Primary Care Approach to Treating Substance Use Disorders—a Webinar Series from the Montana Primary Care Association

- Session 3, February 20, 2024
- Buprenorphine Initiation and Maintenance
- Daniel A. Nauts, MD, FASAM
- CME approved by the American Society of Addiction Medicine (ASAM)

Disclosure information

Primary Care Approach to Treating SUD

February 20, 2024, Session 3,
Buprenorphine Initiation and Maintenance

Daniel A. Nauts, MD, FASAM

- No disclosures

"Strong scientific evidence unequivocally shows that for opioid use disorder, medication is the essential component of treatment, not merely one component. Despite this settled knowledge, some vocal constituents within the addiction treatment community and some policy makers continue to lobby for treatment of opioid use disorder without medication."

Andrew Saxon, Elinore McCance-Katz, Journal Addiction Med, May/June 2016

Receipt of opioid use disorder treatments prior to fatal overdoses and comparison to no treatment in Connecticut,2016-2017

HEIMER, ET AL, DRUG AND ALCOHOL DEPENDENCE 254 (2024) 111040

Medication vs. Non-medication Treatment

- Relative risk is reduced following exposure to MOUD treatment, even if treatment was not continued.
- Exposure to non-MOUD treatment provided no protection against fatal opioid poisoning.
- To reduce overdose deaths access to agonist-based treatment needs to expand.
- This is unlikely to succeed if access to non-MOUD treatment is made more available through misappropriation of opioid settlement dollars to non-evidence based intensive outpatient and residential treatment.
  - Heimer, R., et al, Drug and Alcohol Dependence 254 (2024) 111040

MEDICATIONS are the MOST EFFECTIVE Treatment for OUD

- **Opioid use disorder does not respond to the same treatments as alcohol use disorder**.
- **Non-medication therapies generally DO NOT WORK**: ~80 – 90+% annual relapse rate. Incarceration with forced abstinence, also does not work. Both increase the risk of lethal overdose post-discharge. Only 28% of residential programs provide MOUD.
- Twelve Step programs alone, without medications have a LOW rate of patient retention and sobriety at one year, when treating OUD (possibly <10%).*
- Retention rates in MOUD programs vary broadly, dependent upon multiple factors, with 1 year recovery of ~10 to 80%, but average ~40-50%.

Kakko, 2003

*Poor data collection from most of these programs.

Initial Assessment

- Key point: An extensive assessment is not necessary.
- NYS Best Practices:
  - Assess enough of the patient's history to establish a diagnosis of moderate to severe OUD, other substance use of relevance, e.g., alcohol, benzodiazepines, stimulants, and xylazine, history of treatment, and significant medical and psychiatric history and current acuity.
  - Conduct a focused physical examination.
  - Order relevant laboratory tests—results are not required to initiate prescribing.
  - Review PDMP
  - Initiate treatment.
    - NYS Department of Health

DSM5 interview

1. Have you found that when you started using, you ended up using more than you intended to?

2. Have you wanted to stop or cut down on using opioids?

3. Have you spent a lot of time getting or using opioids?

4. Have you had a strong desire or craving to use opioids?

5. Have you missed work or school or often arrived late because you were intoxicated, high or recovering from the night before?

6. Has your use of opioids caused problems with other people such as with family members, friends, or people at work?

7. Have you had to give up or spend less time working, enjoying hobbies, or being with others because of your opioid use?

DSM5 interview

8. Have you ever gotten high before doing something that requires coordination or concentration like driving, boating, hunting, climbing a ladder, or operating heavy machinery?

9. Have you continued to use even though you knew that the opioid caused overdoses, infections, and emotional problems such as depression, anxiety, agitation, and irritability?

10. Have you found you need to use much more drug to get the same effect that you did when you first started using it?

11. When you reduced or stopped using, did you have withdrawal symptoms or felt “dope sick” when you cut down or stopped using?

Mild=2-3, moderate=4-5, severe=6 or more. 1 point for each yes.

MOUD AND OPIOID MORTALITY 17,568 OD SURVIVORS

Decrease in opioid related mortality

- ***59% methadone***
- ***38% buprenorphine***
- ***Both meds associated with a decrease in all cause mortality***

No association found between Naltrexone and mortality!

