# Pharmacotherapy for Opioid Use Disorder (OUD)

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12/16/19; 12pm-1pm

NJ Centers of Excellence – Learning Collaborative

# MAT NJ Centers of Excellence Contact Information

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PLEASE DIRECT ALL FEEDBACK FOR THE PRESENTATION TO COE@NJMS.RUTGERS.EDU. ALL FEEDBACK IS GREATLY APPRECIATED.

# Objectives

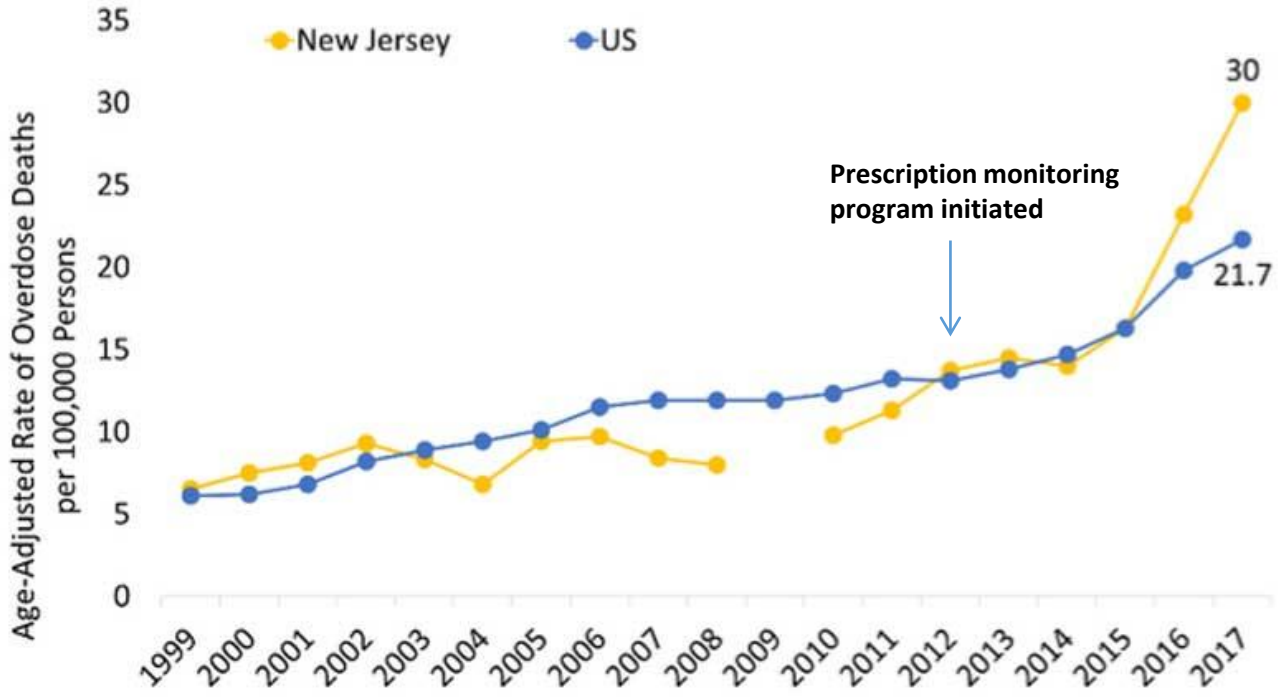
- Review mortality data of the opioid crisis in New Jersey
- Review basic neurobiology of the addicted brain
- Provide an overview of medication-assisted treatment for OUD
- Discuss the evidence, pearls, and literature concerning MAT
- Identify adjunctive treatment for opioid withdrawal
- Identify potential future therapies for OUD

# Mortality of OUD in New Jersey and Review of Neurobiology of OUD

# Mortality in New Jersey

- Drug overdose deaths increased 29.3% from 2016 to 2017
- Opioids account for over 50% of deaths
- In 2018, Essex County had highest number of drug overdose deaths
  - About 12% of approximately 3,100 deaths
- 37% of adults in Essex county who required treatment for a substance use disorder were unable to access care

