OPTIMAL DOSING OF MOUD IN THE AGE OF FENTANYL

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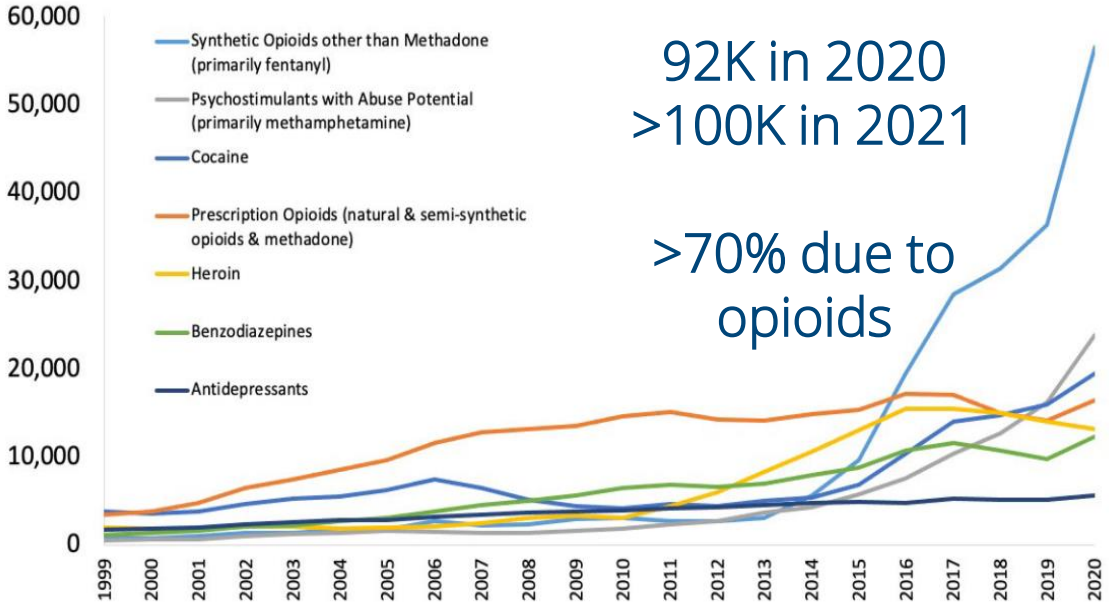
MEDICATION-ASSISTED TREATMENT
CENTERS OF EXCELLENCE

Objectives

1. Provide an overview of the role of fentanyl and its implications in people with OUD
2. Describe literature behind effective doses of sublingual buprenorphine doses for OUD
3. Identify an induction strategy for patients onto buprenorphine and methadone
4. Discuss best practices for maintenance outpatient dosing regimens

Overdose Deaths – An Update

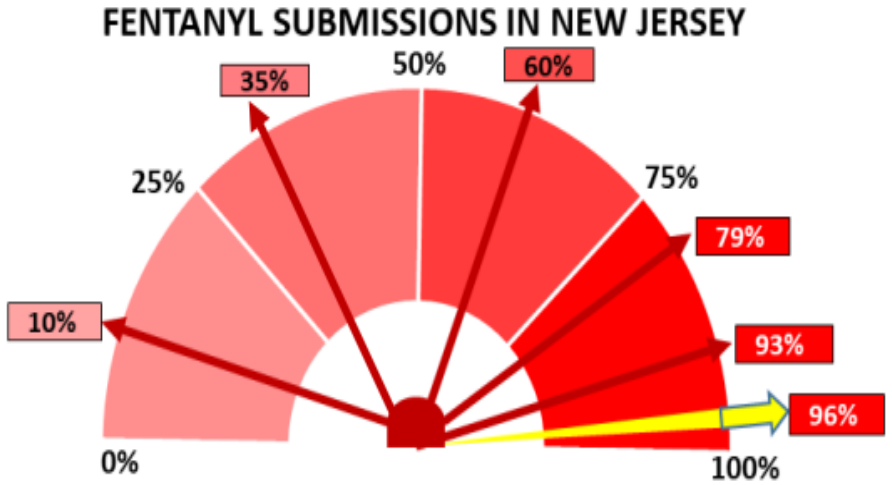
Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020



92K in 2020
>100K in 2021

>70% due to opioids

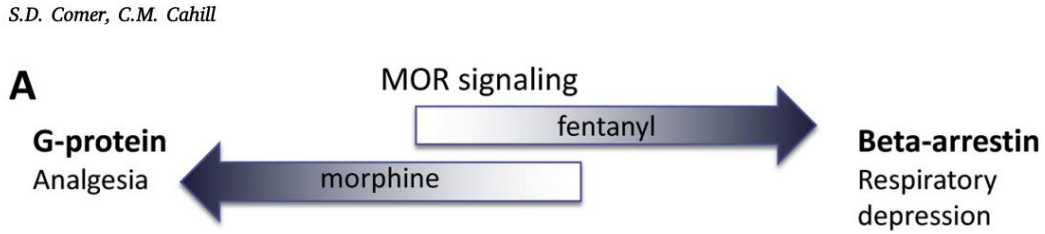
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease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



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).

