WELCOME

- The Proper Prescribing Lecture will begin shortly after 4:45 p.m. to allow all attendees to login.

- If you have any questions for the presenter, click the Q&A button that is located on the bottom of your screen. The presenter will answer all questions at the conclusion of the lecture.

- If you are experiencing technical difficulties, please click the Q&A button located on the bottom of your screen for guidance. You can also call 800-274-1972.

Medication Assisted Treatment for Opioid Addiction

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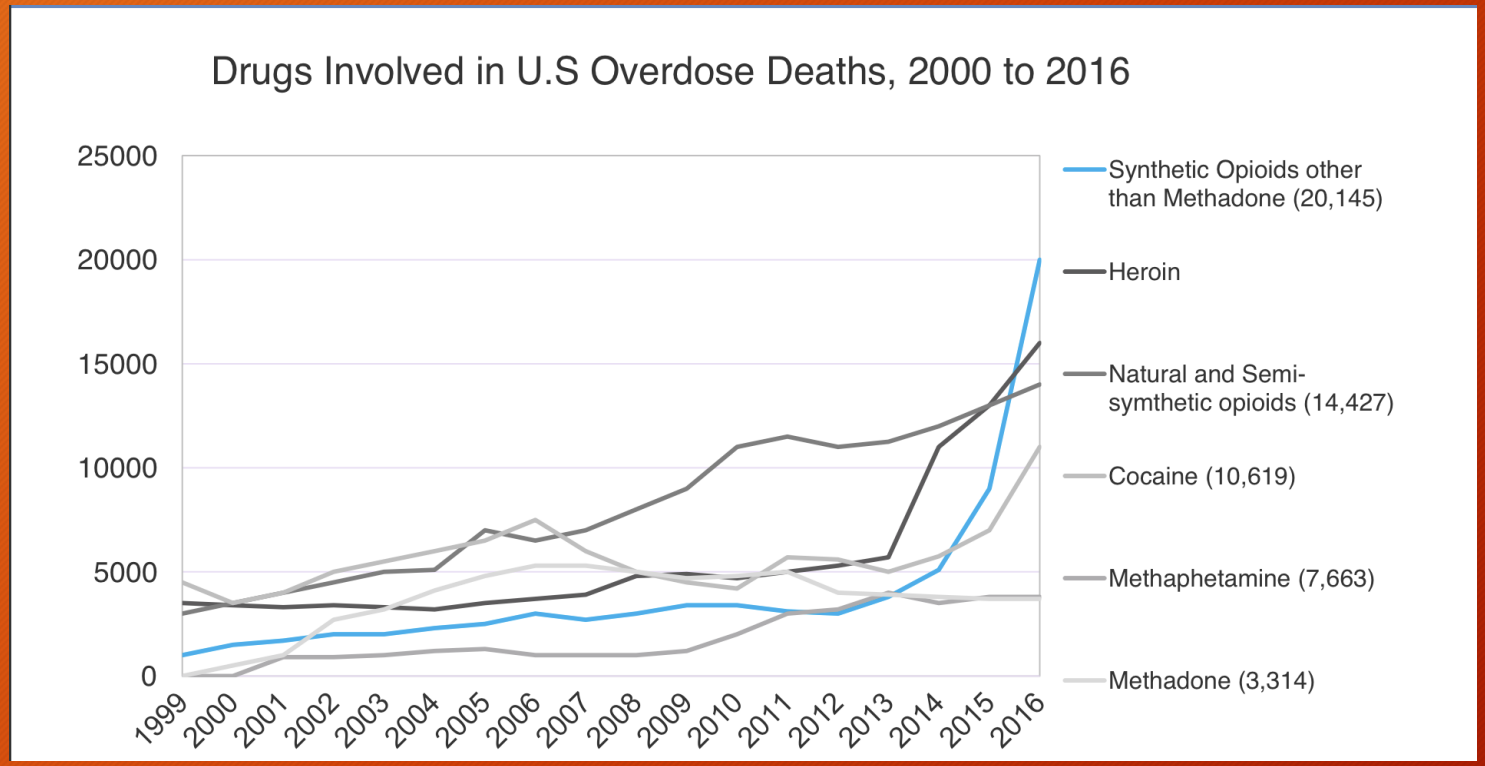
Disclosures

- I have nothing to disclose

Objectives

- Define addiction as a chronic brain disease
- Review goals of medication assisted treatment
- Review the FDA approved medication assisted treatment options for opioid addiction
  - Methadone
  - Buprenorphine
  - Extended-release naltrexone