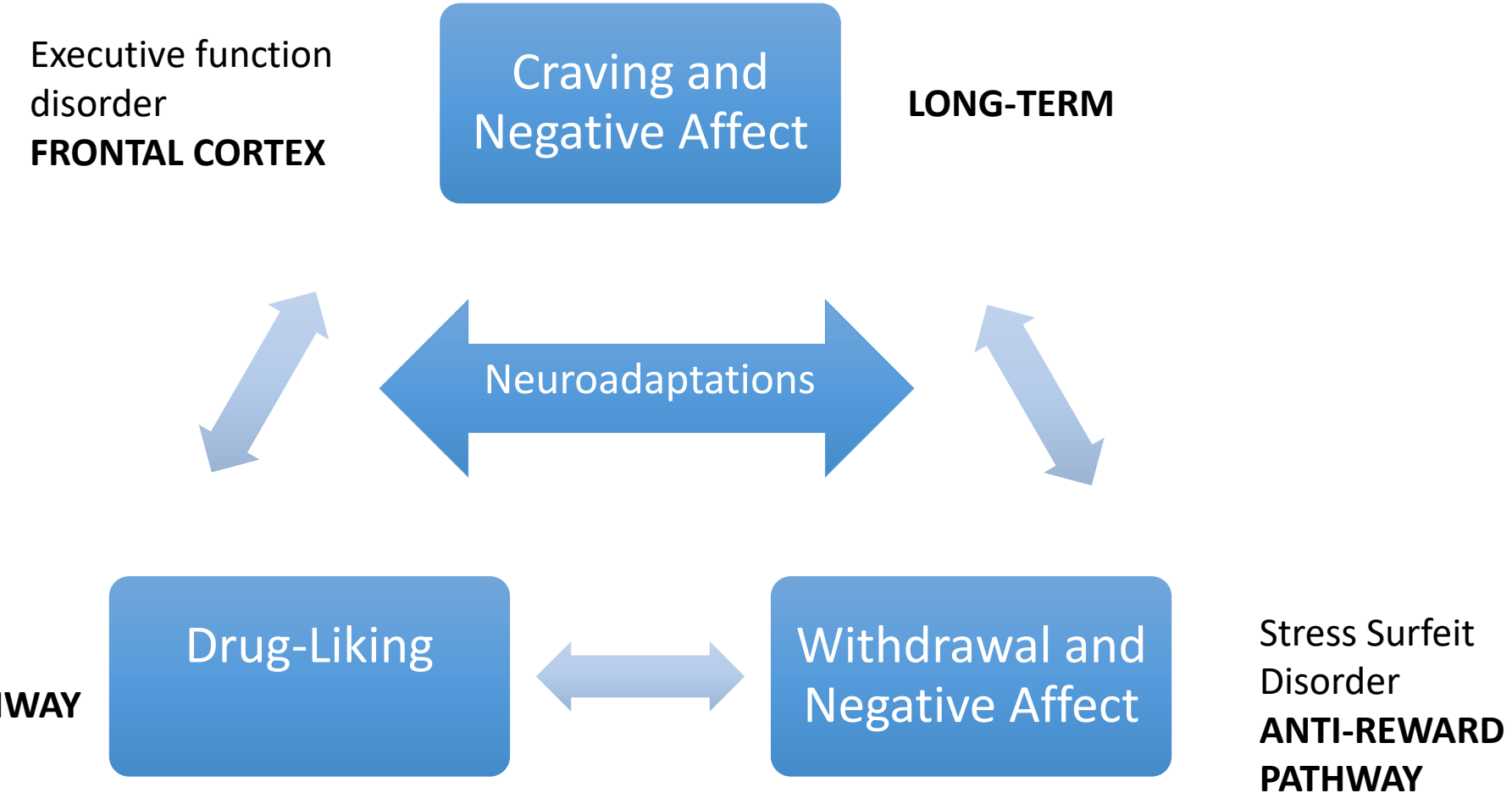
Drug Overdose Deaths, Rate per 100,000 Persons




Scholl L, et al. MMWR Morbidity and Mortality Weekly Report 2019;67:1419–1427

Department of Health, Division of Mental Health and Addiction Services, Office of Planning, Research, Evaluation and Prevention. *New Jersey Drug and Alcohol Abuse Treatment Substance Abuse Overview 2017 Essex County*. Trenton, New Jersey; 2018.