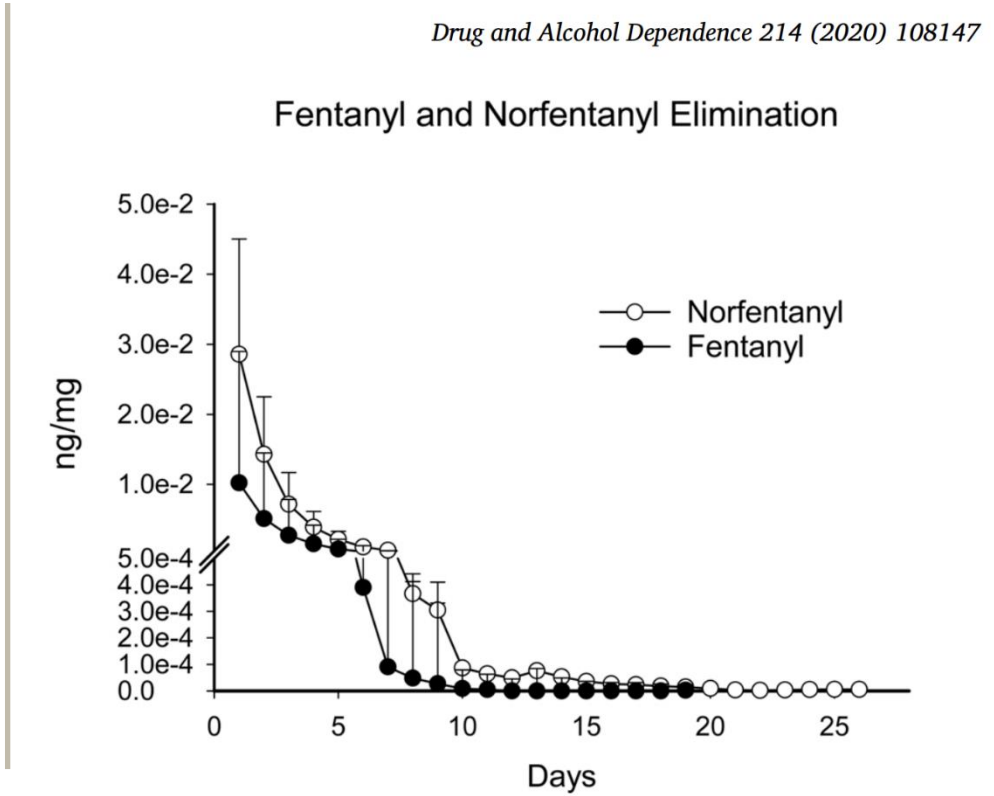
https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates; NJ Office of Drug Montoring and Analysis 2021 Third Quarter Report

Age of Fentanyl – Pharmacology



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

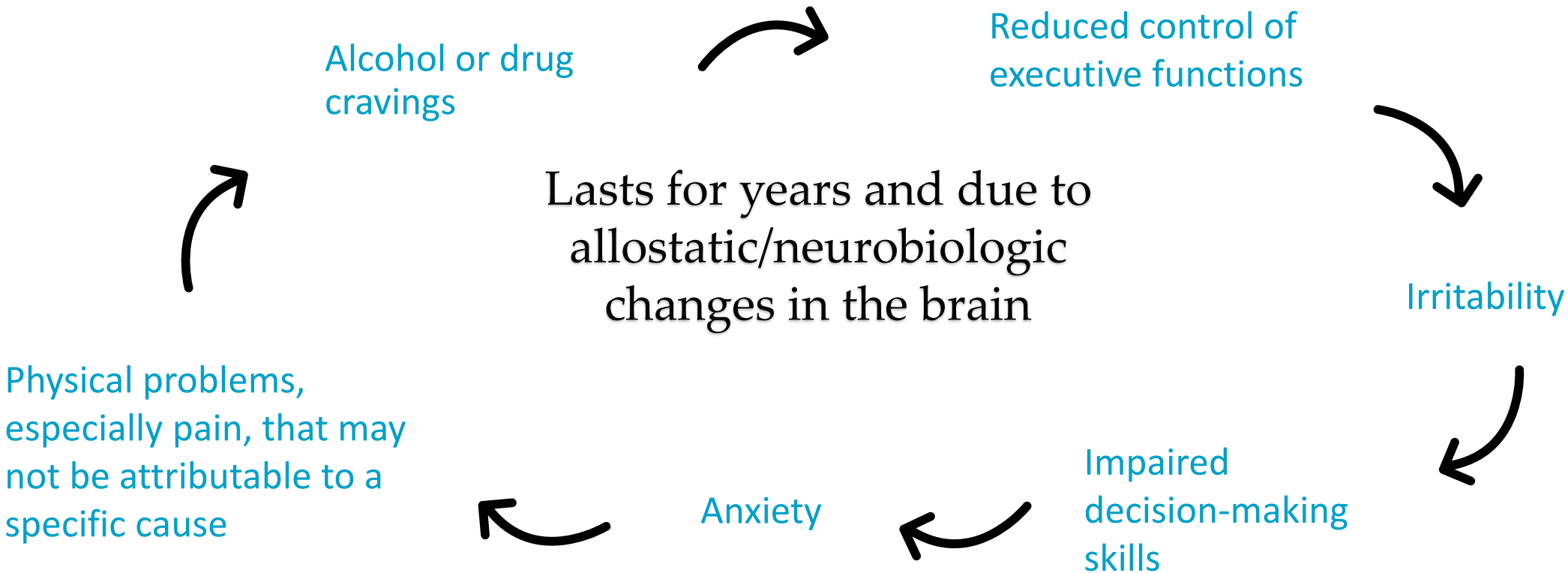


Comer SD, et al. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Sep 1;214:108147.