The Opioid Epidemic



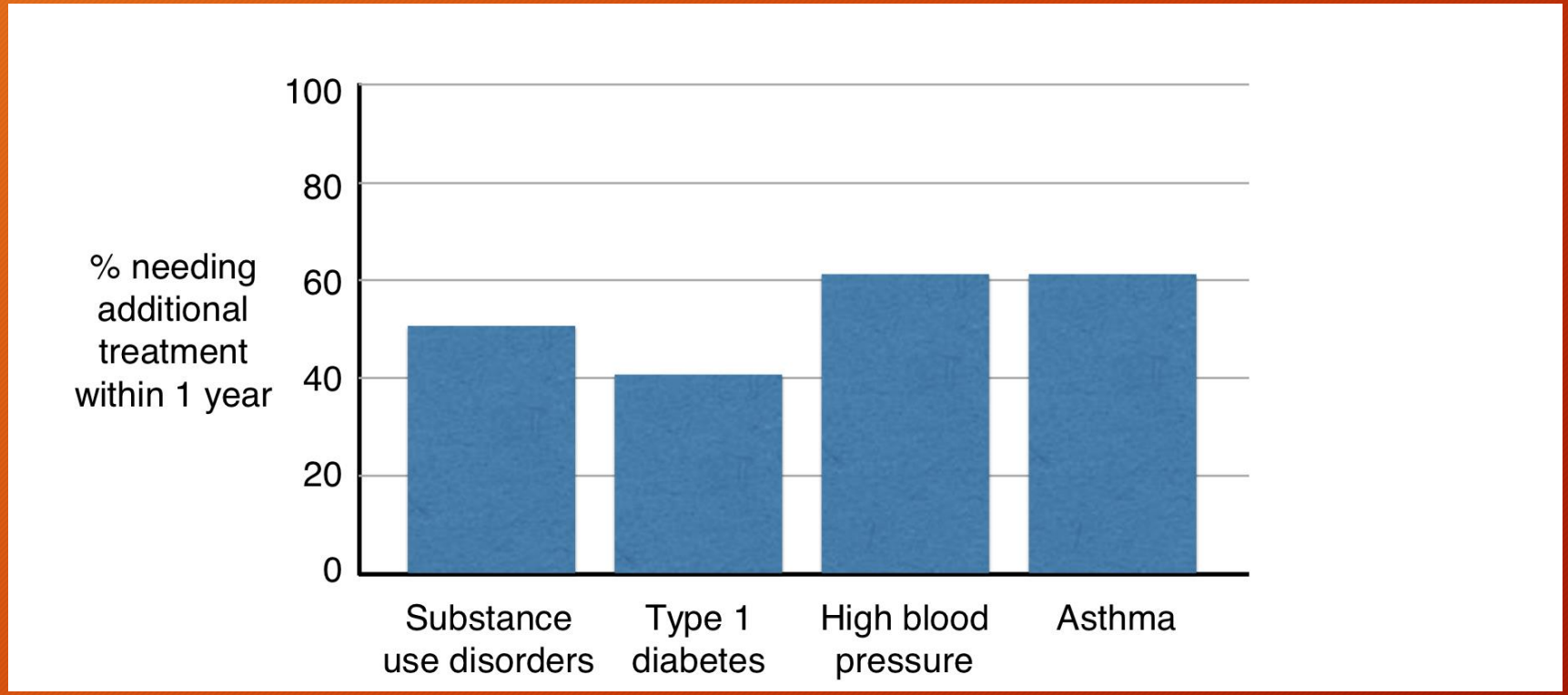
Center for Disease Control and Prevention. WONDER. http://wonder.cdc.gov/mcd.html.

Definition of Addiction

- Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry
- Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations
- An individual with addiction pathologically pursues reward and/or relief by substance use and other behaviors
- Like other chronic diseases, addiction often involves cycles of relapse and remission
- Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death

Ries RK. ASAM Principles of Addiction Medicine, 5th Ed. 2014.

Treatment Adherence Comparison Amongst Chronic Diseases



McLellan AT. JAMA. 2000, 284(13): 1689-1695.

Characteristics of Opioid Addiction

- Inability to consistently abstain
- Impairment of behavioral control
- Craving
- Diminished recognition of significant problems in one's behaviors and interpersonal relationships
- Dysfunctional emotional responses

Ries RK. ASAM Principles of Addiction Medicine, 5th Ed. 2014.