Marc Larochelle, Annals of Internal Med, Aug 2018

INFORMED CONSENT—OPTIONS FOR MOUD

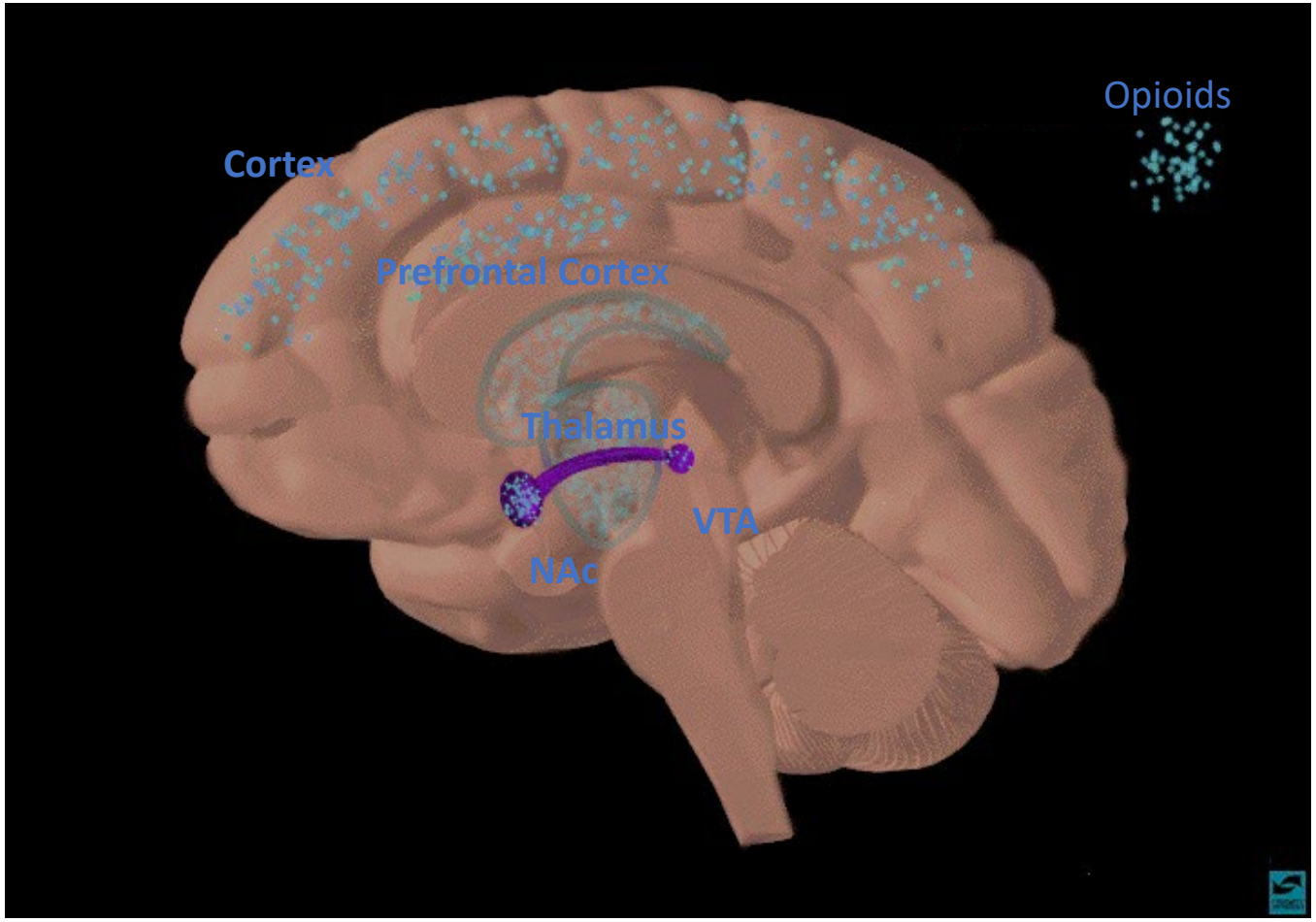
Methadone

Buprenorphine

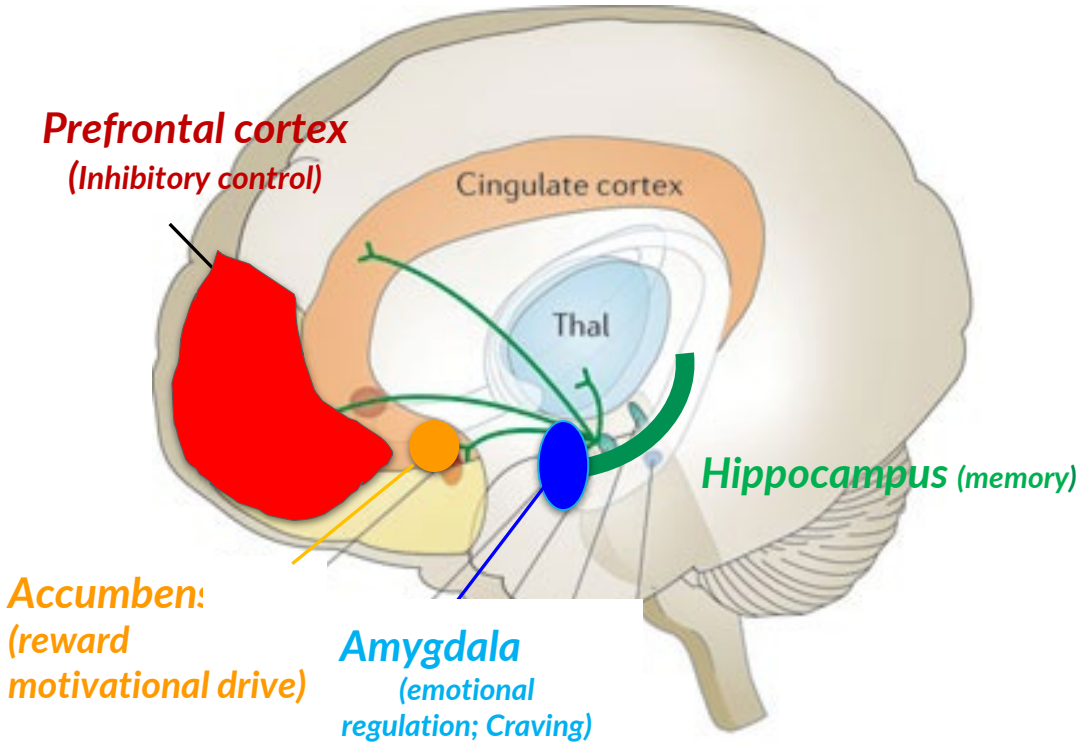
Naltrexone-XR

Non-medication treatment

Opioid Binding



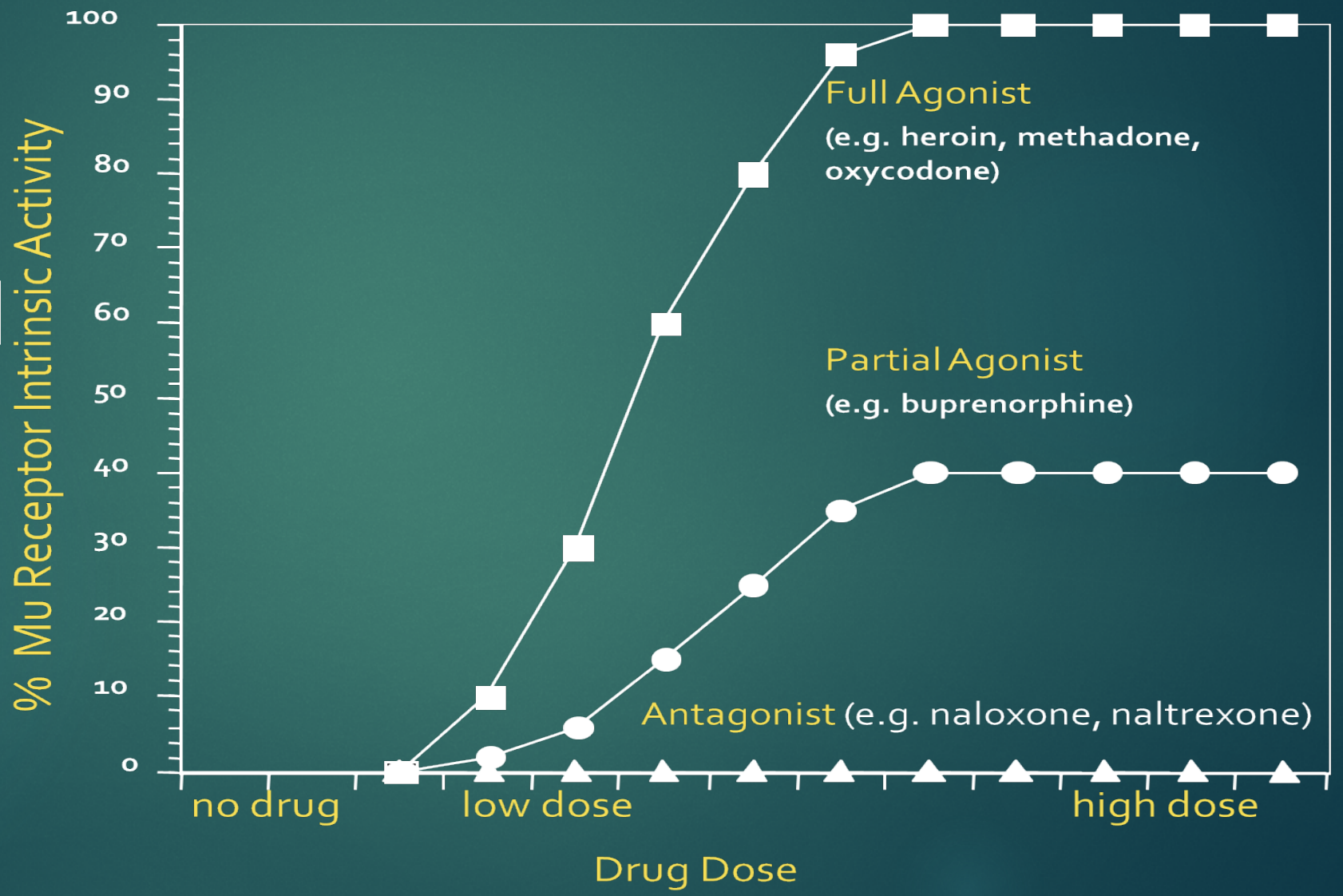
NIDA, 2017



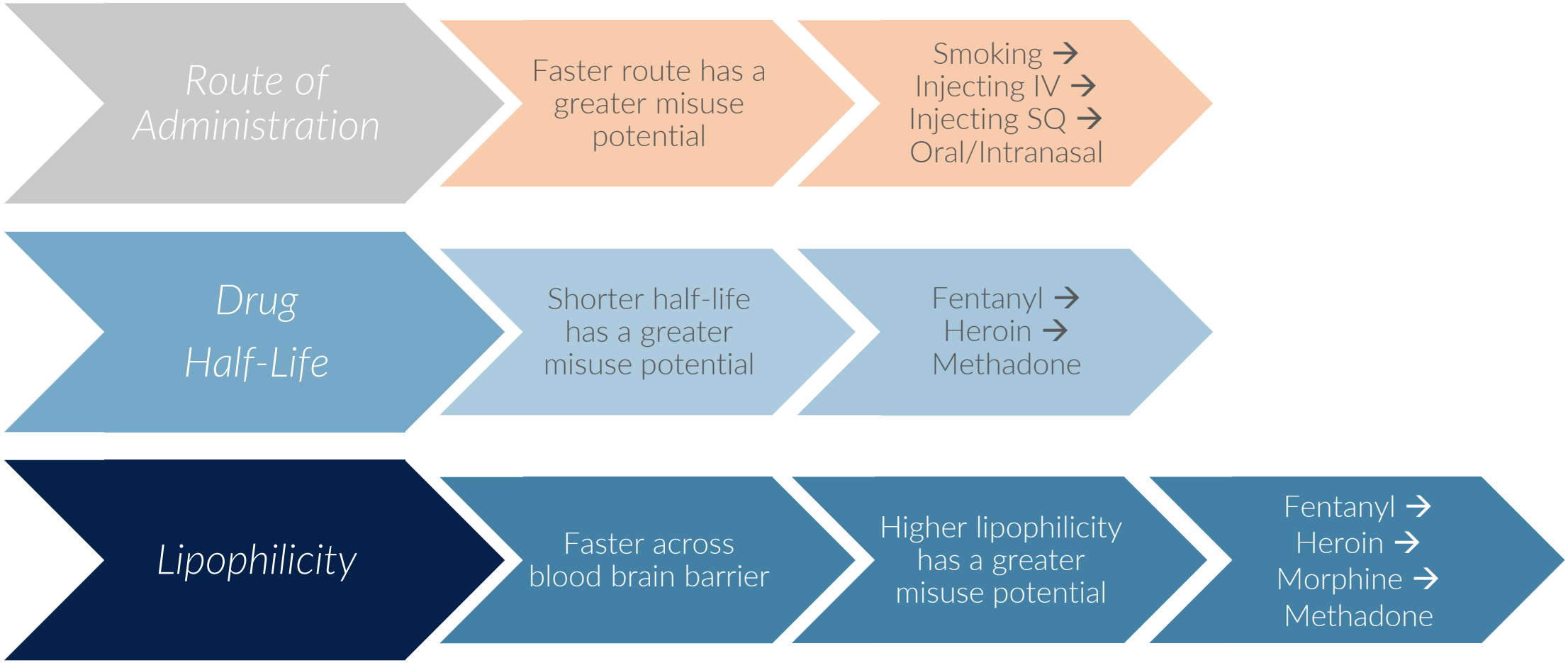
- *Inhibitory control*
- *Increase reward drive*
- *Craving*
- *Drug memories*