What are the Implications of all this?

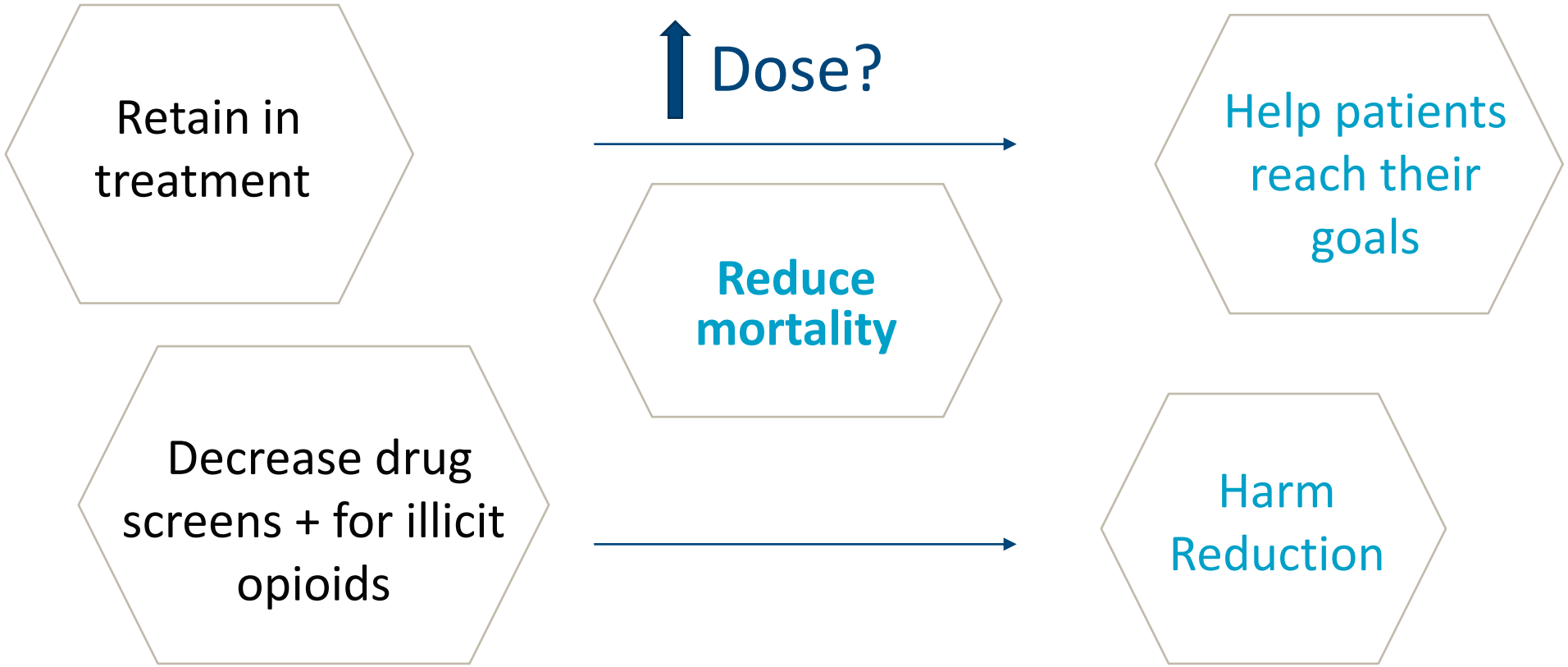
- Fentanyl, its analogs, and synthetic opioids have properties that are much different than opiates like heroin and morphine
- Many illicit drugs are contaminated with fentanyl, which plays a major part in deaths due to drug use
- Fentanyl is often the primary opioid in the illicit opioid drug supply
- 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

CHRONIC Post-Acute Withdrawal Syndrome (PAWS)



MOUD Background and Optimal Dose: A Focus on Buprenorphine and Methadone

Goals of Providing MOUD



At What Dose is Buprenorphine Effective?

Cochrane review (2014):