Biology of Addiction

Positive reinforcement

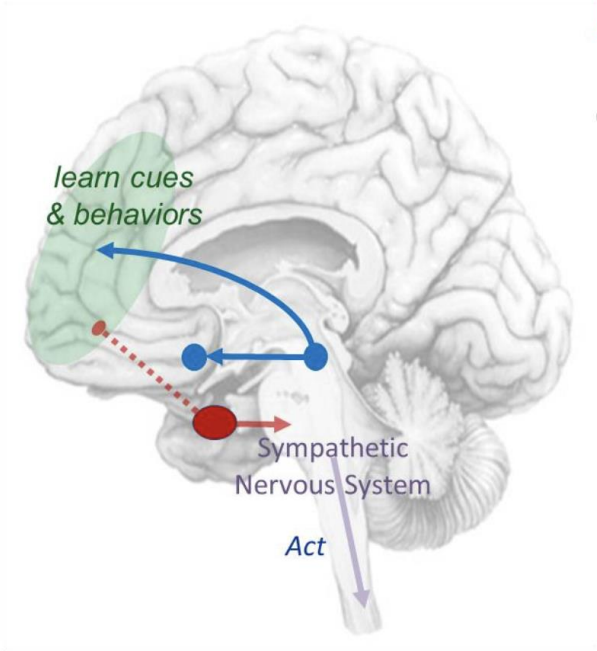
cells in the brainstem release **dopamine** in the **nucleus accumbens**

↓

liking and wanting

↓

seek out and do more



Negative reinforcement

cells in the **amygdala** are stimulated

↓

anxiety, fear, distress

↓

avoid things that cause, do things that relieve fear

Attention, thinking, and judgment use the **prefrontal cortex**

Volkow ND. NE Journal of Medicine. 2016, 374(4): 363-371.

Milestones in Medication Assisted Treatment

- 1970: Methadone is approved by the FDA for detoxification
- 1973: Methadone is approved by the FDA for maintenance
- 1974: Opioid Treatment Programs (OTPs) able to dispense methadone for maintenance treatment
- 1984: Oral naltrexone is approved by FDA
- 2000: Drug Addiction Treatment Act of 2000 (DATA 2000) allowed qualified physicians to offer office based opioid treatment
- 2002: Buprenorphine approved by the FDA
- 2010: Extended-release naltrexone approved by the FDA
- 2016: Comprehensive Addiction and Recovery Act (CARA) allows nurse practitioners and physician assistants to prescribe buprenorphine

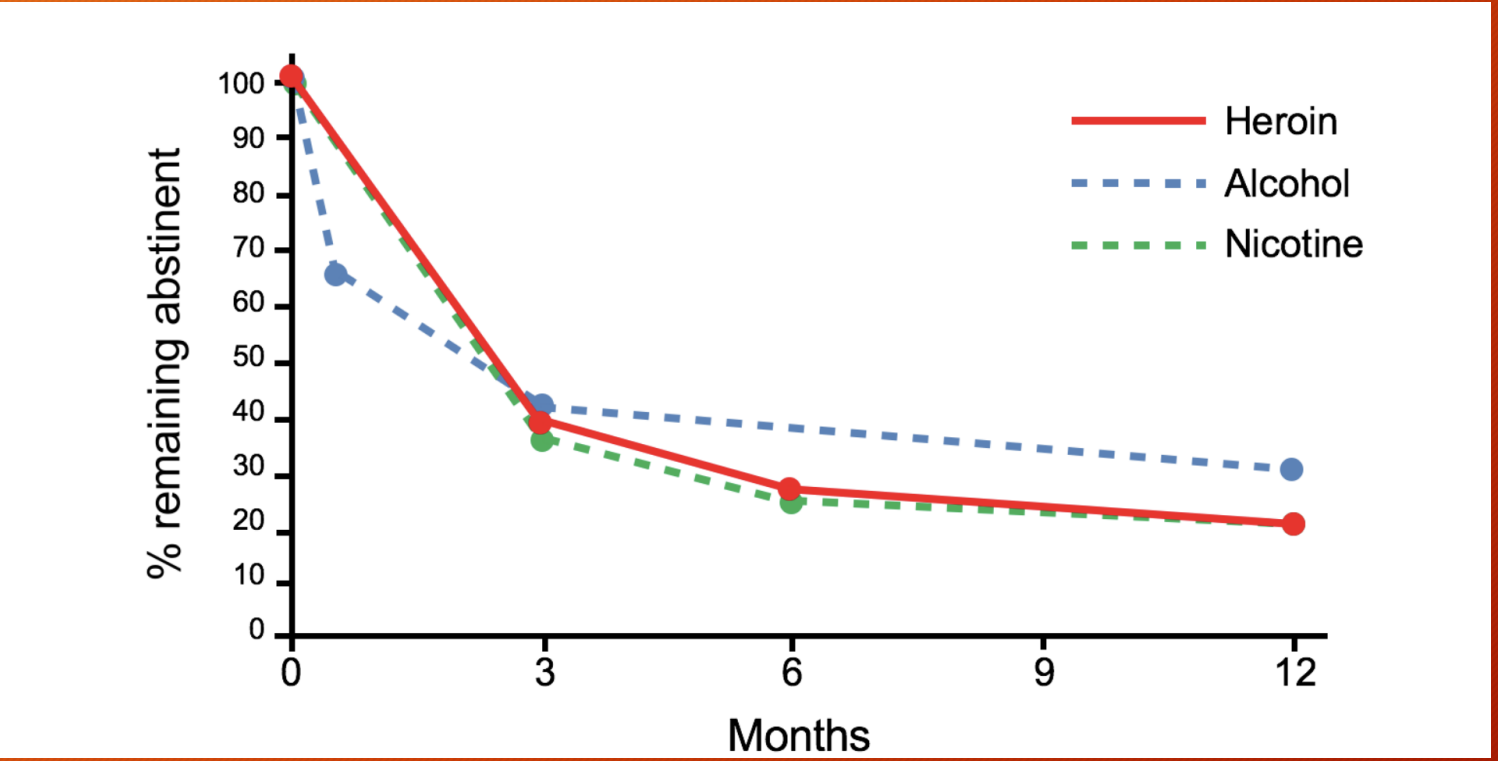
FDA Approved Medications for Opioid Addiction Treatment

