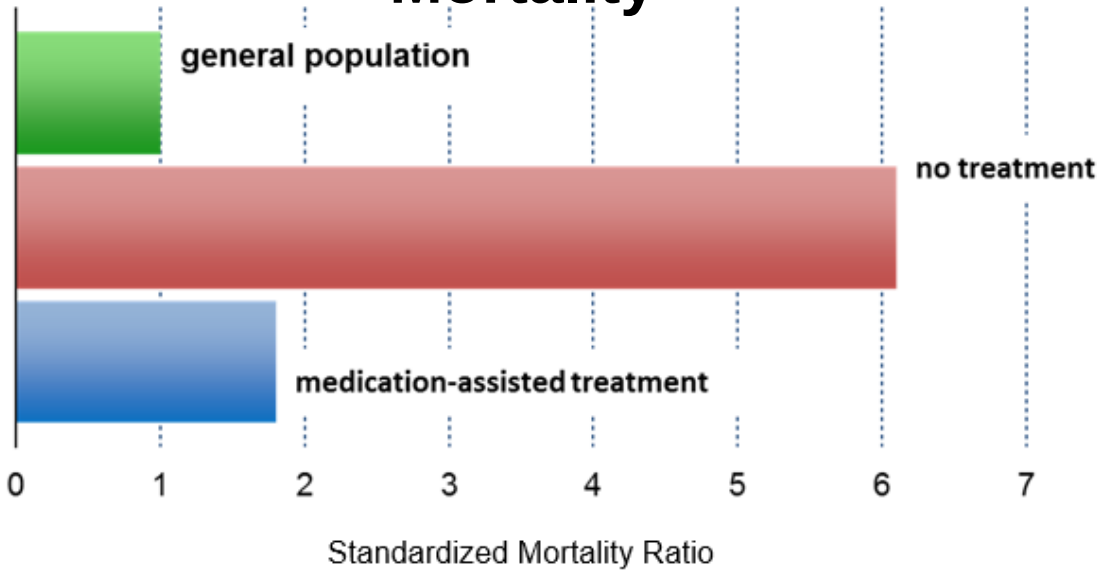
Image from: https://www.samhsa.gov/medication-assisted-treatment