Low dose: 2-6mg

Medium dose: 7-15mg

High dose: 16+ mg

Treatment Retention; illicit opioid use; vs. placebo

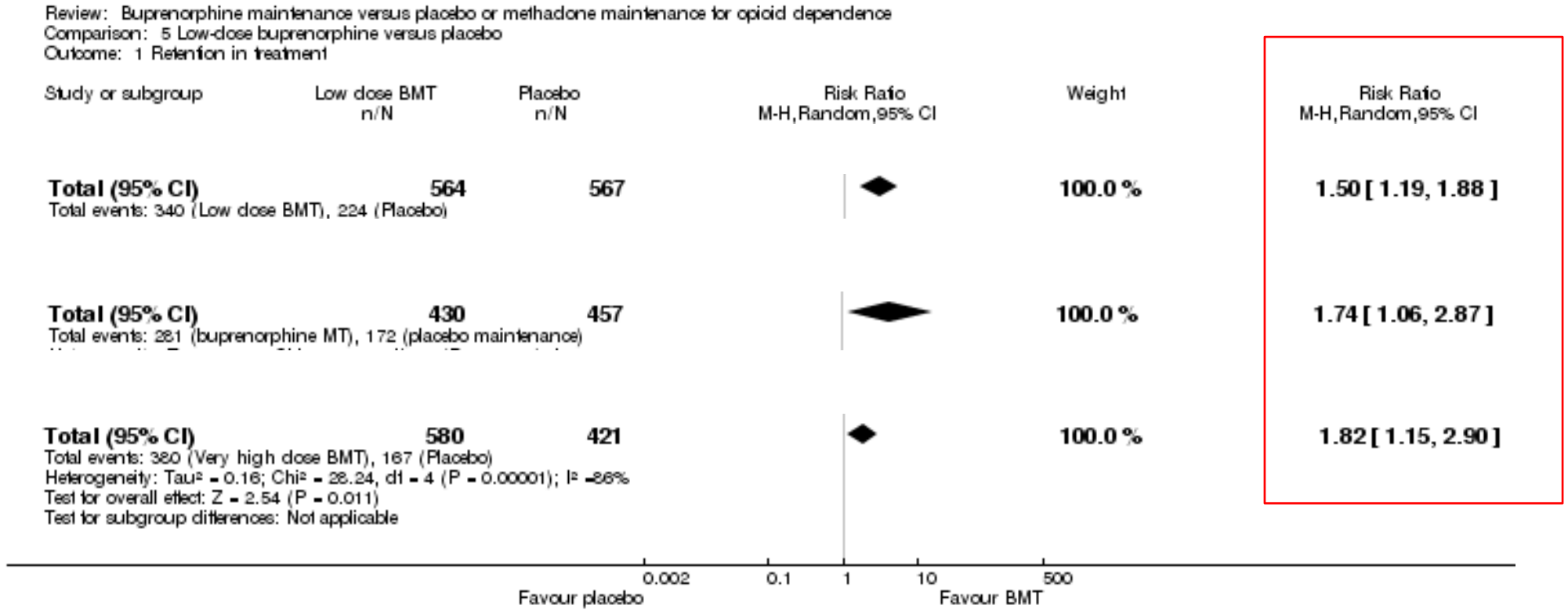
Mattick et al Cochrane Database of Systematic Reviews 2014