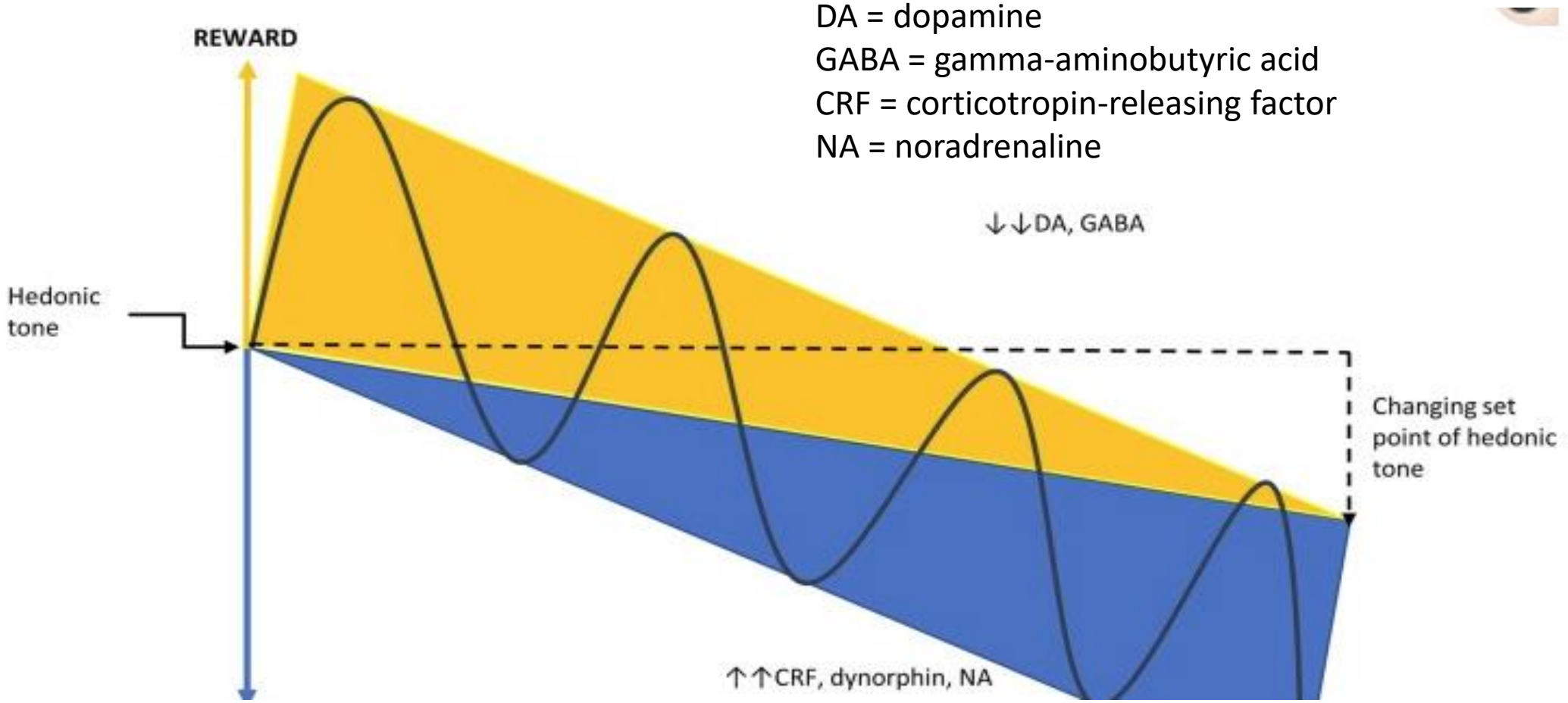
# Addiction Neuroadaptation




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

# Hedonic Tone

DA = dopamine
GABA = gamma-aminobutyric acid
CRF = corticotropin-releasing factor
NA = noradrenaline




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.

# MAT Pharmacology and Treatment Considerations

# Opioid Receptor Subtypes

- Share common analgesic effect on brain circuitry
  - Distributed in the brain, spinal cord, skin, GI tract

| | Mu-Receptor | Kappa-Receptor | Delta-Receptor |
|---|---|---|---|
| Location | Cerebral cortex, nucleus accumbens | Hypothalamus | Basal ganglia |
| Physiologic Response | Stimulates euphoria | Stimulates dysphoria and sedation | Induces anxiolytic effects |
| Implications in OUD | Responsible for the homeostasis of the reward system | May promote relapse via CRF signaling and depressant effects | Increases levels of anxiety that may lead to relapse |

Wang S. *Cell Transplant.* 2019 Mar;28(3):233-38.