Benefits of MAT

- 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

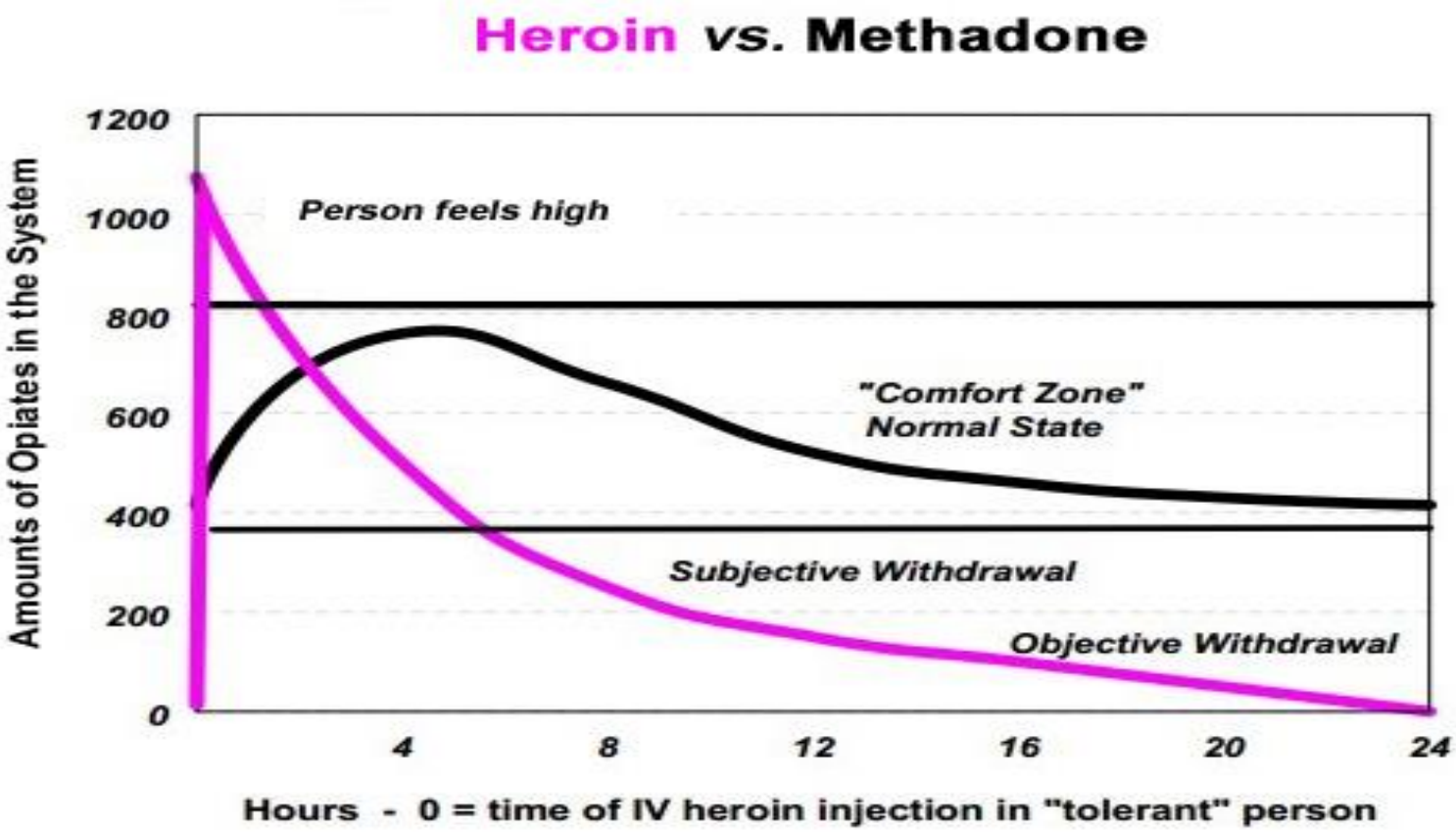
Sordo, et al. *BMJ.* 2017 Apr 26;357:j1550.
Liebschutz JM, et al. *JAMA Intern Med.* 2014 Aug;174(8):1369-76.
D'Onofrio G, et al. *JAMA* Apr 28;313(16):1636-44.