Dose: Retention in Treatment

Low Dose

Medium Dose

High Dose

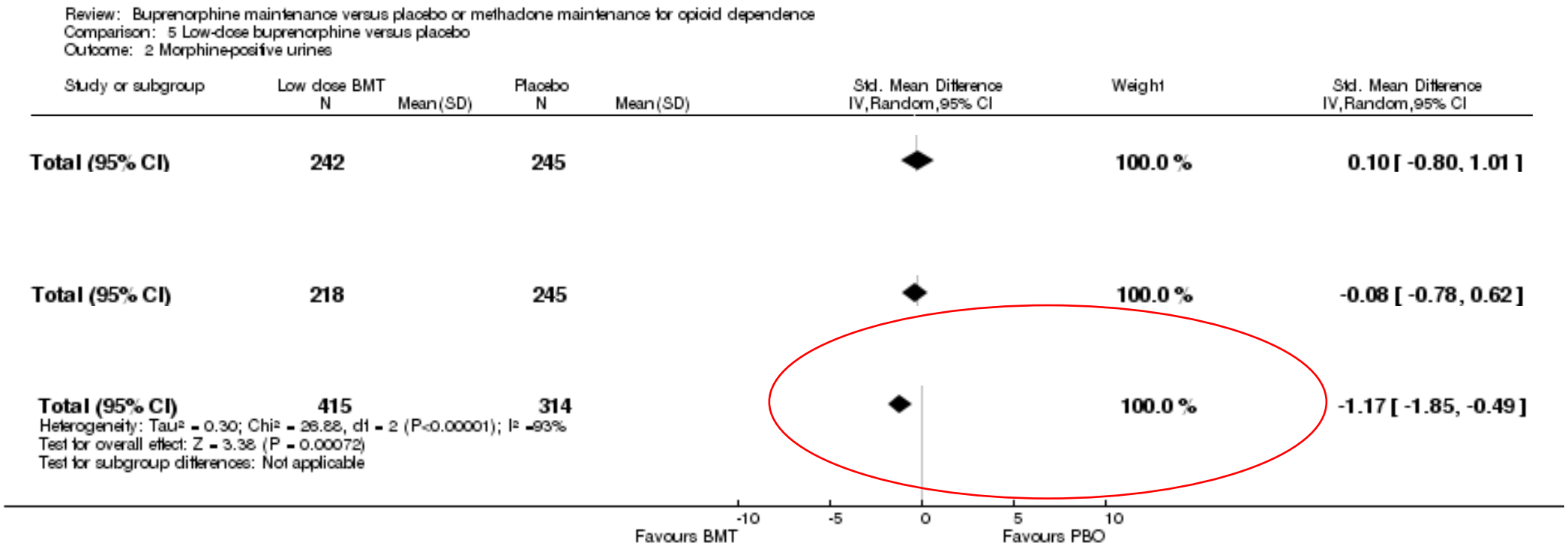


Dose: Morphine Positive Urine Test

Low Dose

Medium Dose

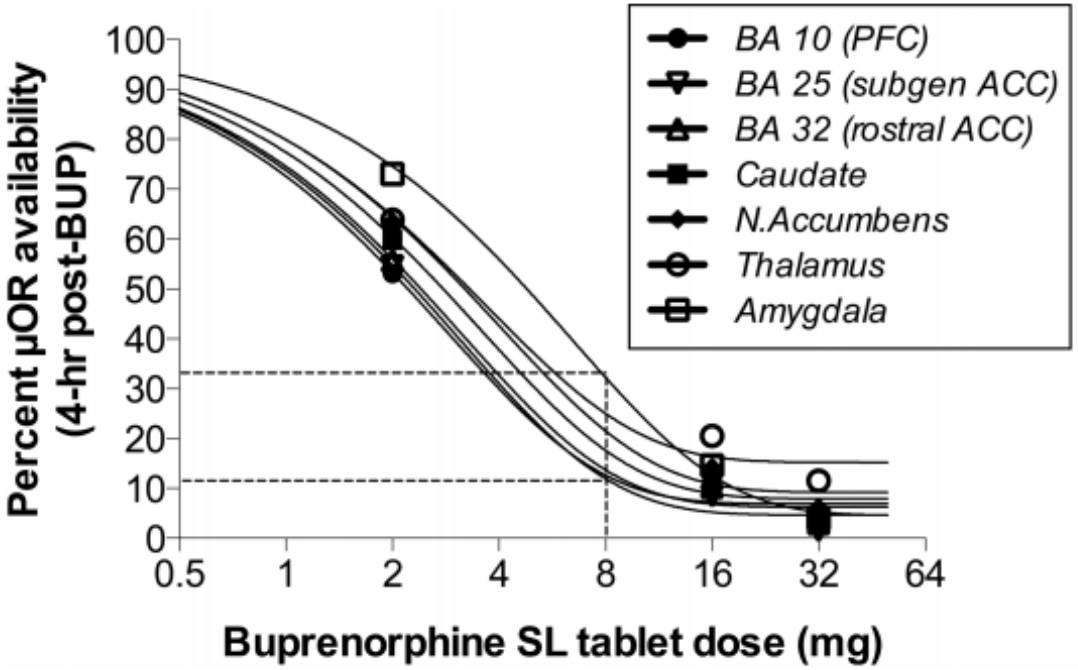
High Dose

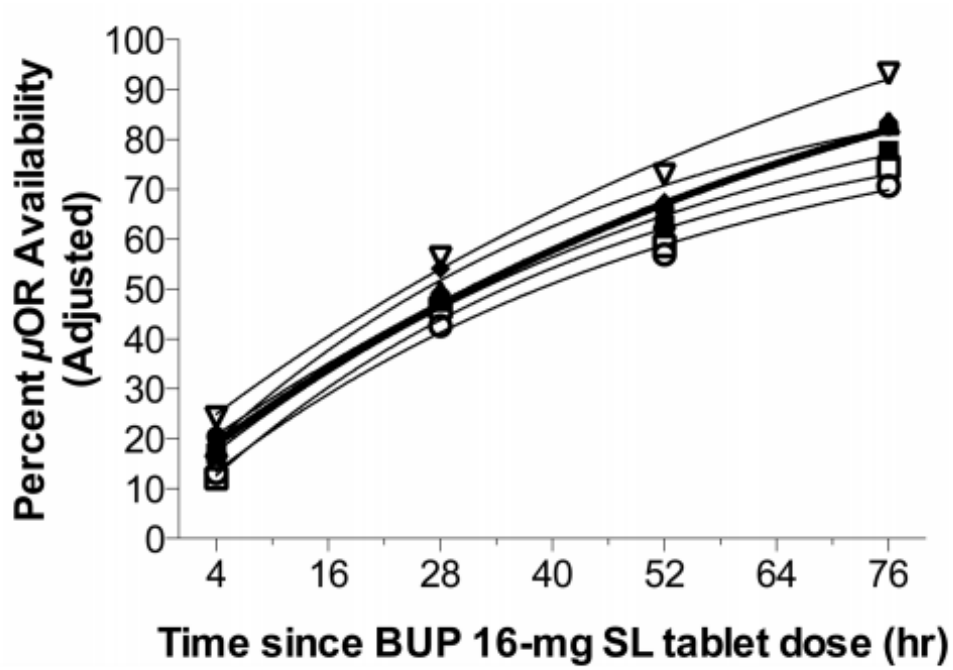


Buprenorphine Maintenance Dosing

Most patients require <20% uOR availability to reduce the reinforcing effects of full opioids: <8mg found to be ineffective in producing blockade