# Overview of MAT

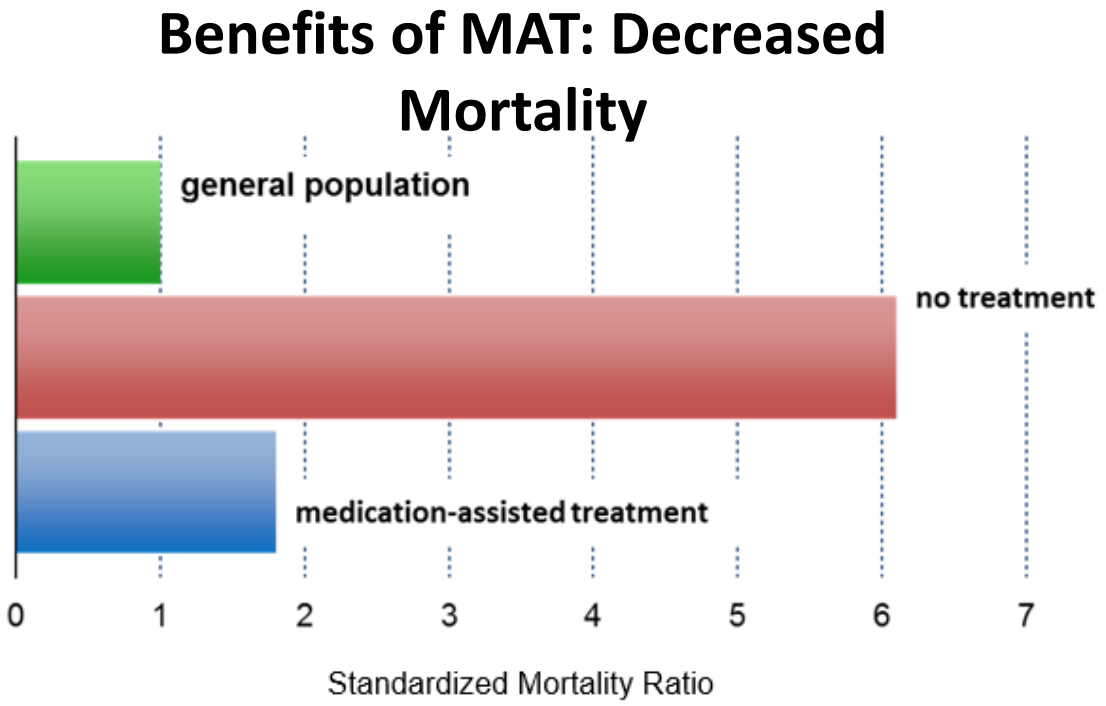

- Shown to reduce substantial risk for all-cause and overdose mortality by 66% when patients retain in treatment with methadone
  - Meta-analysis of 19 cohorts of following ~123,000 people
- Has shown to improve **treatment follow-up and retention** among those started from an inpatient stay or emergency department to the outpatient.
  - Liebschutz, JM, et al RCT of 145 opioid-dependent patients
  - D'Onofrio G, et al – RCT of 329 opioid-dependent patients
  - ⬇ in reduced self-reported illicit opioid use
  - ⬇ use of inpatient addiction treatment services
- Studies ongoing to demonstrate treatment retention of MAT from prisons to outpatient

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.