Benefits of MAT: Decreased Mortality

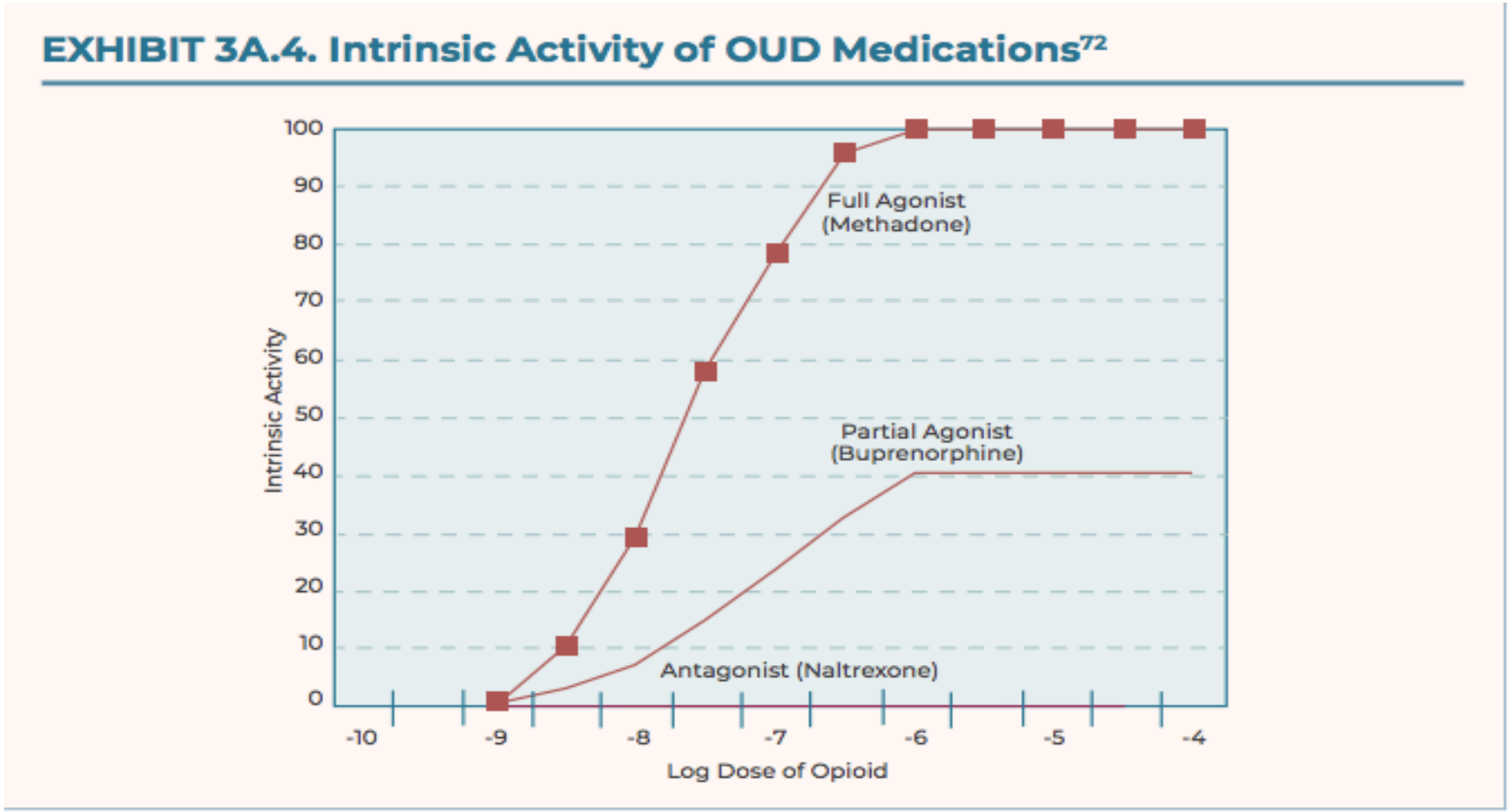


Less than 1/3 of OUD patients ever receive MAT

Why Does MAT Work?



Comparison of Agonist Activity of MAT



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

Methadone

- Full opioid agonist
  - Metabolized via N-demethylation via CYP to inactive metabolites
  - t1/2 = 24-36 hours

- Steady state may take 5 days
  - Peak 2-4 hours after dose
  - Initial dose of 30-40mg daily
  - Maintenance dose of 80-120mg daily

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

- Requires enrollment in opioid treatment program (OTP)

Methadone. Lexicomp online. Wolters Kluwer Health, Inc.

Naltrexone ER Injection

Vivitrol® (naltrexone for extended-release injectable suspension)

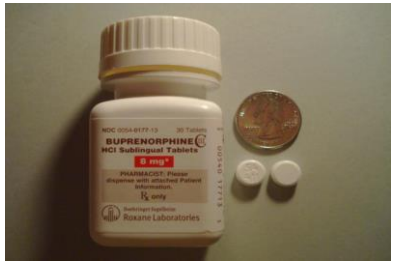
- Full μ-opioid antagonist with high affinity for the opioid receptor
  - Not metabolized by CYP enzymes
- Intramuscular depot formulation to prevent relapse dosed at 380mg monthly
- Requires 7-10 days of opioid-free state
- Shown to reduce return to illicit opioid use, increased treatment retention, and craving vs. placebo

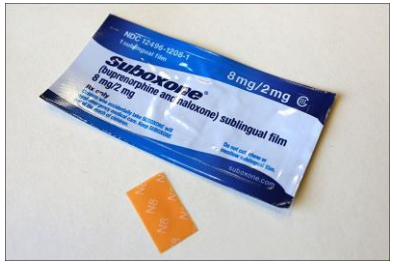
- Population that may benefit most from naltrexone ER
  - After a period of incarceration/inpatient stay
  - Fully motivated

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

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
- 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.