Greenwald et al. Page 22

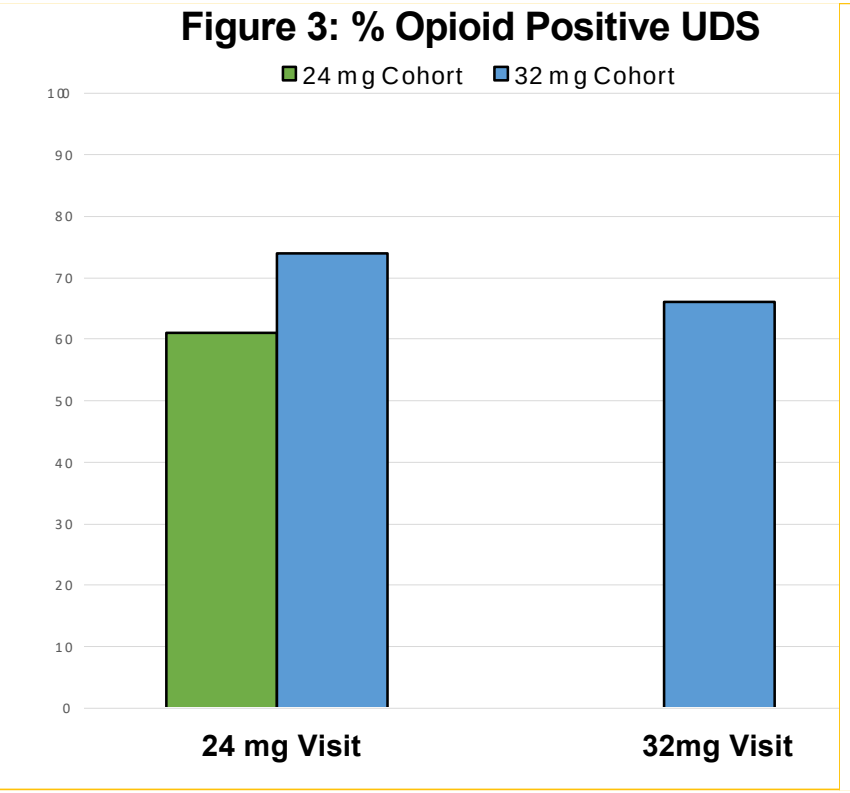


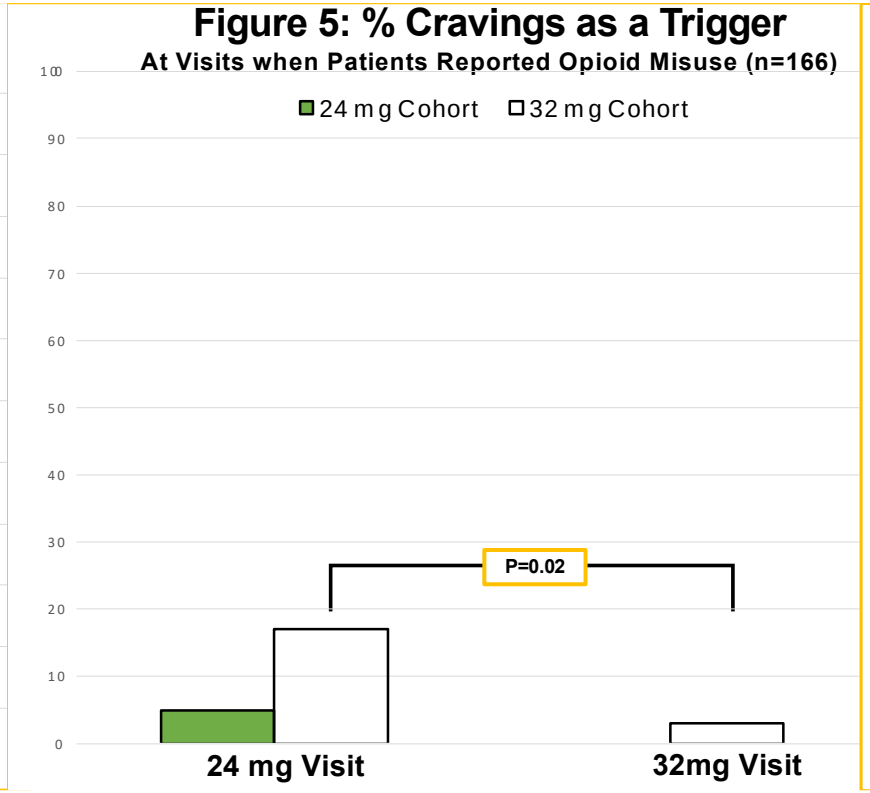


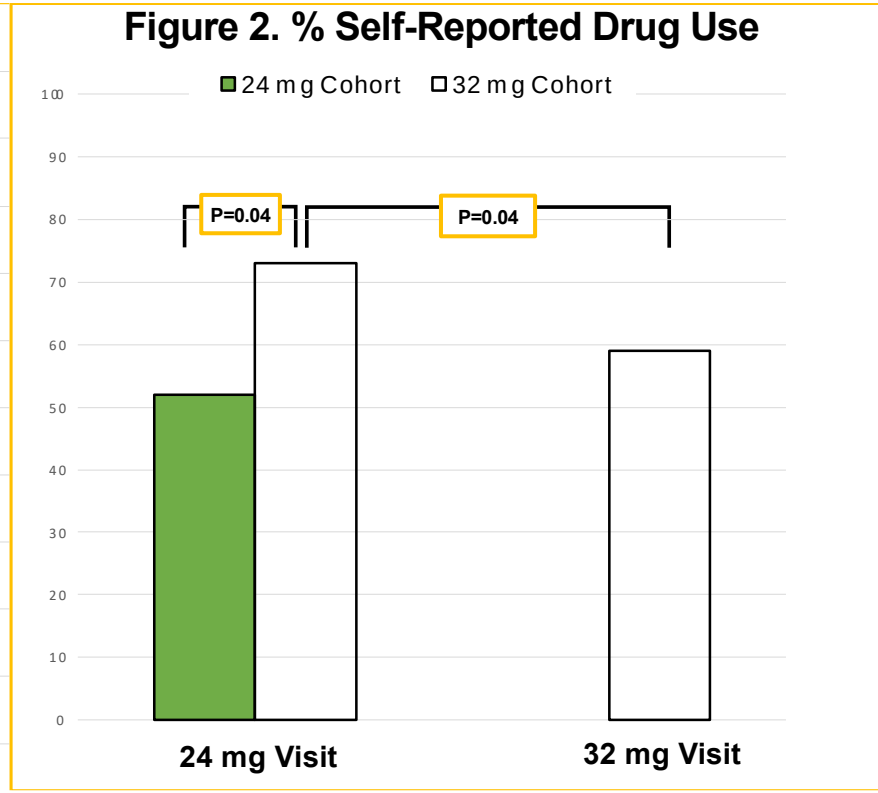
Evidence suggests 16mg/day or more may be more effective than lower doses