- Mu Opioid Receptor Full Agonist
  - Methadone (requires administration in opioid treatment program)
- Mu Opioid Receptor Partial Agonist
  - Buprenorphine (requires waiver to use)
  - Buprenorphine/Naloxone (requires waiver to use)
- Mu Opioid Receptor Antagonist
  - Extended Release Naltrexone

Goals of Medication Assisted Treatment

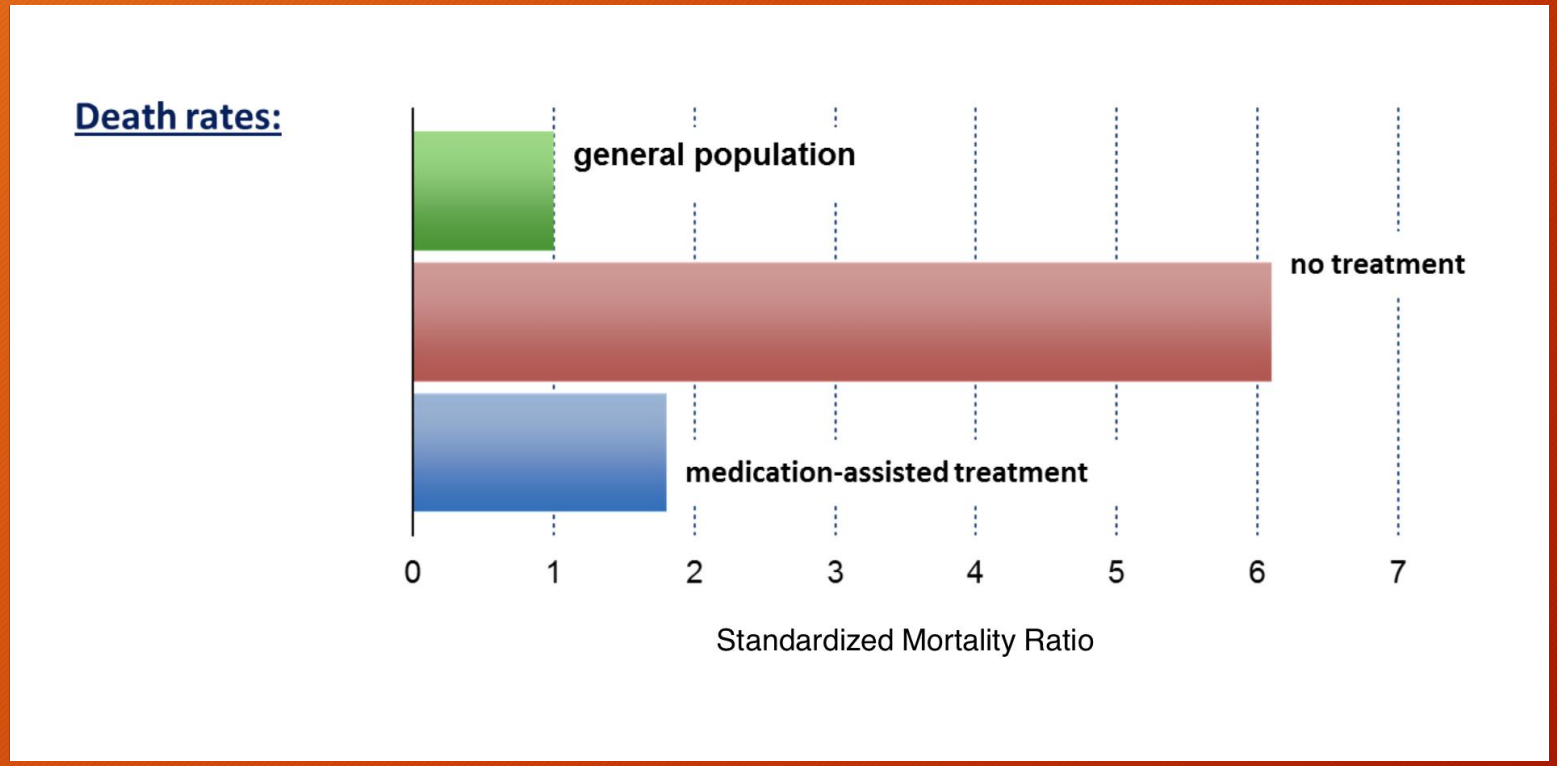
- Reduce opioid use
- Retain in treatment
- Protect against opioid-related overdoses
- Prevent injection behaviors
- Reduce criminal behaviors
- Improve daily function