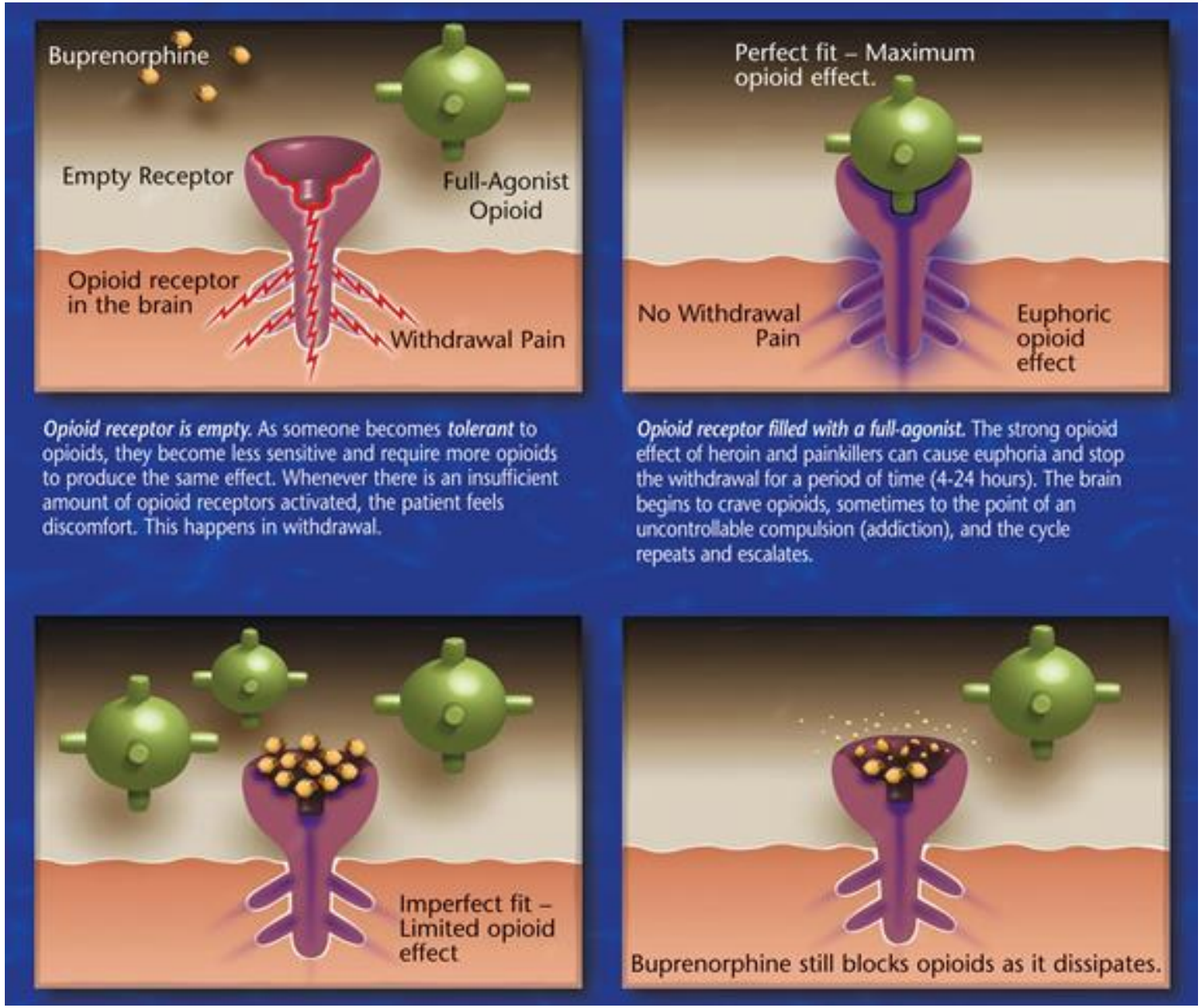
Types of Buprenorphine Approved for OUD

- **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
- **Buccal film (Bunavail®)**
- **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