Source: Yasmin Hurd, PhD

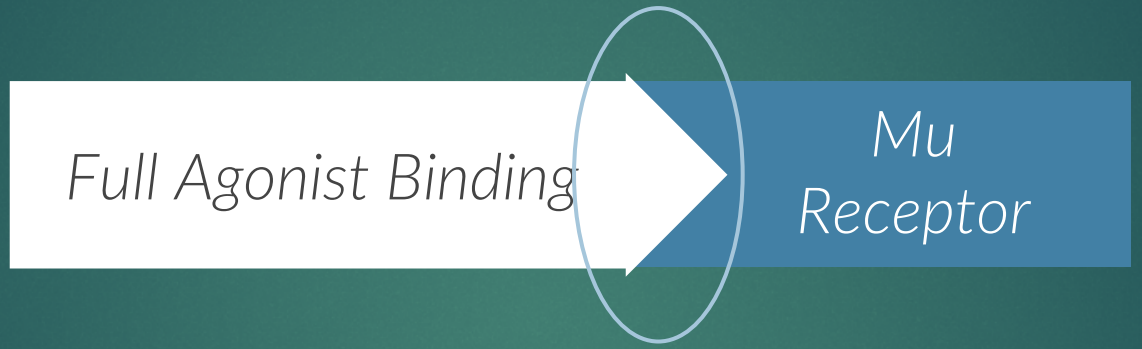
Opioid Agonists and Antagonists



Opioid Characteristics that Increase Euphoria



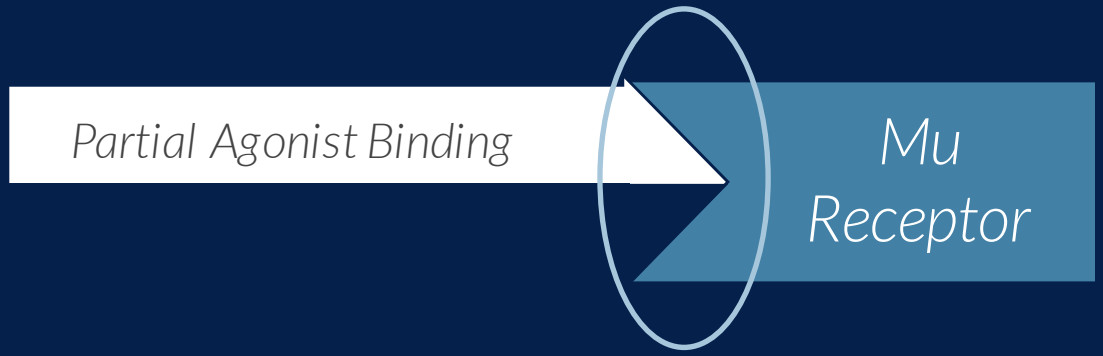
Full Opioid Agonist



A full agonist

- activates the Mu receptor.
- is reinforcing/rewarding.
- is the riskiest opioid type (i.e., sedation and respiratory depression).
- includes fentanyl, heroin, methadone, & others.

Partial Opioid Agonist



A partial agonist

- activates the Mu receptor with ceiling effect.
- is relatively less reinforcing/rewarding.
- is a less risky opioid type (i.e., sedation and respiratory depression).
- includes buprenorphine.

Receptor Affinity

Buprenorphine's Affinity

- ***Affinity*** is the strength with which a drug physically binds to a receptor.
- ***Buprenorphine's affinity*** is very high; it will displace full agonists.
- ***Receptor binding strength,*** high or low, is NOT the same as receptor activation (agonist or antagonist).

High Affinity binding

Mu Opioid Receptor Range of Ki Value	
Buprenorphine	0.21 to 1.5
Fentanyl	0.7 to 1.9
Methadone	0.72 to 5.6
Naloxone	1 to 3 (antagonist effects)
Morphine	1.02 to 4
Codeine	65 to 135

PDSP Ki Database https://pdsp.unc.edu/databases/pdsp.php

Wang D, Sun X, Sadee W. Different effects of opioid antagonists on μ, δ-, and κ-opioid receptors with and without agonist pretreatment. *J Pharmacol Exp Ther.* 2007;321(2):544-52.

Receptor Dissociation

DISSOCIATION is the speed (slow or fast) of dis-engagement of drug from the receptor

Buprenorphine's dissociation is slow

Buprenorphine stays on the receptor a long time and blocks full agonist from binding

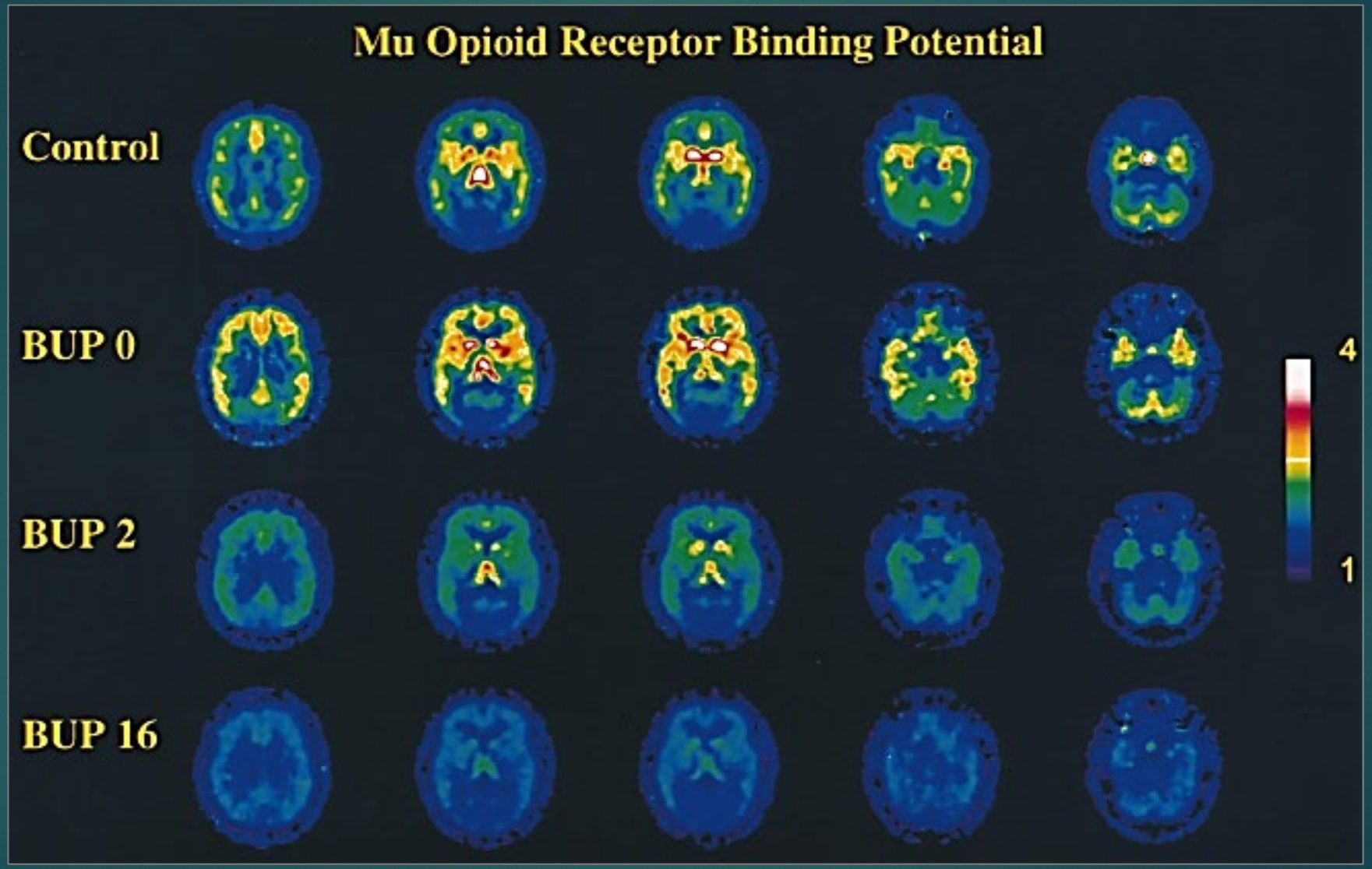
Mu Receptor

Bup dissociation is slow

Therefore, Full Agonists can't bind

Slide created by Tom Pichot, MD

Opioid Blockade



Binding Potential (Bmax/Kd)