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.

Observational Data: Reduced Cravings and Self-Reported Drug Use at 32mg vs. 24mg







J Mount et al "How High Should You Go: Buprenorphine Dosing in the ANCHOR Investigation" ASAM 2021

Summary

Buprenorphine doses of >2mg appear to be equally effective in retaining patients in treatment across multiple RCTs

One study showed improved treatment retention at higher doses >16mg

→ Higher dose (>= 16mg) buprenorphine is more effective than lower doses in suppressing illicit drug use

Laboratory evidence showing equivalent full agonist blockade for doses 16-32mg **for suppressing illicit opioid use**

→ Some observational evidence for improved clinical effect at >16mg (decreased cravings, reported drug use, improvement in + UDS)

→ Evidence across opioid blockade studies generally show that doses <8mg are ineffective in providing opioid blockade

Buprenorphine Dosing 16mg vs. 4-8mg

High quality evidence

Pro	Con
Reduced illicit drug use	Increased constipation
Evidence of improved opioid blockade in the lab Likely lower risk of overdose in community	Increased nausea
No increased risk of respiratory depression/overdose	Increased (very small) chance for adrenal insufficiency (Risk of diversion)
	No evidence of improved treatment retention

Buprenorphine Dosing >16mg

Low quality evidence (limited studies)

Pro	Con
Potentially: Increased treatment retention (limited data) Lower cravings (limited data) Self-reported drug use (limited data) +UDS (limited data) No increased risk of respiratory depression/overdose	Increased constipation Increased nausea Increased (very small) chance for adrenal insufficiency (Risk of diversion) Lack of additional blockade in lab – no overdose benefit? (limited data)

INITIATING BUPRENORPHINE

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 16-24mg 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.*

- Take 2-4mg every 2 hours as needed for a maximum of 24mg on day 2*

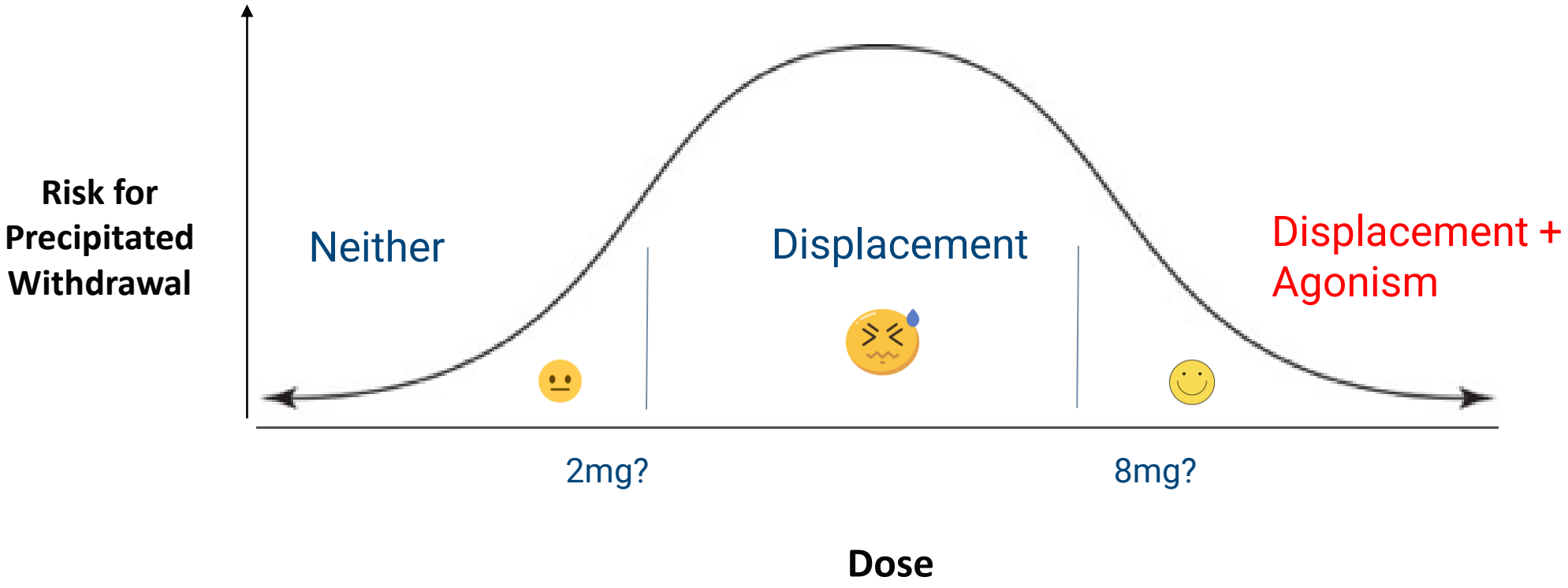
Steady state may take 5-7 days

*As per guidance, day 1 and 2 maximum doses are 16mg and 24mg, respectively.