Buprenorphine SL Traditional Induction

- Start with a dose of 2-4mg of buprenorphine when patient exhibits mild-moderate withdrawal (COWS 6-10)
  - Take 2-4mg every 2 hours as needed for a maximum dose of 8mg on day 1*
- On day 2, take the total daily dose of day 1 and may divide the dose. Patient can take up to a maximum dose of 16mg on day 2.*
- Steady state may take 5-7 days
- *As per PCSS guidance, day 1 and 2 maximum doses are 16mg and 24mg, respectively

SAMHSA. Tip 63. Medications for opioid use disorder. 2018
Casadonte PP, et al. Buprenorphine Induction. Providers' clinical support system for medication assisted treatment, 2013.

Induction with Buprenorphine from Fentanyl

- Concerns about:
  - Lipophilicity of fentanyl with chronic use
  - Protracted renal clearance – mean time of fentanyl/norfentanyl clearance was 7.3 and 13.3 days, respectively

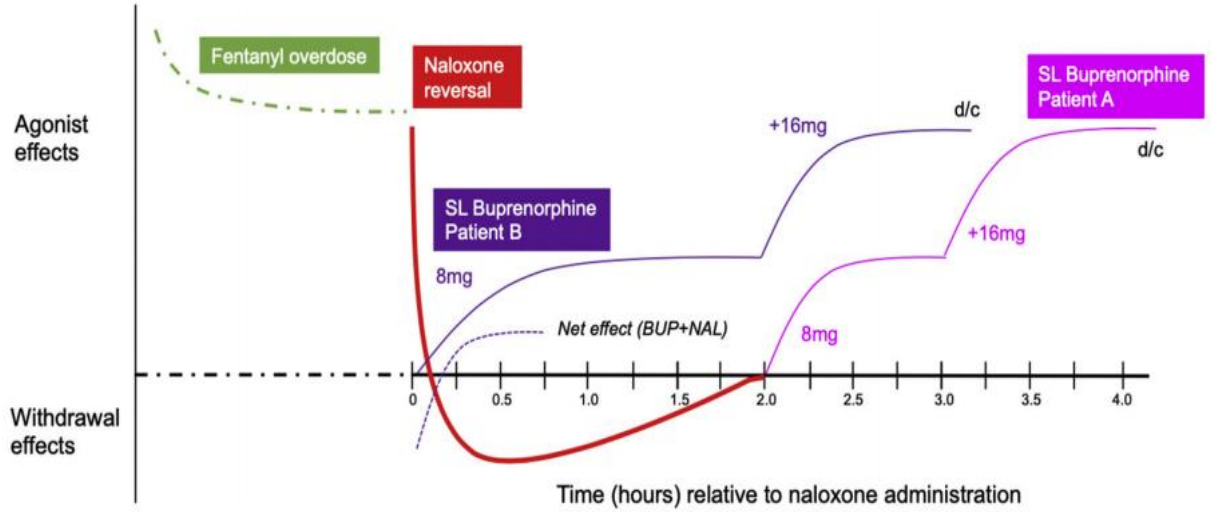
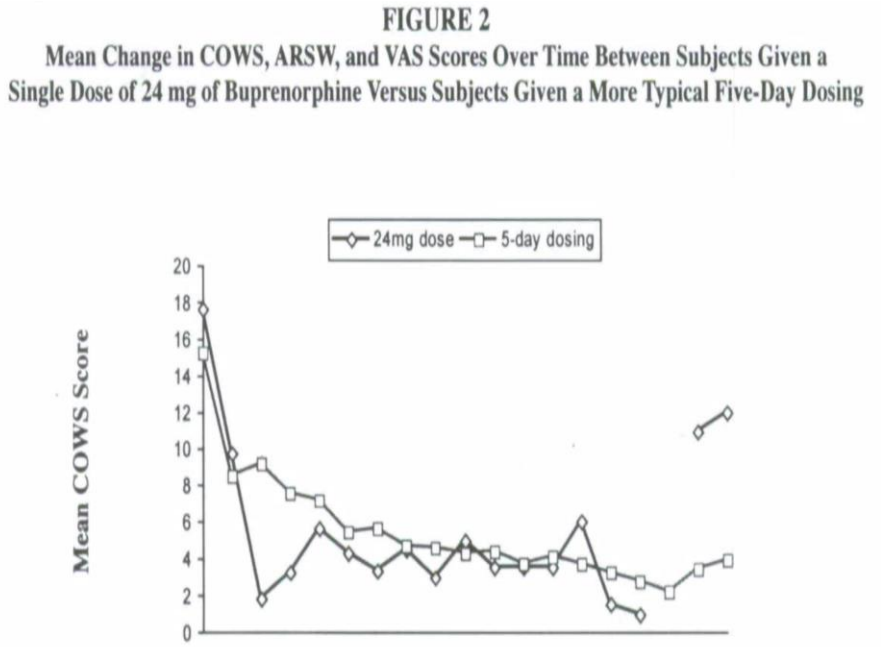