Zubieta et al. Neuropsychopharmacology 23:326–334, 2000

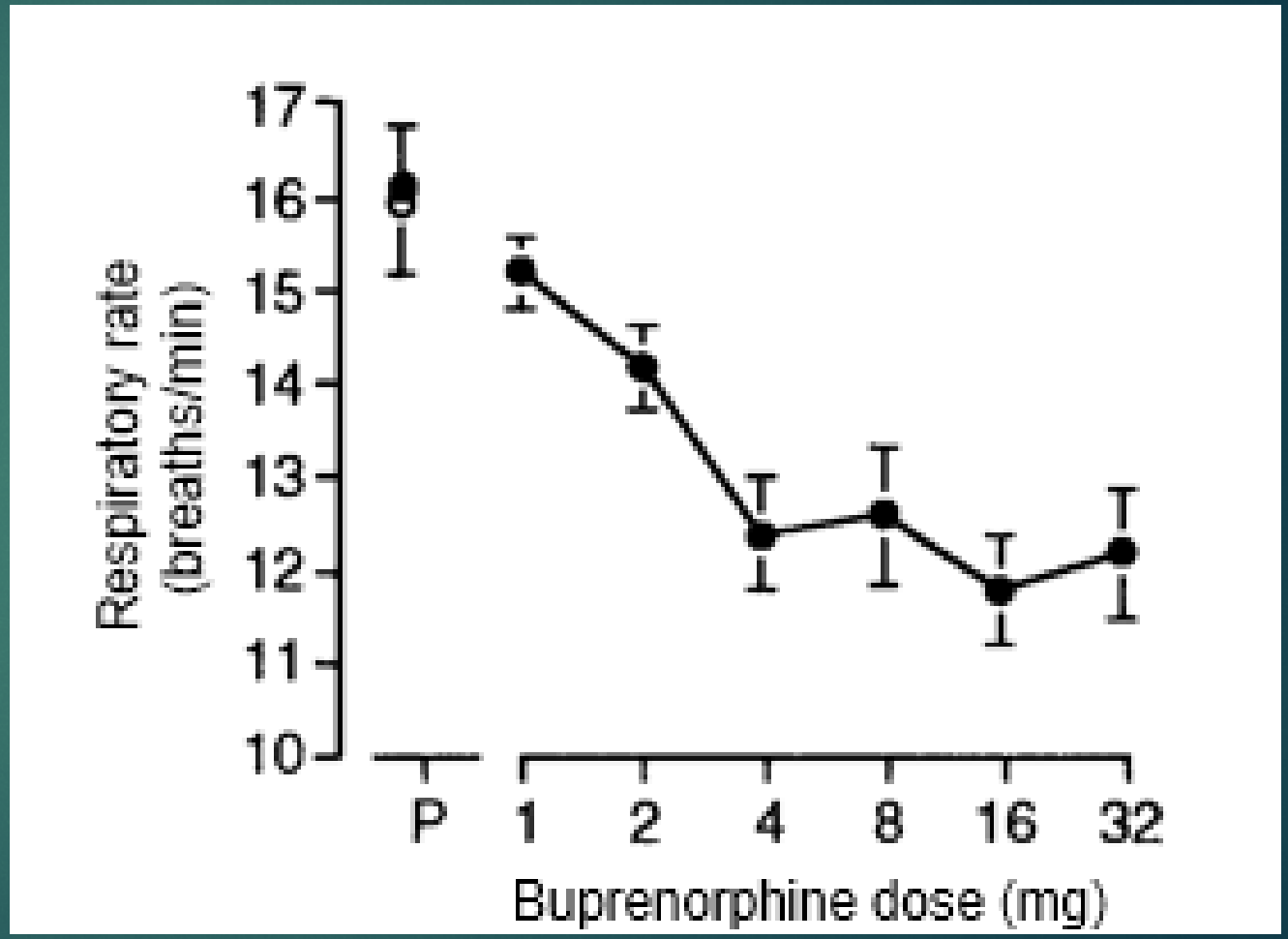
Pharmacology Highlights Buprenorphine

- Generally given sublingually
  - Moderate (~30%) bioavailability
  - ~0%-5% when swallowed
- Can also be given IV at a much lower dose (0.3mg) due to 100% bioavailability