Abstinence without Medication Assisted Treatment



Hunt, WA. Journal of Clinical Psychology. 1971, 27(4): 455-456.

Decreased Mortality with Medication Assisted Treatment



Dupouy J. Annuals of Family Medicine. 2017, 15(4): 355-358.

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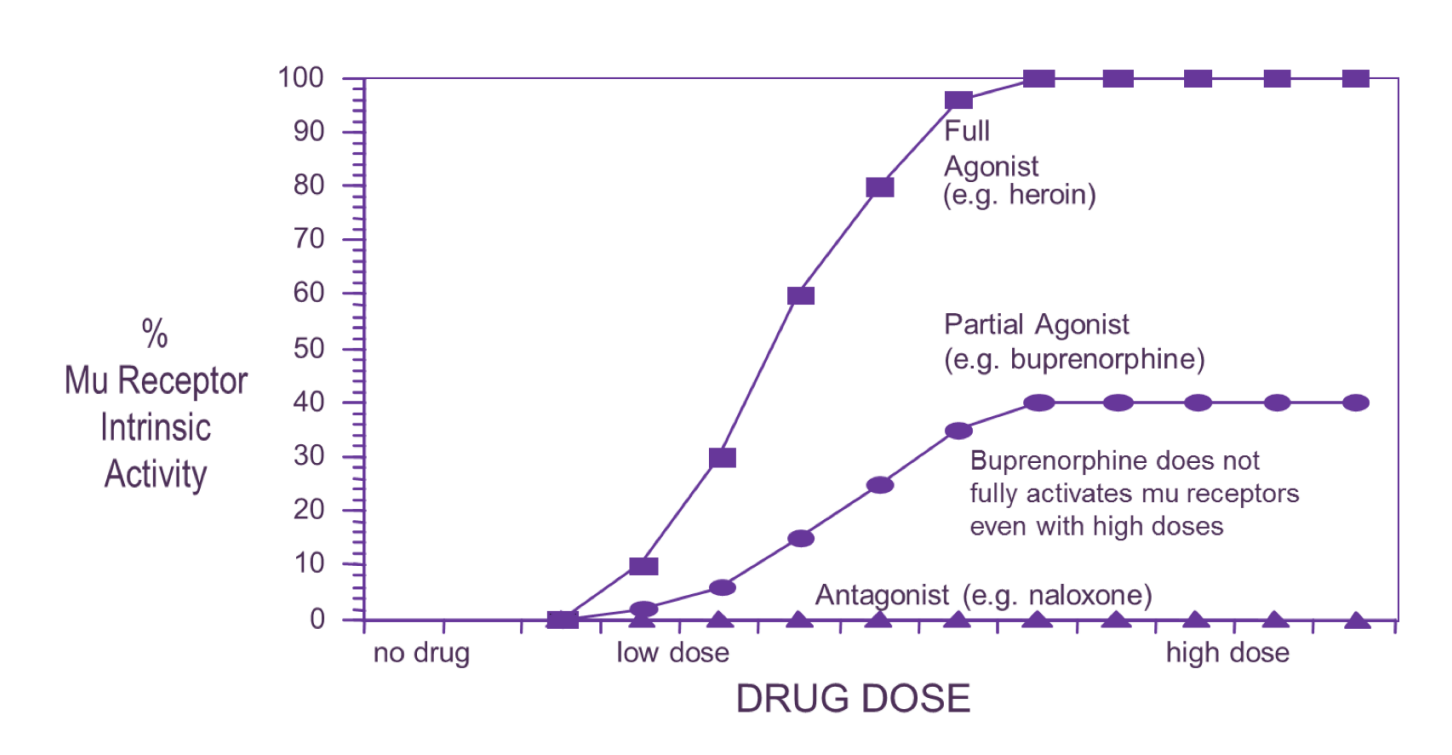
Ries RK. ASAM Principles of Addiction Medicine, 5th Ed. 2014.