Requires the patient to continually assess withdrawal over several days

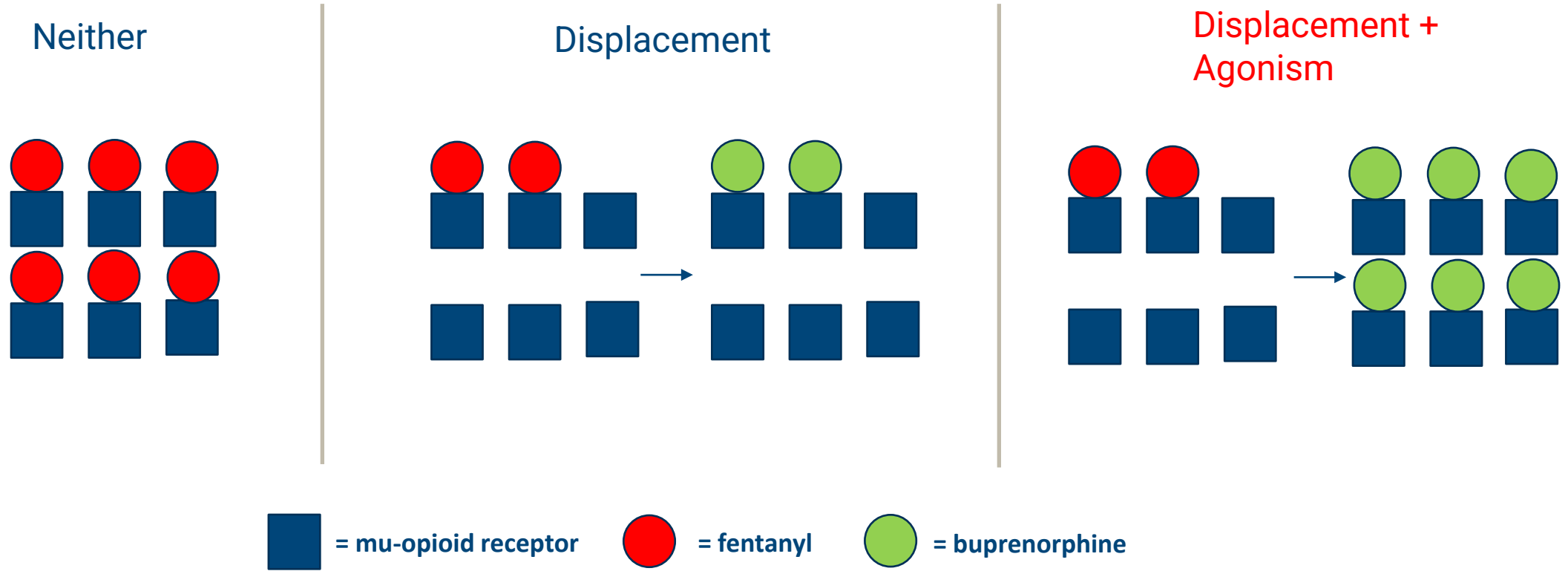
SAMHSA. Tip 63. Medications for opioid use disorder. 2018
Casadonte PP, et al. Buprenorphine Induction. Providers' clinical support system for medication assisted treatment, 2013.

Buprenorphine Induction
Think of a Bell-Shaped Curve…



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.

Buprenorphine Induction
Think of a Bell-Shaped Curve…



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Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

What About Methadone?

Methadone still shown to be protective in those who use fentanyl

Evidence also suggests higher doses of methadone

Current treatment practices: reduce diversion and risk of methadone overdose/safety concerns

- Starting dose of 30mg methadone → 5-10mg every 3-5 days
  - Achieving maintenance dose would take weeks/months
- However, tolerance!
- QTc prolongation/EKG monitoring?

New treatment practice: Focus on treatment retention and reductions in mortality

Stone AC, et al. *J Sbust Abuse Treat.* 2020 Agu;115:108031.chencl
Buresh M, et al. *J Subst Abuse Treat.* 2022 Oct;141:108832.

New Methadone Protocols?

- Initiate at 30mg; increase by 10-15mg every 3-5 days not at high risk for methadone toxicity. Once dose of 75-80mg reached, then can be increased by 10mg every 5-7 days
- Methadone 30mg on day 1; up to 50mg by day 3; then 20mg per week increase
- Day 1: 40mg; Day 2: 60mg; Day 3: 80mg; followed by 10-20mg increase every 4 days up to 140mg
  - Doses can be increased further following continued evaluation
- Take Home Messages
  - Must individualize therapy as difficult to measure each person's tolerance and comorbidities
  - Reduce duration of suboptimal doses to prevent drop-out and subsequent overdose risk

Buresh M, et al. *J Subst Abuse Treat.* 2022 Oct;141:108832.

Clinical Experiences

Dr. Susan Neshin's methadone experiences in the age of fentanyl

Dr. Louis Baxter's buprenorphine experiences in the age of fentanyl