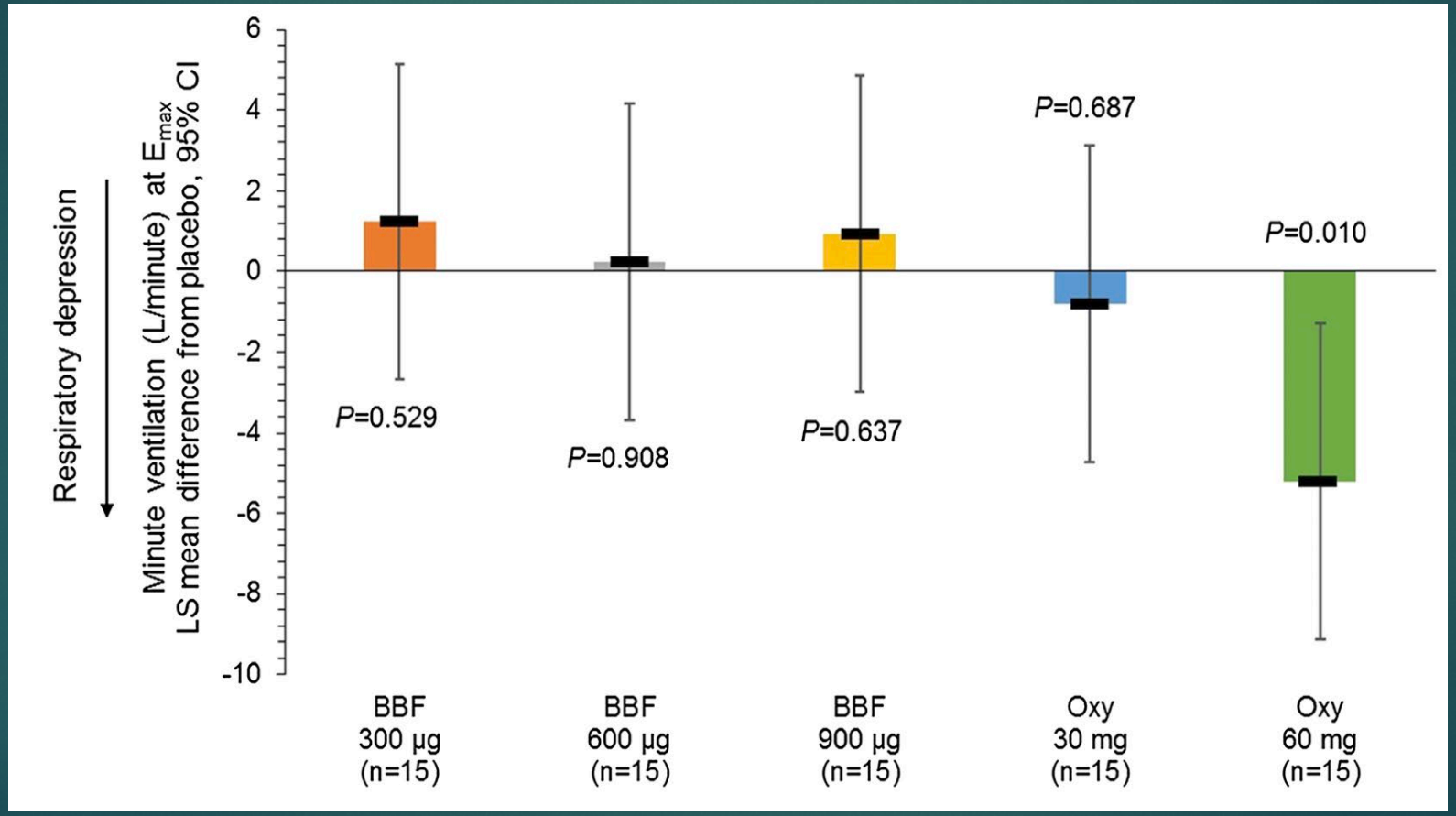
Opioid Agonist Therapy

Pharmacology Highlights Buprenorphine

- Walsh, 1994



Pharmacology Highlights Buprenorphine



Webster, 2020

Ceiling Effect

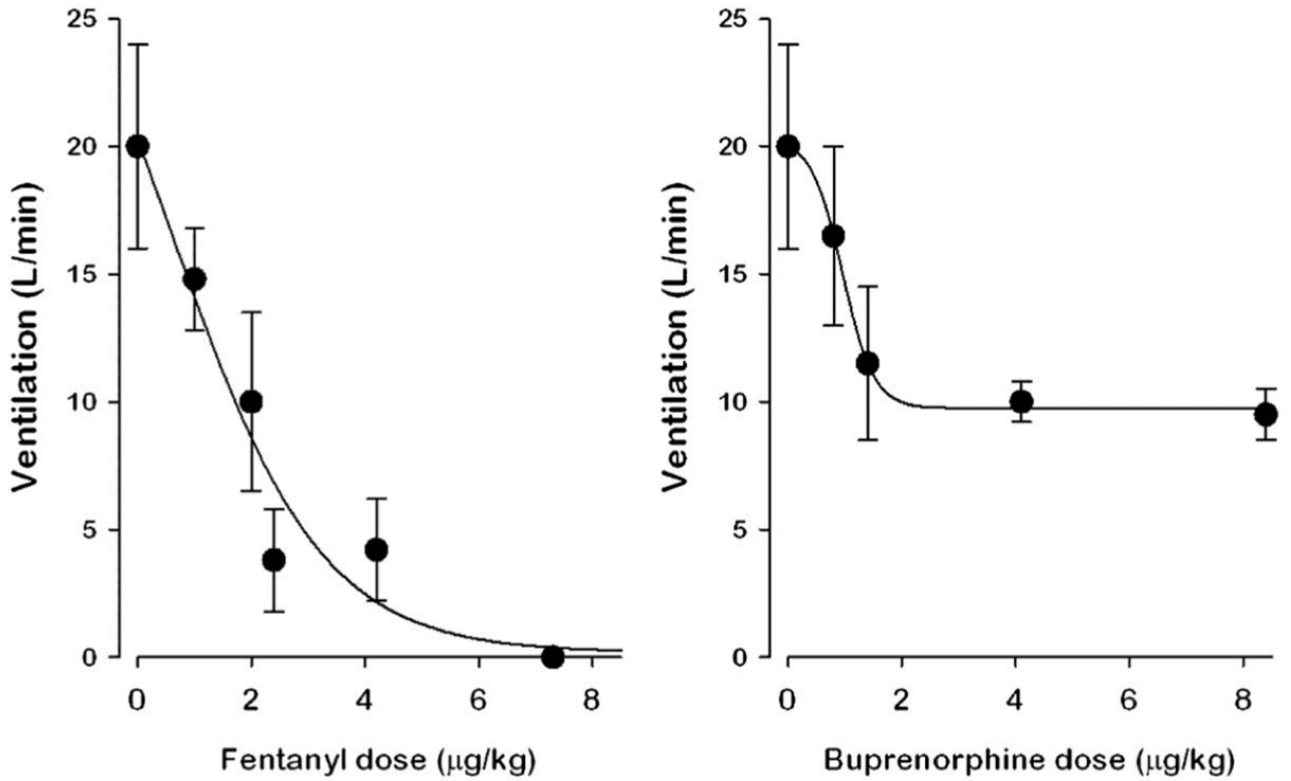
British Journal of Anaesthesia 96 (5): 627–32 (2006)
doi:10.1093/bja/ael051 Advance Access publication March 17, 2006

BJA

Buprenorphine induces ceiling in respiratory depression but not in analgesia

A. Dahan[1]*, A. Yassen[2], R. Romberg[1], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Danhof[2]

A

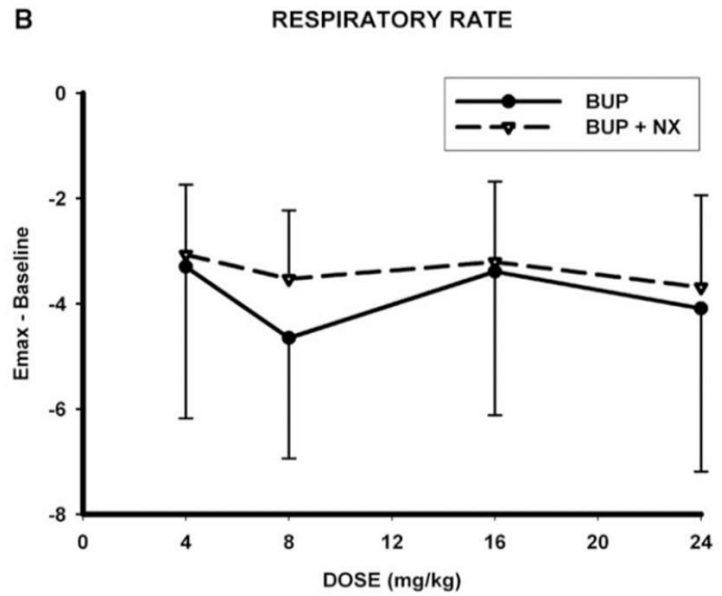


Pharmacokinetics and Pharmacodynamics of Multiple Sublingual Buprenorphine Tablets in Dose-Escalation Trials

Domenic A. Ciraulo, MD, Robert J. Hitzemann, PhD, Eugene Somoza, MD, Clifford M. Knapp, PhD, John Rotrosen, MD, Ofra Sarid-Segal, MD, Ann Marie Ciraulo, RN, David J. Greenblatt, MD, and C. Nora Chiang, PhD

38 subjects

B



Endogenous Opioids and Their Receptors

Endogenous Ligand	Opioid Receptor Types
Beta Endorphins	**Mu**
Enkephalins	Delta
Dynorphins	**Kappa**
Nociceptin /OrphaninF / Q	ORL-1

Most of the clinically-significant effects of prescribed and illicit opioids are attributed to activity at the **mu-opioid receptor**

Buprenorphine Kappa-opioid Receptor Antagonist

Stimulation of kappa-opioid receptor with dynorphin-like peptides

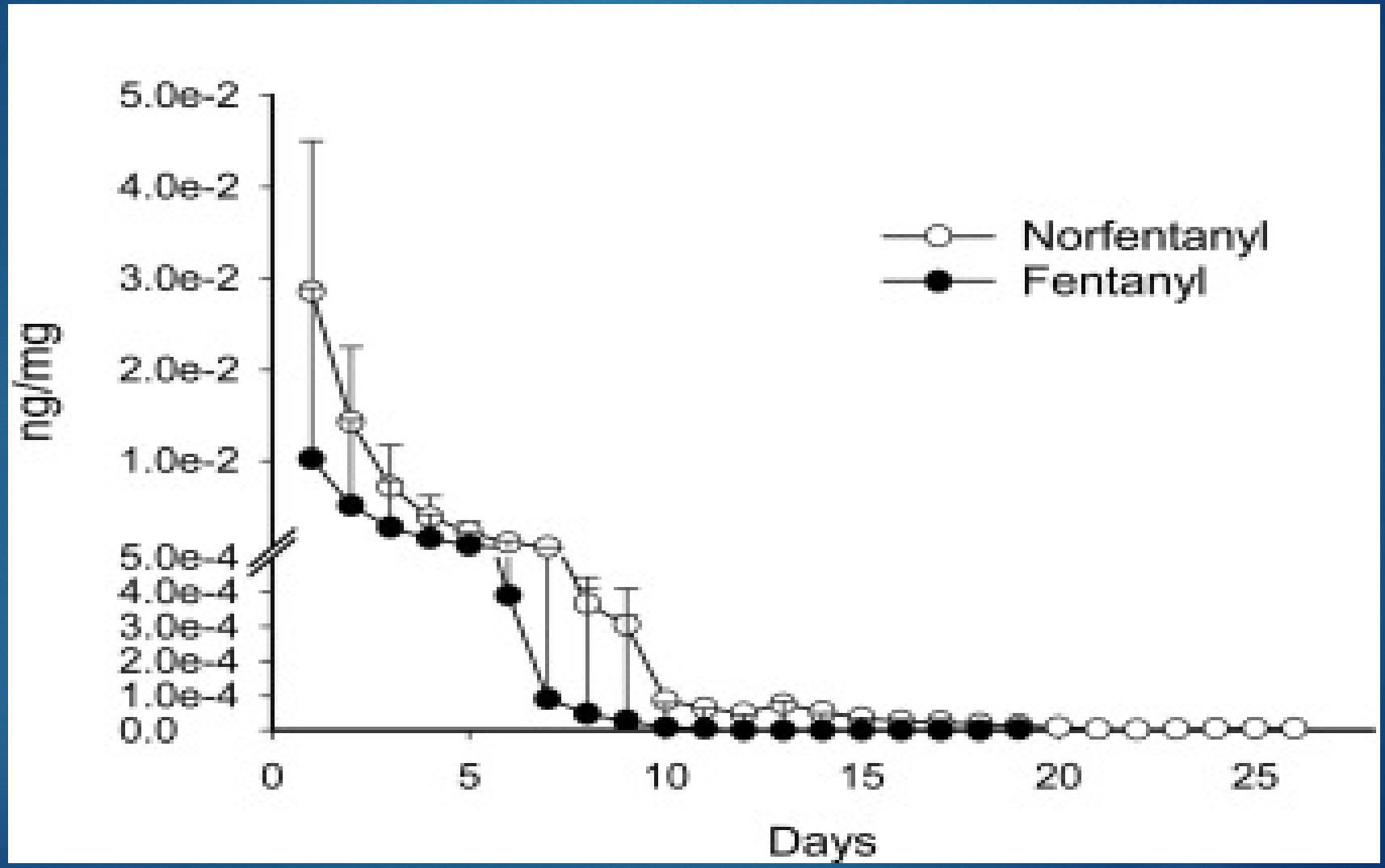
- Inhibits dopamine release in the striatum (nucleus accumbens and caudate putamen), inducing negative mood state in humans and animals

Buprenorphine is an antagonist at the kappa receptor

- Antidepressant-like effects
- Anxiolytic effects
- Prevent stress-induced negative emotional states