RCT = randomized clinical trial

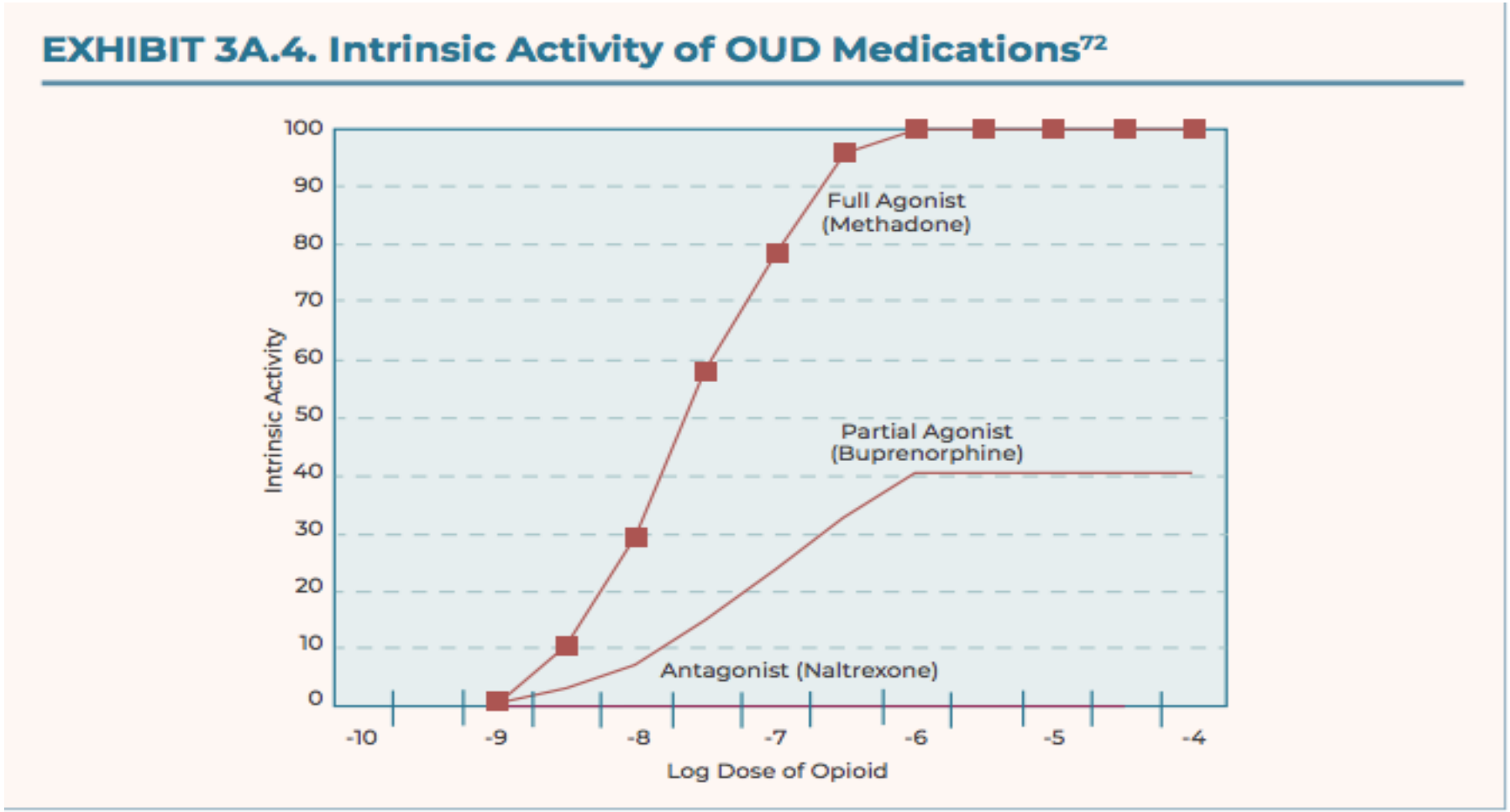
# Benefits of MAT

- 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.

# Comparison of Agonist Activity of MAT




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

# Methadone

- Full opioid agonist with variable pharmacokinetics
  - Metabolized via N-demethylation via CYP3A4, 2D6, 2B6, 2C9, 2C10, etc to inactive metabolites
  - t1/2 = 24-36 hours
- Effects may not realized until approximately 5 days of therapy
  - Initial dose of 30-40mg daily
  - Maintenance dose of 80-120mg daily
- Risk for QTc prolongation and mortality when dose exceeds tolerance
- Most evidence for MAT is from methadone
- Requires enrollment in opioid treatment program (OTP)

Methadone. Lexicomp online. Wolters Kluwer Health, Inc.

# Naltrexone ER (Vivitrol®)


- No special certification needed to prescribed
- Full μ-opioid antagonist with high affinity for the opioid receptor
  - Not metabolized by CYP enzymes
- Intramuscular depot formulation to prevent relapse particularly after detox
- 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?
- Risk of hepatotoxicity?

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 = 24-60 hours
  - Inhibited by 3A4 primarily – no major clinically significant interactions
- *Has a ceiling effect that reduces risk of respiratory depression and euphoria with greater doses
- *Initiate when patient develops period of moderate withdrawal symptoms
- Thomas CP, et al.
  - Buprenorphine is associated with improved outcomes compared to placebo in individuals and **pregnant patients** with OUD


1. Buprenorphine. Lexicomp online. Wolters Kluwer Health, Inc.
2. 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 General Dosing

- Start with a dose of 2-4mg of buprenorphine when patient exhibits mild-moderate withdrawal
  - Take 2-4mg every 2 hours as needed for a maximum dose of 16mg 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 24mg on day 2.