Full Agonist vs Partial Agonist vs Antagonist



Orman JS. Drugs. 2009. 69(5): 577-607.

Methadone

- Methadone is a full agonist of the mu opioid receptor
  - Full agonist effect allows for analgesia/pain control
  - Full agonist effect can also result in euphoria at high doses
- Methadone has a weak affinity for the mu opioid receptor
  - It can be displaced from the receptor by other opioid agonists, partial agonists, and antagonists

Ries RK. ASAM Principles of Addiction Medicine, 5th Ed. 2014.

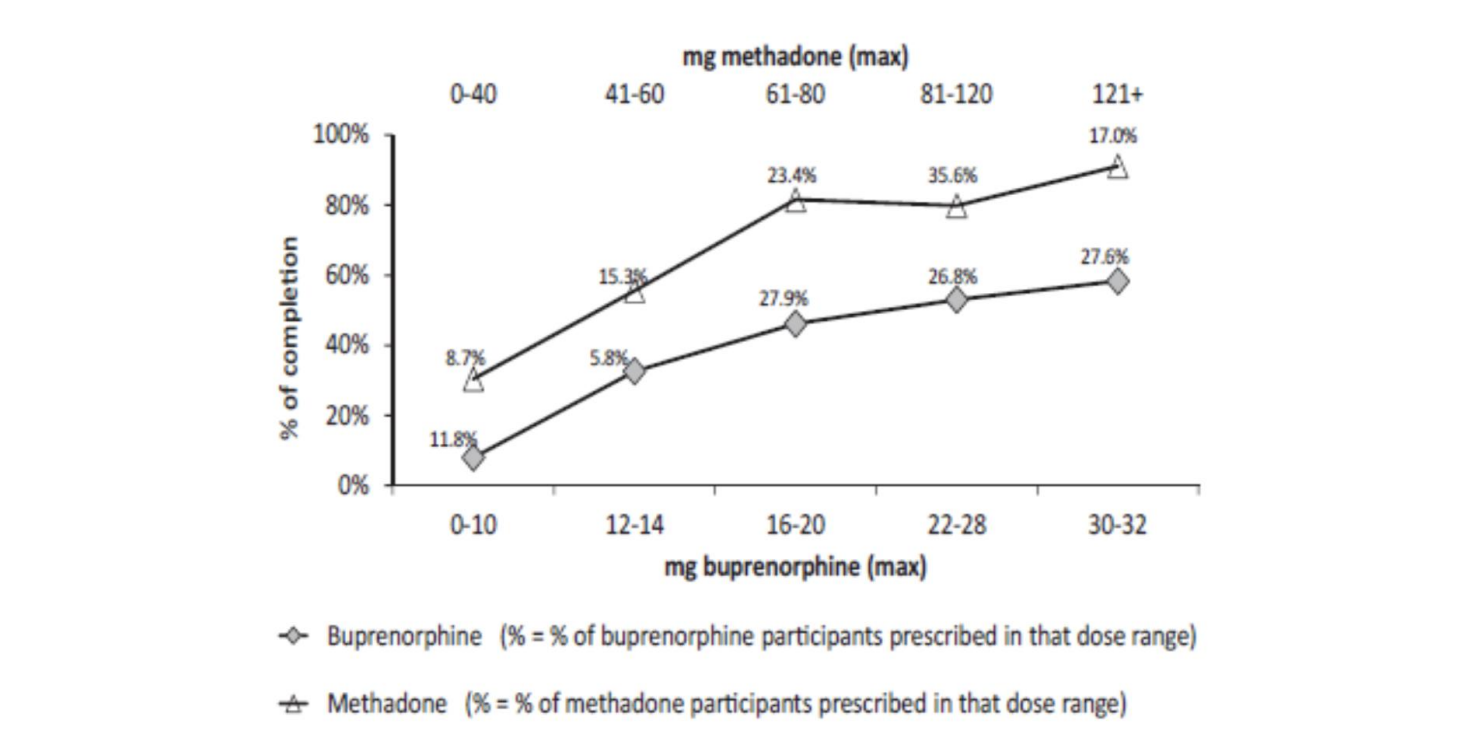
Benefits of Methadone Maintenance

- High dose methadone leads to superior retention in treatment when compared to high dose buprenorphine
- Psychosocial services are required and embedded into the opioid treatment program
- Has superior pain relief properties compared to buprenorphine
- Less expensive than both buprenorphine and extended-release naltrexone

Disadvantages of Methadone Maintenance

- Requires daily visits to the opioid treatment program initially
- May not successfully block other opioids
- Use of other sedatives including alcohol and benzodiazepines increase risk for overdose
- Causes opioid withdrawal when medication is ceased
- Interferes with other medications
- Increases risk of cardiac arrhythmias

Benefit of Methadone: Increased Retention



Hser Y. Addiction. 2014, 109(1): 79-87.