BEWARE OF KRATOM--ASK

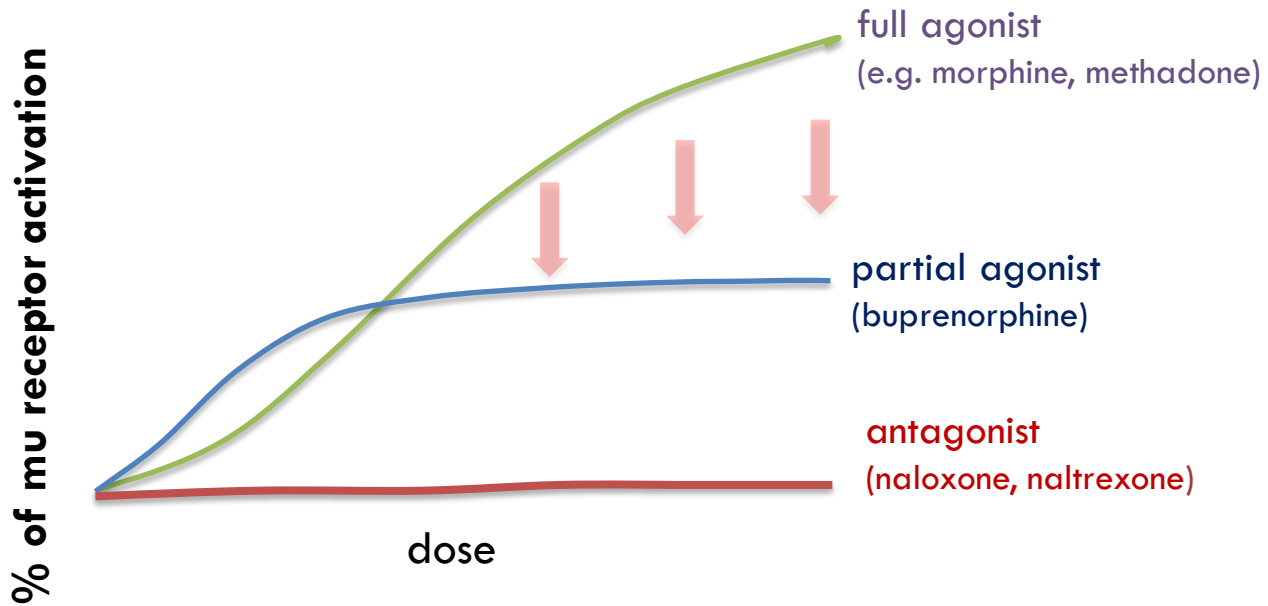
Fentanyl and Norfentanyl Elimination



Huhn, AS, et al. Protracted renal clearance of fentanyl in person with opioid use disorder. Drug and Alcohol Dependence. 2020; 214: 1-4

PRECIPITATED WITHDRAWAL

- Because of its high affinity for mu opioid receptors, buprenorphine can displace other agonists (such as heroin, fentanyl, methadone) that are already present
- The sudden drop from full-agonist to partial-agonist stimulation of opioid receptors can cause sudden and severe withdrawal symptoms, a condition known as ***precipitated withdrawal***



SAMHSA, 2018
Orman & Keating, 2009

Goals of Initiation/Induction

- Minimize withdrawal
  - Avoid precipitating withdrawal
  - Avoid prolonging opioid withdrawal unnecessarily

Goals of Initiation/Induction

- Minimize use of illicit opioids
    - Provide adequate dose of buprenorphine
    - Increase as tolerated

Goals of Initiation/Induction

- Achieve Buprenorphine Maintenance
    - Decreased Mortality
    - Improved outcomes

Menu of Initiations/Inductions[1]

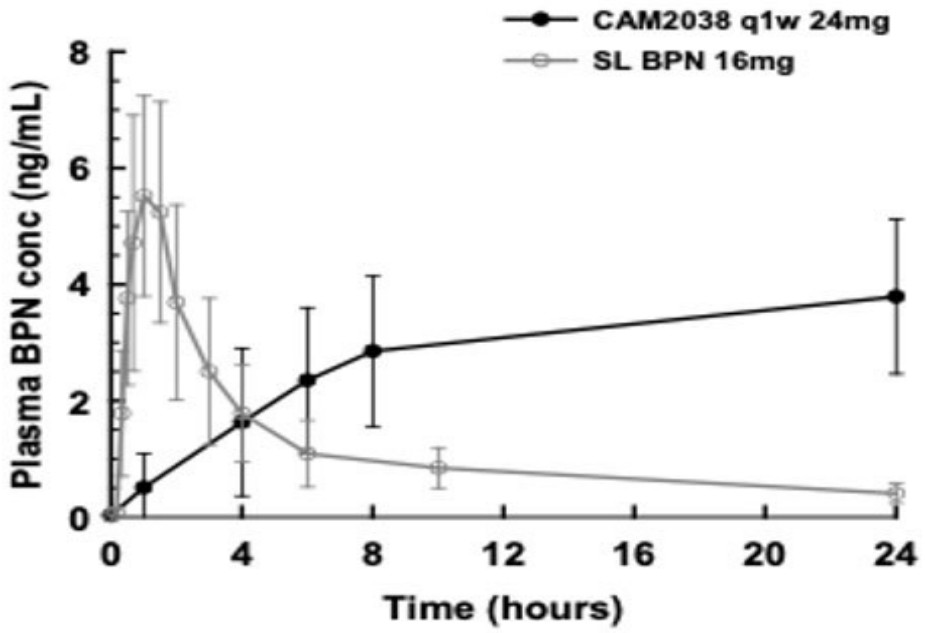
- Standard Induction
- High-Dose Induction
- Low-Dose induction, previously microdosing/microinduction

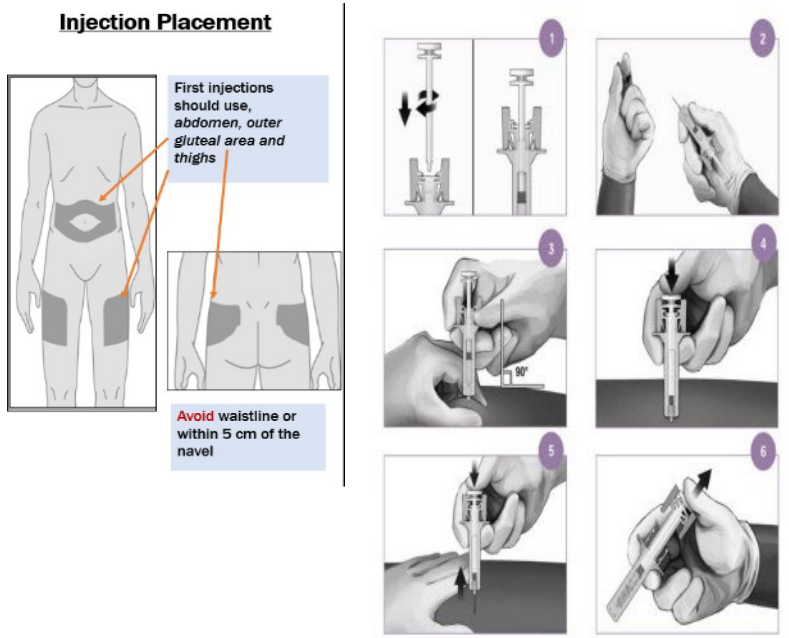
Greenwald, M. K., Herring, A. A., Perrone, J., Nelson, L. S., & Azar, P. (2022). A neuropharmacological model to explain buprenorphine induction challenges. *Annals of Emergency Medicine*.

ED INNOVATION

ED-INitiated BupreNOrphine VAlidaTION Network Trial

Pharmacokinetics of XR- & SL- Buprenorphine





Upon injection **CAM2038** forms into a viscous liquid crystalline gel, producing a sustained, non-fluctuating levels of buprenorphine in the blood **avoiding the peaks and troughs of daily dosing**

3UG1DA015831

PCSS Providers Clinical Support System

JAMA Network Open

Research Letter | Substance Use and Addiction

Incidence of Precipitated Withdrawal During a Multisite Emergency Department–Initiated Buprenorphine Clinical Trial in the Era of Fentanyl

Gail D'Onofrio, MD, MS; Kathryn F. Hawk, MD, MHS; Jeanmarie Perrone, MD; Sharon L. Walsh, PhD; Michelle R. Lofwall, MD; David A. Fiellin, MD; Andrew Herring, MD

Introduction

Buprenorphine treatment is associated with decreased mortality and morbidity,[1] yet the treatment gap remains wide. Emergency departments (EDs) offer an effective, low-barrier setting in which to initiate buprenorphine.[2] Retrospective case series[3] have raised concerns about increased incidence of precipitated withdrawal (PW) when buprenorphine is initiated in persons using fentanyl, a high-potency μ-opioid agonist with high affinity and slow dissociation from the μ receptor. With long-term use, its high lipophilicity leads to bioaccumulation and prolonged metabolite excretion. As confidence in standard buprenorphine inductions has eroded, alternative strategies, such as low-dose buprenorphine, have emerged, often prompting continued use of illicit opioids. Thus, there is a need for high-quality evidence from prospective studies using uniform surveillance and operational definitions of PW. We report the incidence of PW as part of an ongoing randomized clinical trial[4] comparing traditional sublingual buprenorphine with CAM2038, a 7-day extended-release injectable form of buprenorphine, conducted in sites with high prevalence of fentanyl.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Buprenorphine induction in the ED remains safe and effective, even with fentanyl present

Results: Patient Characteristics

Total Enrolled to Date (n=1200)

- Male 67%
- Age (Mean) 38
- Race: 56% White, 30% Black, Multiracial 2% American Indian
- Urine Drug Screen
  - 84% Multiple Drugs
  - 76% Fentanyl
  - 33% Cocaine
  - 46% Marijuana
  - 45% Opiates

Patients with PW (n=9)

- Male 67%
- Age (Mean) 38
- Race: 2 (22%) White, 4 (60%) Black, 2 (22%) Multiracial 1 (10%) American Indian
- Urine Drug Screen
  - 68% Multiple Drugs
  - 100% Fentanyl
  - 67% Cocaine
  - 44% Marijuana
  - 22% Opiates

High-Dose Buprenorphine (>12mg)Induction for Treatment of Opioid Use Disorder

CTN 0069-A1

Accelerated induction achieves therapeutic buprenorphine levels in < 3-4 hours vs typically 2-3 days… extended-release increases safety during the crucial gap between ED & follow-up care… particularly in context of COVID limitations

Retrospective case series –

2018 calendar year at a single site – Highland Hospital, Oakland CA.