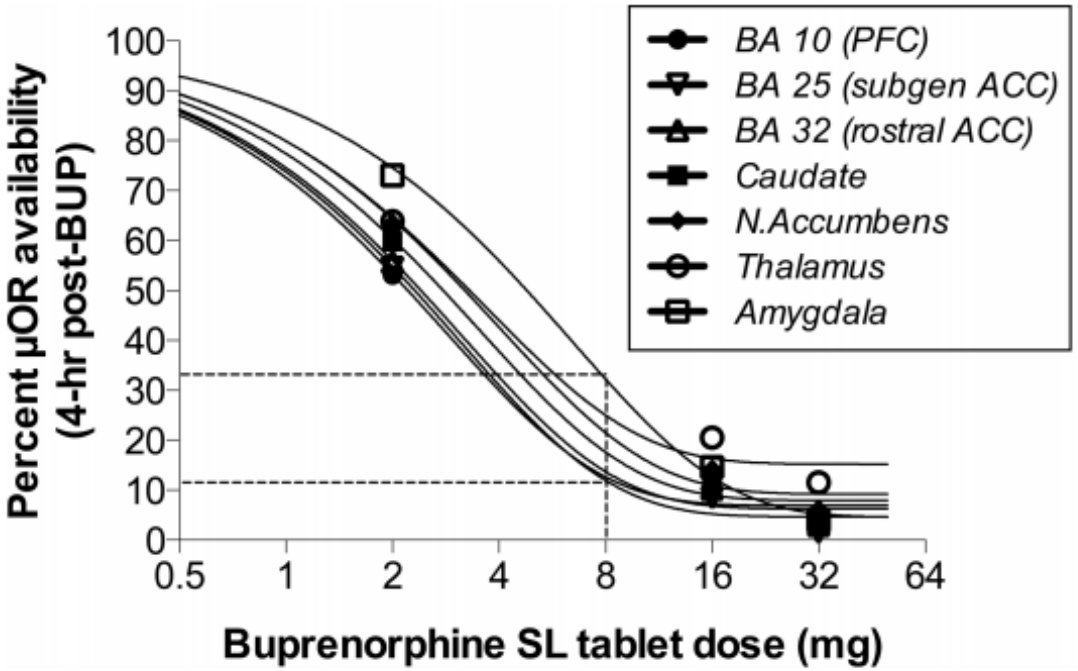
- Steady state may take 5-7 days

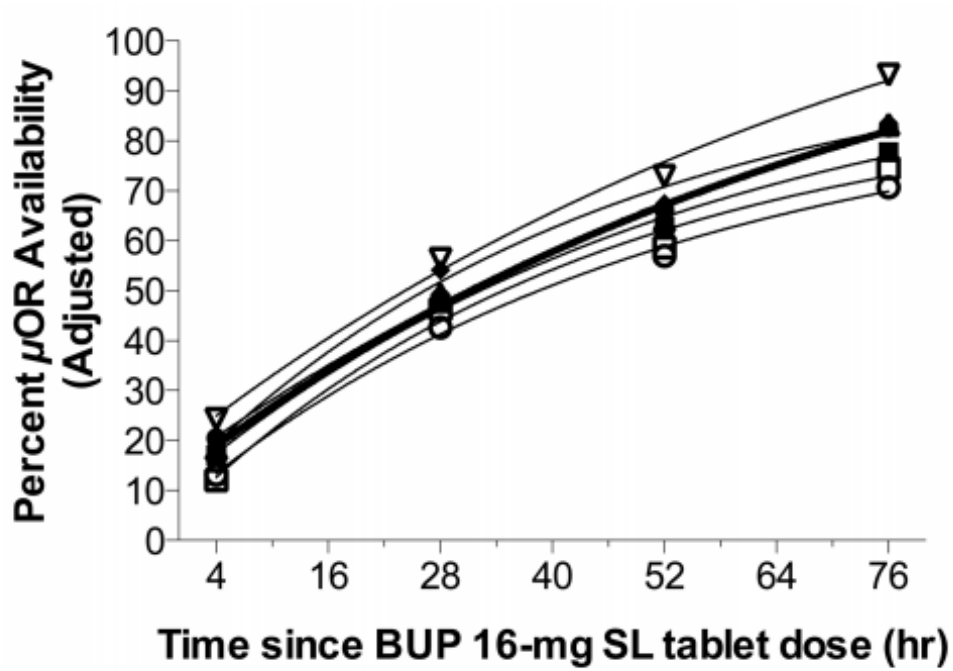
SAMHSA. Tip 63. Medications for opioid use disorder. 2018

# Buprenorphine Dosing – Ceiling Effect

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






Greenwald MK, et al. *Drug Alcohol Depend.* 2014 Nov 1;144:1-11.

# 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

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.