Buprenorphine

- Buprenorphine is a partial agonist of the mu receptor
- Buprenorphine has a high mu receptor affinity
  - Therefore, it will displace most full mu agonists
- Buprenorphine has slow mu receptor dissociation
  - Therefore, it will remain on the receptor a long time and prevents binding of full mu agonists
  - Despite slow dissociation it has relatively short analgesics effects

Ries RK. ASAM Principles of Addiction Medicine, 5th Ed. 2014.

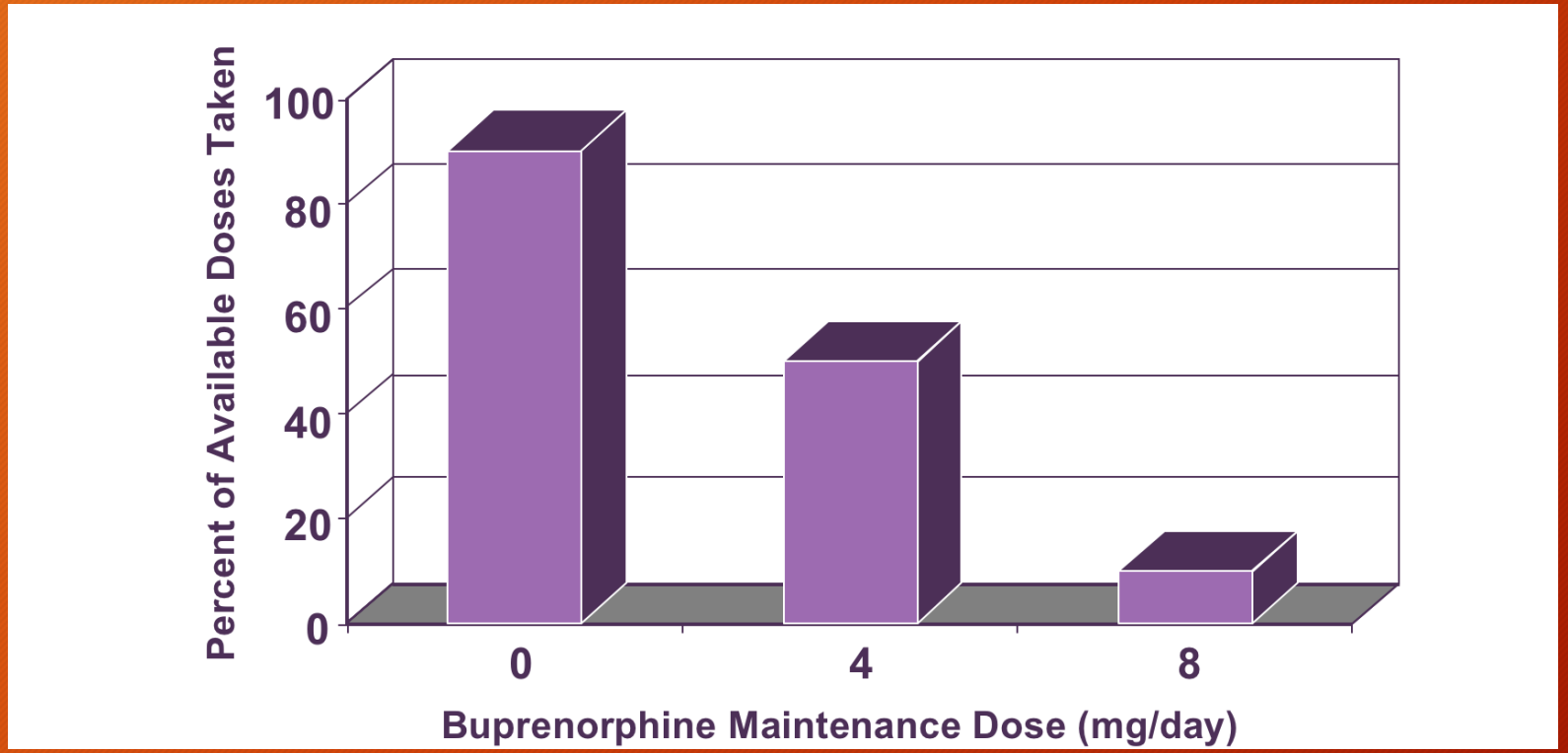
Benefits of Buprenorphine Maintenance

- Buprenorphine provides an option for outpatient based opioid treatment
- Buprenorphine reduces risk of opioid overdose
- Buprenorphine improves retention in treatment
- Buprenorphine reduces the overall use of other opioids
- Buprenorphine reduces heroin and other opioid cravings