Fig. 3. Hypothesized opioid agonist/withdrawal outcome of ED-based naloxone reversal and buprenorphine administration for patients A and B following fentanyl overdose.

Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

High-Dose Buprenorphine: 24mg SL Dose

- ↑ rapid decrease in symptoms
- Mean COWS = 17.6
  - ↓ < 12
- Precipitated withdrawal was transient (<4 hours) for one patient
- Minimal use of ancillary medications



Ang-Lee K, et al. *J Psychoactive Drugs.* 2006 Dec;38(4):505-12.

Buprenorphine Microdosing

63 year old woman with history of multiple sclerosis and stage 4 decubitus ulcers

Box 1: Outpatient microdosing induction schedule for buprenorphine–naloxone

- Day 1: 0.5 mg once a day
- Day 2: 0.5 mg twice a day
- Day 3: 1 mg twice a day
- Day 4: 2 mg twice a day
- Day 5: 3 mg twice a day
- Day 6: 4 mg twice a day
- Day 7: 12 mg (stop other opioids)

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

Day	Buprenorphine dosage	Methadone dose
1	0.5 mg[a] SL once/day	Full dose
2	0.5 mg[a] SL twice/day	Full dose
3	1 mg SL twice/day	Full dose
4	2 mg SL twice/day	Full dose
5	4 mg SL twice/day	Full dose
6	8 mg SL once/day	Full dose
7	8 mg SL in A.M. and 4 mg SL in P.M.	Full dose
8	12 mg SL/day	Stop

SL = sublingually.
[a]For our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Table 3. Protocol Use in Patient 2

Protocol day	Buprenorphine total daily dose, mg	Methadone total daily dose, mg	Maximum pain score, 0–10
0	0	100	7
1	1.0	100	8
2	1.5	100	6
3	3	100	8
4	6	100	7
5	8	100	8
6	8	100	8
7	12	100	6
8	16	0	6
9	16	0	8
10	20	0	8
11	24	0	6