- 391 unique patients (579 encounters)
- No cases of respiratory depression or sedation
- 5 cases of precipitated withdrawal not dose related


JAMA Network Open

Original Investigation | Substance Use and Addiction

High-Dose Buprenorphine Induction in the Emergency Department for Treatmen of Opioid Use Disorder

Abstract

Key Points

High dose buprenorphine induction was safe and well tolerated in untreated OUD patients

Herring, JAMA Netw Open. 2021 July

PRECIPITATED WITHDRAWAL

- Rapid onset of withdrawal symptoms within 1-hour of administration of buprenorphine (described for SL-BUP)

- Assessment is based on rapidity of onset of withdrawal symptoms and clinical factors, similar to when a patient receives full naloxone rescue. COWS scores reflect this rapid deterioration and skyrocket to moderate/severe levels.

  (e.g., timing since last use, duration and use of opioid agonist(s))

Rosado, Alcohol Depend 2007;90(2-3):261-269 https://doi.org/10.1016/j.drugalcdep.2007.04.006
Comer S, et al. National practice guideline for the use of medications in the treatment of addiction involving opioid use. American Society for Addiction Medicine. 2015;66.

LESSONS LEARNED: TREATMENT OF PW

- **More Buprenorphine 24-32 mg (Use mono**

- **Ancillary Medications**
  - Muscle aches and pains: Acetaminophen, NSAIDs: Ibuprofen, ketorolac
  - Abdominal cramps and diarrhea: Dicyclomine, Loperamide
  - Nausea: Antiemetics
  - Elevated blood pressure, tachycardia and/or anxiety/restlessness: Clonidine
- **Consider IV Fluids & small doses of lorazepam**
- **Best to find a dark quieter place or send home if possible**

Low-Dose Buprenorphine Initiation

- Start with a small dose that doesn't precipitate withdrawal
- Continue Opioids to prevent withdrawal, and taper as tolerated
- Titrate up as tolerated

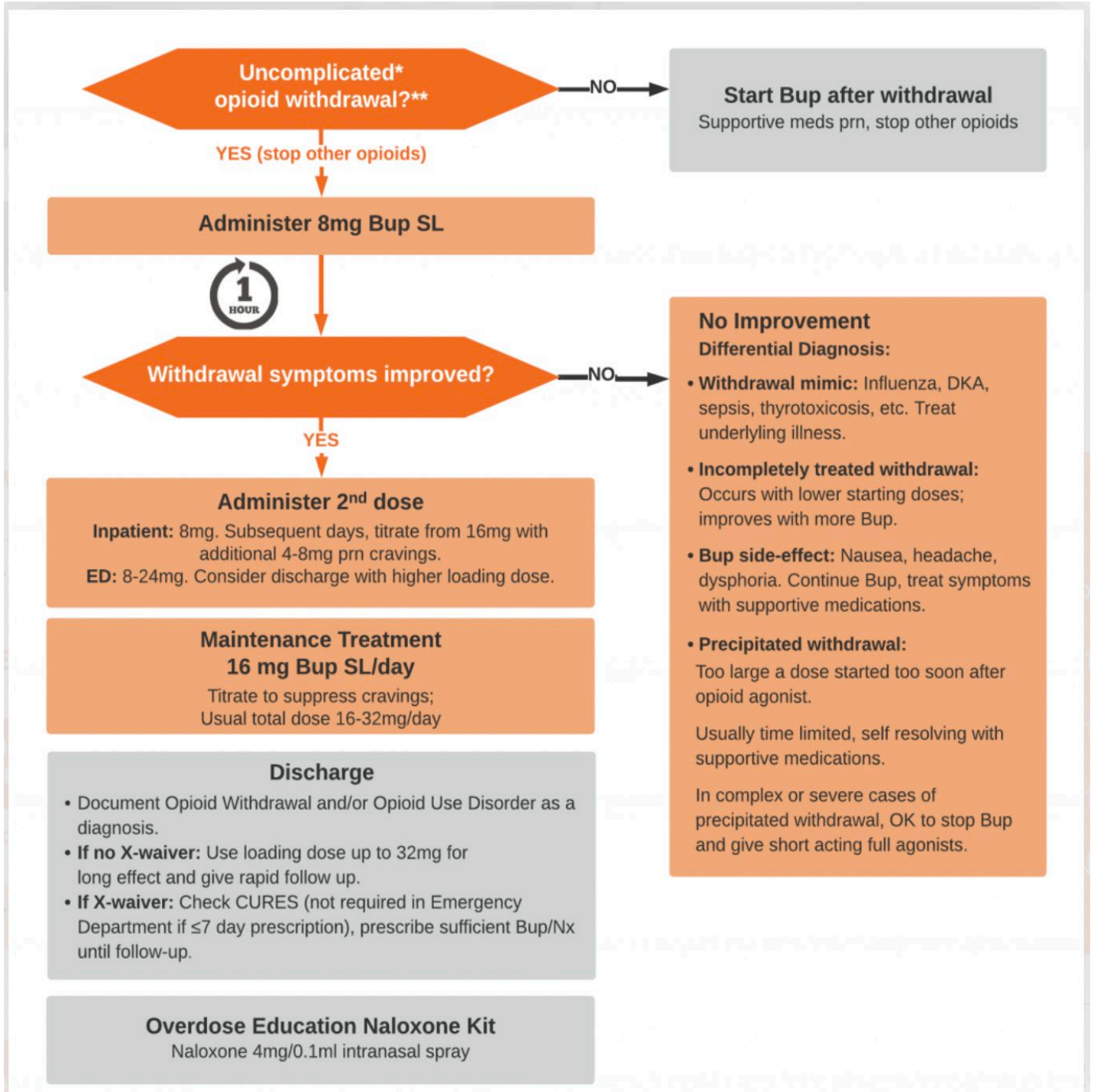
Quirk K, Stevenson M. Buprenorphine Microdosing for the Pain and Palliative Care Clinician. J Palliat Med. 2022 Jan;25(1):145-154. doi: 10.1089/jpm.2021.0378.