# Buprenorphine Microdosing

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

**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.

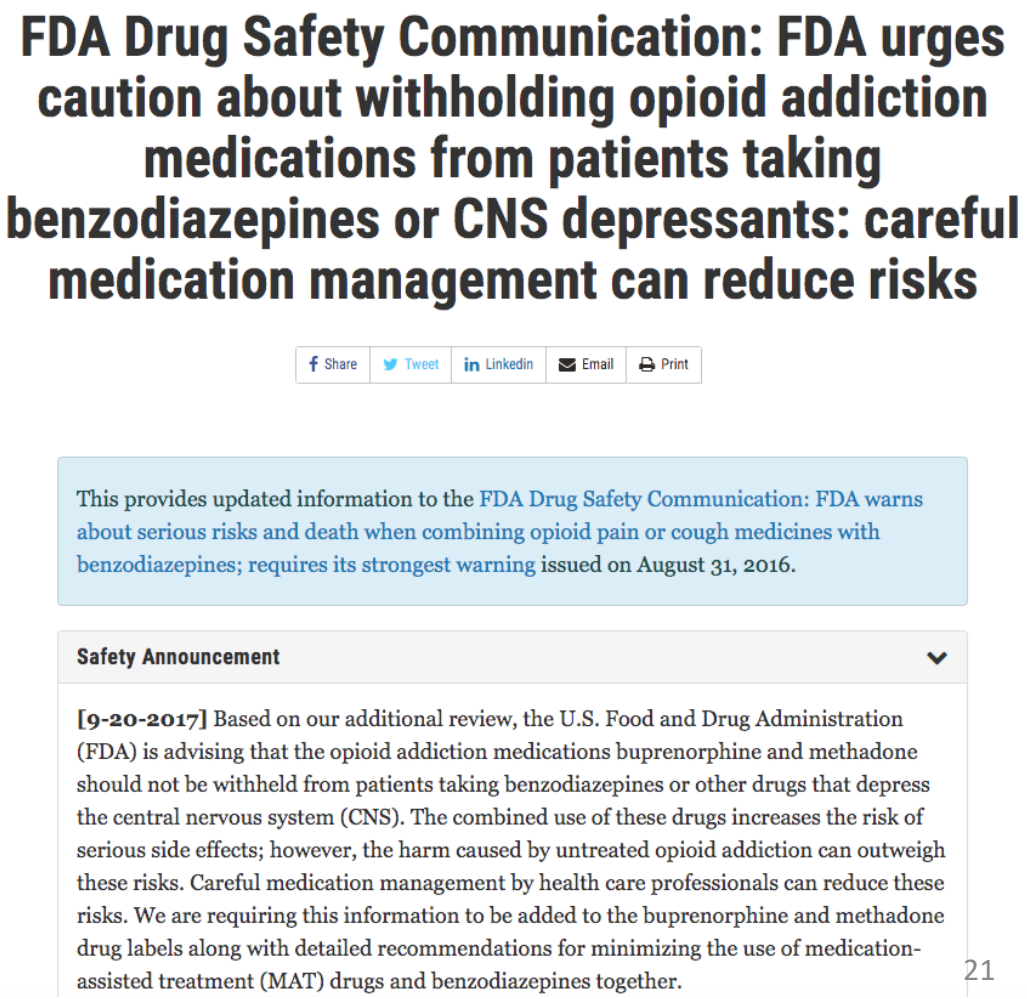
**Table 3. Protocol Use in Patient 2**

| 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.

# Are There Contraindications to MAT Therapy with Buprenorphine and Naltrexone?

- Generally, benefits >> risk – start low, go slow!
  - Pregnancy
  - Severe liver disease
  - Concurrent benzodiazepines and CNS depressants
- Concerns with treatment of acute pain on MAT



**FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks**

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This provides updated information to the FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning issued on August 31, 2016.

**Safety Announcement**

**[9-20-2017]** Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. We are requiring this information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.

# Approach to treatment of Acute Pain in OUD

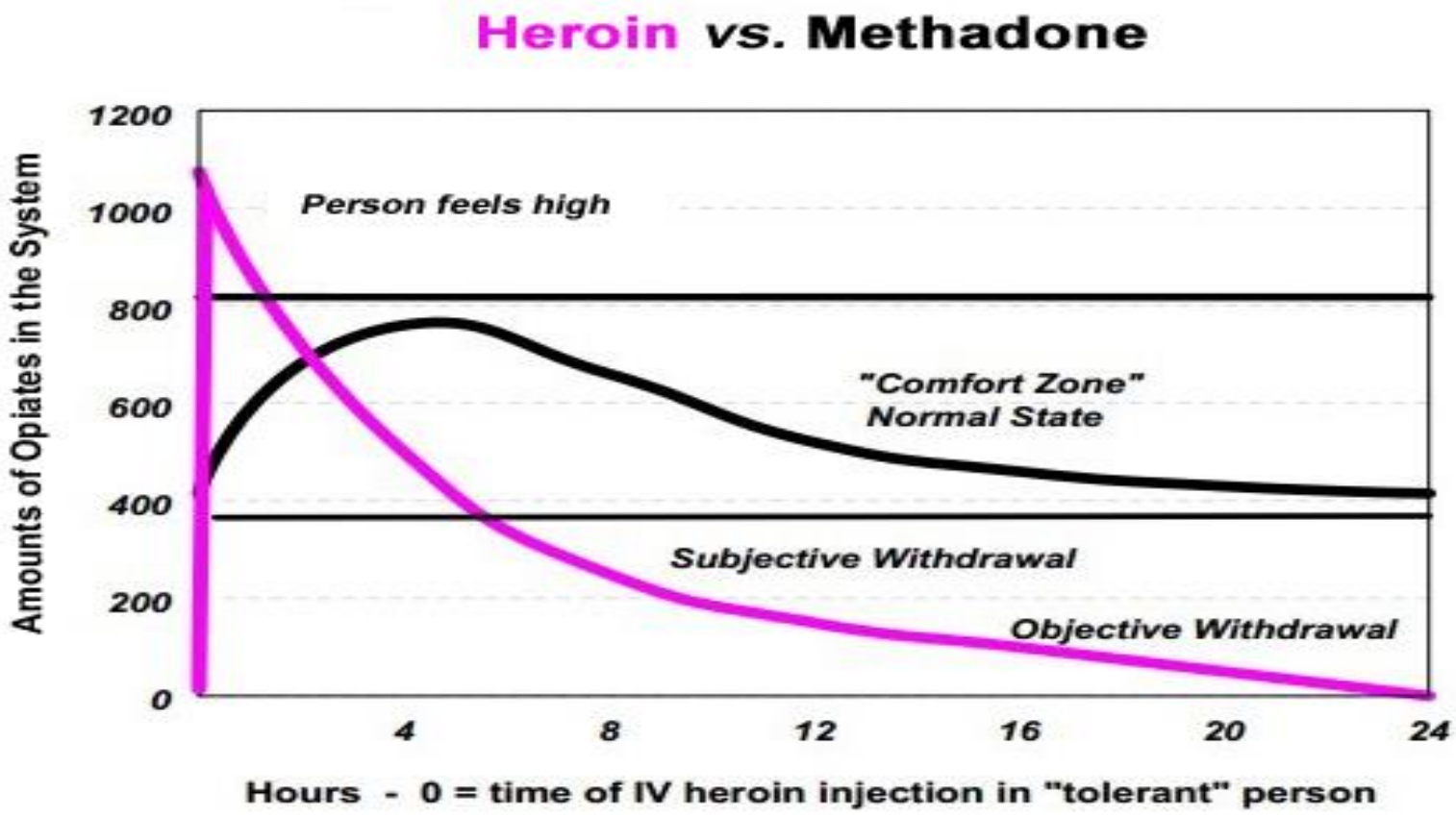
- First-line: non-opioids → NSAIDs, APAP, topicals
- Dividing buprenorphine dose every 6-8 hours to potentiate analgesic effect
- Use opioids for shortest amount of time of 3-7 days
- Buprenorphine generally continued even during peri-operative period
  - 12mg dose or less due to receptor availability