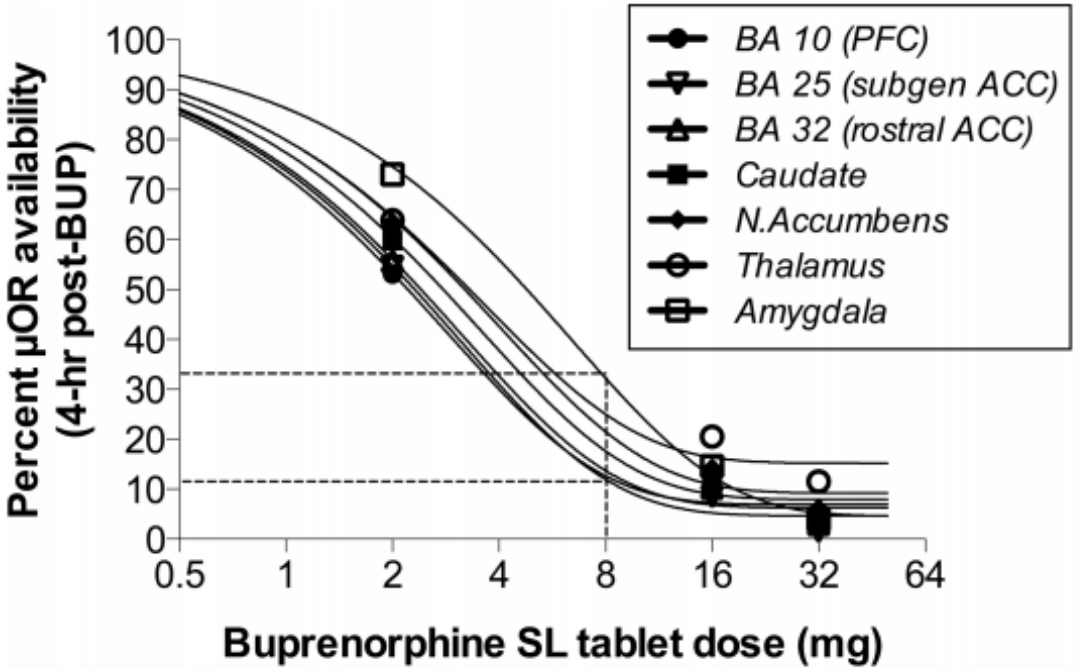
Terasaki, et al. *Pharmacotherapy.* 2019 Oct;39(10):1023-29.

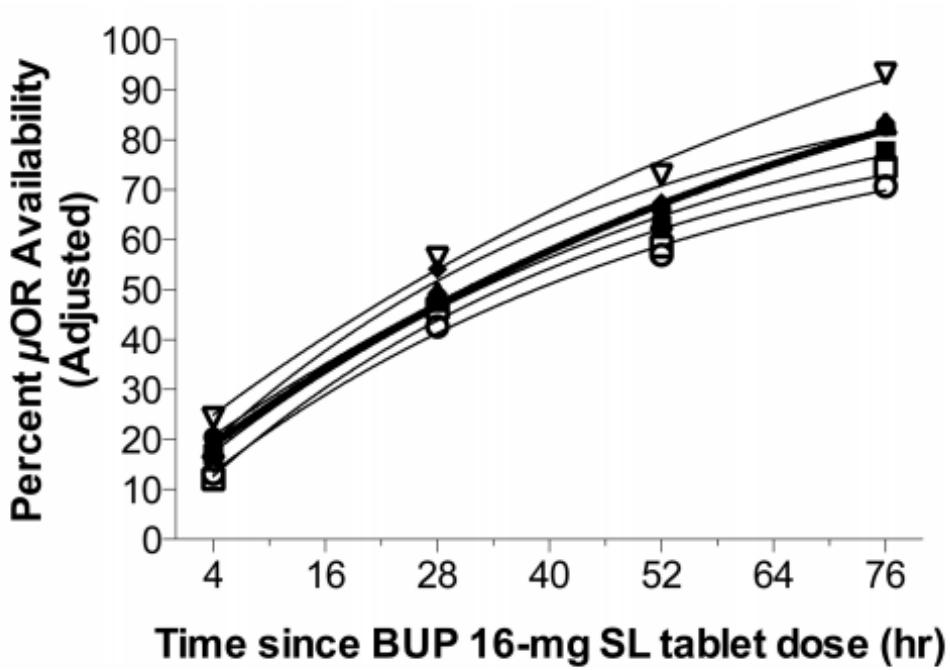
Buprenorphine Dosing – Receptor Availability

Most patients require <20% uOR availability to reduce the reinforcing effects of full opioids

Greenwald et al.