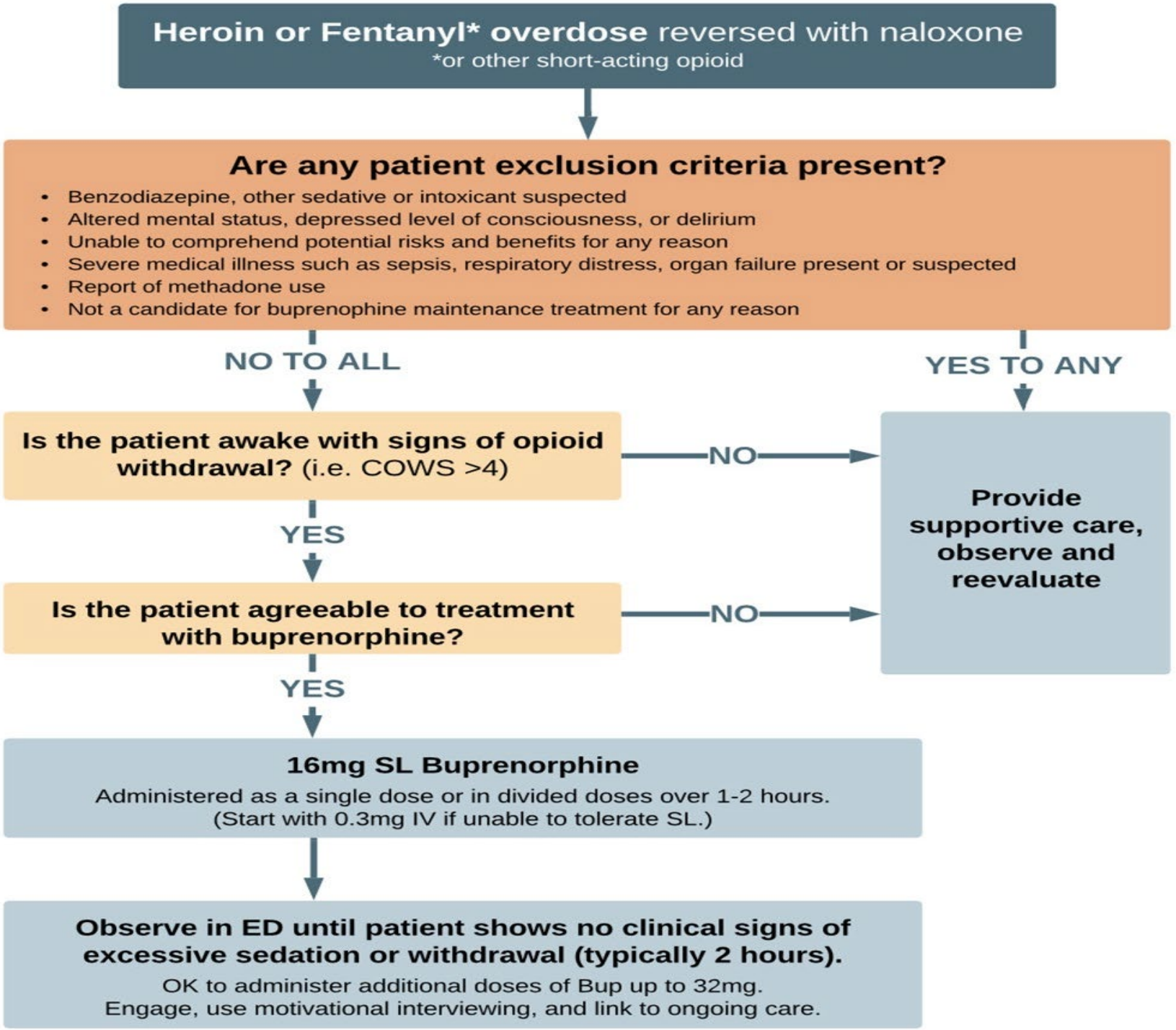
Low-Dose Buprenorphine Initiation

- Transmucosal
  - Sublingual
    - Start: 0.5mg (1/4 film or tablets), 0.25mg
    - Duration: Reach 12mg dose by day 3, typically 4-7 days
  - Buccal
    - Start: 225mcg film
    - Duration: Reach 8mg SL films by day 5, 16mg by day 7

- Transdermal
    - Start: 20mcg/hr patch (or less)
    - Duration: Reach 8 mg dose by day 2, 16mg by day 3

Quirk K, Stevenson M. Buprenorphine Microdosing for the Pain and Palliative Care Clinician. J Palliat Med. 2022 Jan;25(1):145-154. doi: 10.1089/jpm.2021.0378.


Uncomplicated* opioid withdrawal?**
NO
Start Bup after withdrawal
Supportive meds prn, stop other opioids
YES (stop other opioids)
Administer 8mg Bup SL
1 HOUR
Withdrawal symptoms improved?
NO
YES
No Improvement
Differential Diagnosis:
• Withdrawal mimic: Influenza, DKA, sepsis, thyrotoxicosis, etc. Treat underlyling illness.
• Incompletely treated withdrawal: Occurs with lower starting doses; improves with more Bup.
• Bup side-effect: Nausea, headache, dysphoria. Continue Bup, treat symptoms with supportive medications.
• Precipitated withdrawal: Too large a dose started too soon after opioid agonist.
Usually time limited, self resolving with supportive medications.
In complex or severe cases of precipitated withdrawal, OK to stop Bup and give short acting full agonists.
Administer 2nd dose
Inpatient: 8mg. Subsequent days, titrate from 16mg with additional 4-8mg prn cravings.
ED: 8-24mg. Consider discharge with higher loading dose.
Maintenance Treatment
16 mg Bup SL/day
Titrate to suppress cravings;
Usual total dose 16-32mg/day
Discharge
• Document Opioid Withdrawal and/or Opioid Use Disorder as a diagnosis.
• If no X-waiver: Use loading dose up to 32mg for long effect and give rapid follow up.
• If X-waiver: Check CURES (not required in Emergency Department if ≤7 day prescription), prescribe sufficient Bup/Nx until follow-up.
Overdose Education Naloxone Kit
Naloxone 4mg/0.1ml intranasal spray

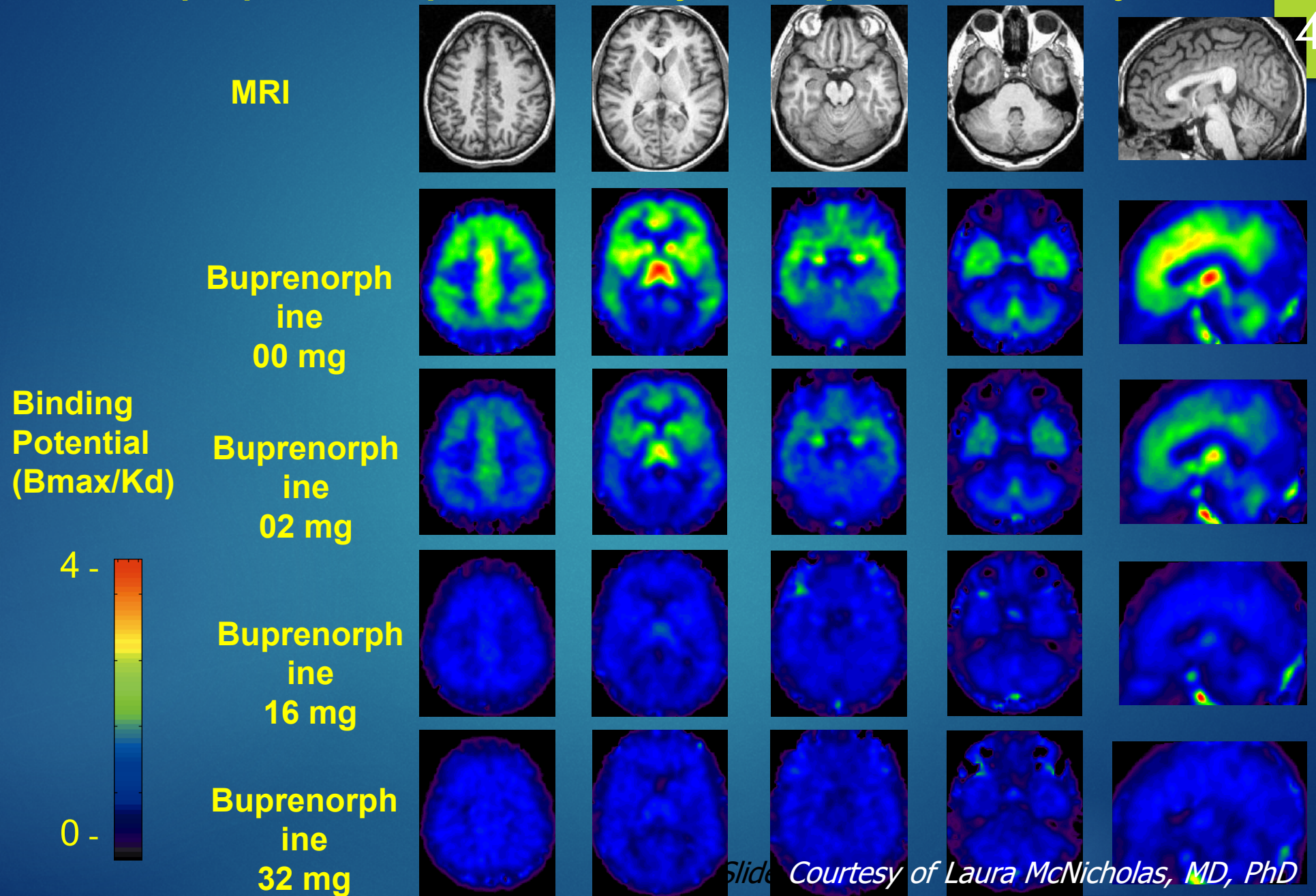


Bup Induction after Overdose

Home Inductions

- Primary method for office-based providers
- Typically, lower doses, starting at 2mg every hour
- First day dose is 12-16mg
- Subsequent doses 16mg daily

Effects of Buprenorphine Dose on μ-Opioid Receptor Availability in a Representative Subject



Slide Courtesy of Laura McNicholas, MD, PhD

Buprenorphine in the ED

- Naloxone precipitated withdrawal
  - Except in severe circumstances, aim to avoid this
    - 0.1 mg naloxone WHILE BVM (Bag Valve Mask) (NP airway and elevated head of bed)
    - Goal RR 10-12—respiration not conversation!
  - If in NPW(Naloxone Precipitated Withdrawal) , can treat and transition with buprenorphine
    - May start with 16mg
    - Add 8mg every 15min to effect
    - When stable, can DC as you would normal induction
    - Not for methadone overdoses

Treatment Course

- Discontinuation of MOUD is associated with relapse, overdose and mortality
  - Only 23% of those tapering off buprenorphine produce opioid negative urine during first follow up
- General conclusion: Discontinuation not recommended
  - But moving from SL to sub-q formulations possible
  - Eventually could try a taper to IM-naltrexone
    - Prevents death with return to use
- Remember and Remind Patients this is a Chronic Disease

Zweben, 2020

Don’t forget naloxone rescue! Every appointment!

But naloxone rescue without treatment engagement only delays death!

Bridge programs with warm hand-offs improve follow through

Low threshold care, diminish barriers, ongoing outcome centered treatment

Long term engagement with motivational enhancement

Contingency management (meth and opioids)