Quaye, et al. *Pain Medicine*. 2019;20(7):1395-1408.

# Summary of MAT Therapy

| | Buprenorphine | Methadone | Naltrexone ER |
|---|---|---|---|
| **Key Pharmacodynamic Property** | Partial μ - agonist<br>Kappa - antagonist<br>Delta - antagonist | Full μ - agonist | Full μ - antagonist |
| **Clinical Pearls** | Low risk of overdose and respiratory depression – "Ceiling Effect" | 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 better candidate?** | Patients with low "hedonic tone" / concurrent psychiatric comorbidities? | Patients with concurrent OUD and chronic pain | Patients who have undergone a period of detoxification |
| **ALL ARE EFFECTIVE FOR REDUCING RISK OF RELAPSE** | | | |

# So Why Does MAT Work?



# Adjunctive Therapies for Opioid Withdrawal

| Withdrawal Symptom | Therapy Options |
|---|---|
| Diarrhea | Loperamide |
| Nausea | Ondansetron, Metoclopramide |
| Anxiety, irritability, Diaphoresis | Clonidine → Lofexidine (Lucemyra®)* |
| Insomnia | Diphenhydramine, Trazodone |
| Pain | APAP/ NSAIDs |

*α-2 agonist blocking stress-induced response at doses lower than the starting dose

Clinical Resource, *Treatment of Opioid Withdrawal. Pharmacist's Letter/Prescriber's Letter.* August 2018

# Future of OUD

# Limitations of Current Therapy

- Continued
  - Stigma and access issues
    - “War on Drugs”
  - Federal laws concerning administration of MAT
  - Rigidity of prescription dosing vs. reality
  - Cravings
    - New targets in therapy?
  - Presence of protracted withdrawal despite long-term MAT

# Potential Future Therapy

- Use of cannabinoids
  - Located in the VTA, nucleus accumbens, and PFC
  - Shown to reduce use of opioids – definite synergy with opioids
  - Possible use as a harm reduction tool as an adjunct?
  - NJ addition of cannabis in OUD treatment protocol
- Targeting the glutamatergic pathway
- Targeting the CRF and cortisol pathway to further restore the HPA axis

HPA = Hypothalamic-Pituitary-Adrenal

Wiese B, et al. *Cannabis Cannabinoid Res.* 2018 Sep 1;3(1):179-89.
Kakko J, et al. *Front Psychiatry.* 2019 Aug 30:10:592.

# Conclusions

- MAT helps neurological recovery and reduces risk of addictive behaviors
- MAT has been shown to reduce risk of opioid overdose and death
- Most evidence for MAT has been with methadone but there has been a greater shift with buprenorphine and naltrexone
- Guidance is available to help prescribers with treating OUD patients
  - NJ Centers of Excellence are working on a manual
  - SAMSHA Tip Sheets (Tip 63)
  - ASAM National Guidelines
  - Provider Clinical Support System – www.pccsnow.org

# Questions?

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