Page 22



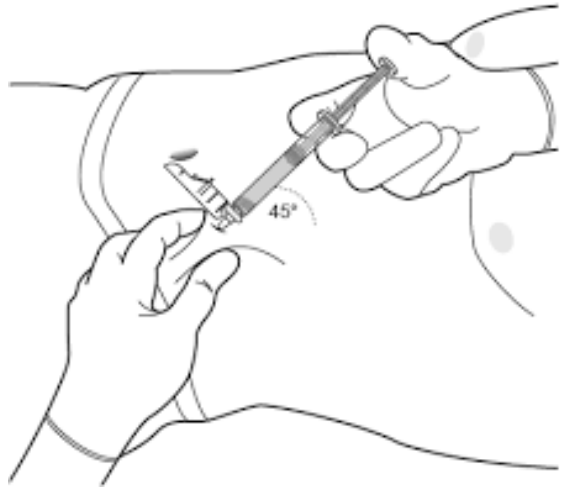


Evidence suggests 16mg/day or more may be more effective than lower doses in reducing illicit opioid use

Greenwald MK, et al. *Drug Alcohol Depend.* 2014 Nov 1;144:1-11.
Mattick RP, et al. *Cochrane Database Syst Rev.* 2014 Feb 6(2):CD002207.

Extended-Release Injectable Buprenorphine

- Prefilled 19-gauge syringe that is refrigerated
- Depot injection
- Dose: Given monthly
  - First 2 months: 300mg SC (1.5 mL)
    - Peak after 24 hours
  - Subsequent months: 100mg SC (0.5 mL)
  - Steady state after 4-6 months from initiation
  - Average concentration: 3-6 ng/mL >> 2-3 ng/mL
- Adverse drug reactions:
  - Injection site reactions, nausea, vomiting, diarrhea



REFERENCES: 1. SUBLOCADE [prescribing information]. North Chesterfield, VA: Indivior Inc.; 2018. **2.** Nasser AF, Greenwald MK, Vince B, et al. Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. *J Clin Psychopharmacol.* 2016;36:18-26.

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

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 for at least a week
  - 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 highly potent synthetic opioids
  - Maintain appropriate levels (less variation) of buprenorphine on mu-receptors

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

Buprenorphine Treatment Duration

- There is no evidence and no defined time limit for treating OUD
  - Consider other diseases and their treatment.
- Studies show low rate of remaining abstinent when buprenorphine is tapered
  - Evidence of neurobiological disease vs. disease of “moral failing”
- Presence of a protracted withdrawal syndrome
  - Cravings
  - Irritability/anxiety
  - Presence of a dysphoric state or depression
  - Trouble sleeping
  - Anhedonia
  - Reduced control of executive functions

Bentzley BS, et al. *J Subst Abuse Treat.* 2015 May;52:48-57.
Weiss, RD, et al. *Arch Gen Psychiatry.* 2011 Dec;68(12):1238-46.

Summary of MAT Therapy

	Buprenorphine	Methadone	Extended-Release Naltrexone
Mechanism	Mu-opioid receptor partial agonist	Mu-opioid receptor full agonist	Mu-opioid receptor antagonist
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	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?	Patients with low “hedonic tone” / concurrent psychiatric comorbidities?	Patients with concurrent OUD and chronic pain	Patients who have undergone a period of detoxification

Reference: SAMHSA Tip 63. Medications for Opioid Use Disorder

Evidence-Based Treatment for OUD

- Comprehensive assessment of the patient is critical for treatment planning but the completion of all assessments should not delay or preclude initiating MAT
- The use of benzodiazepines and other sedative-hypnotics should NOT be a reason to withhold or suspend treatment with MAT
- A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay MAT
- Detox is NOT a treatment method of OUD without ongoing maintenance treatment for OUD.

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