Disadvantages of Buprenorphine

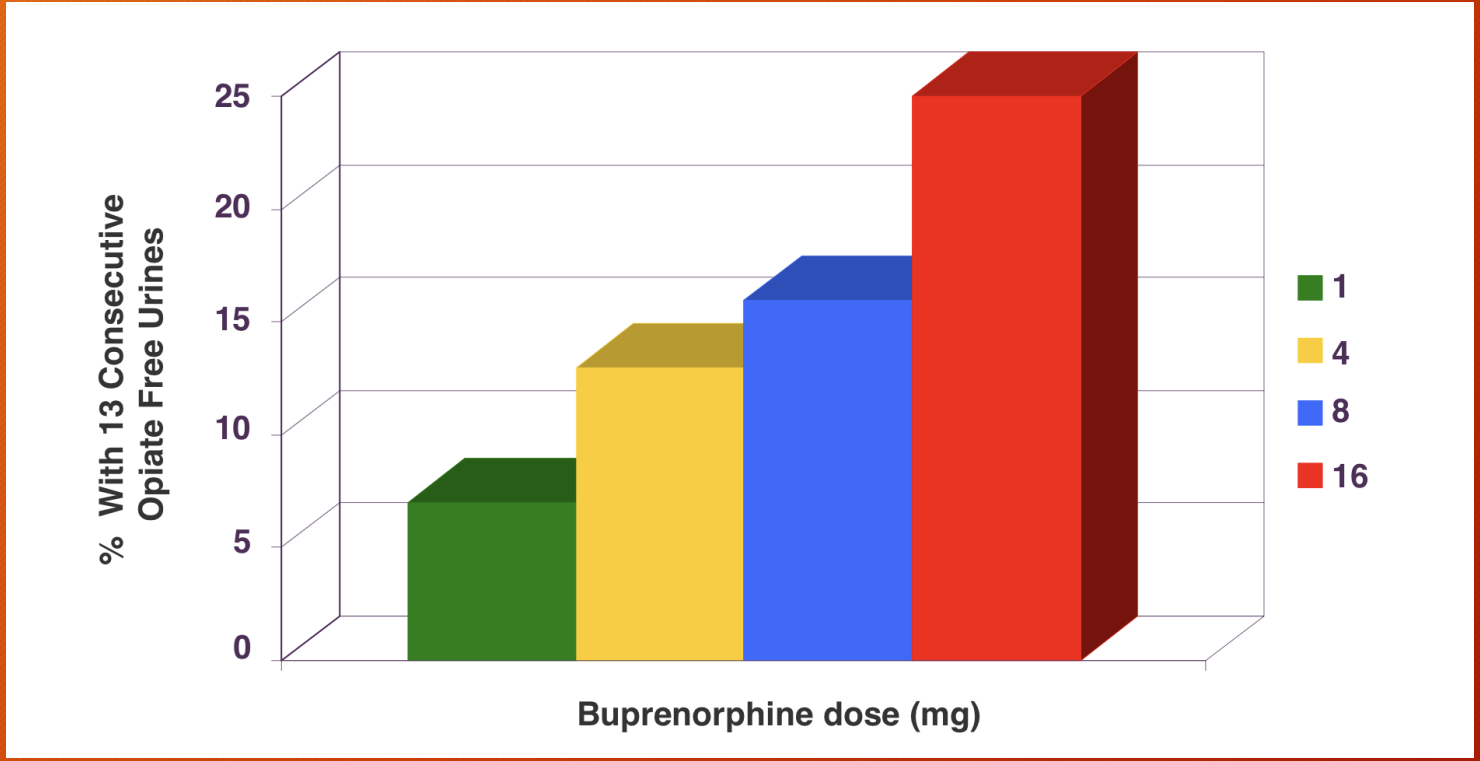
- Use of other sedatives including alcohol and benzodiazepines increase risk for overdose
- Causes opioid withdrawal when medication is ceased
- Diversion of medication is increasing

Heroin Self-Administration During Buprenorphine Maintenance Declines



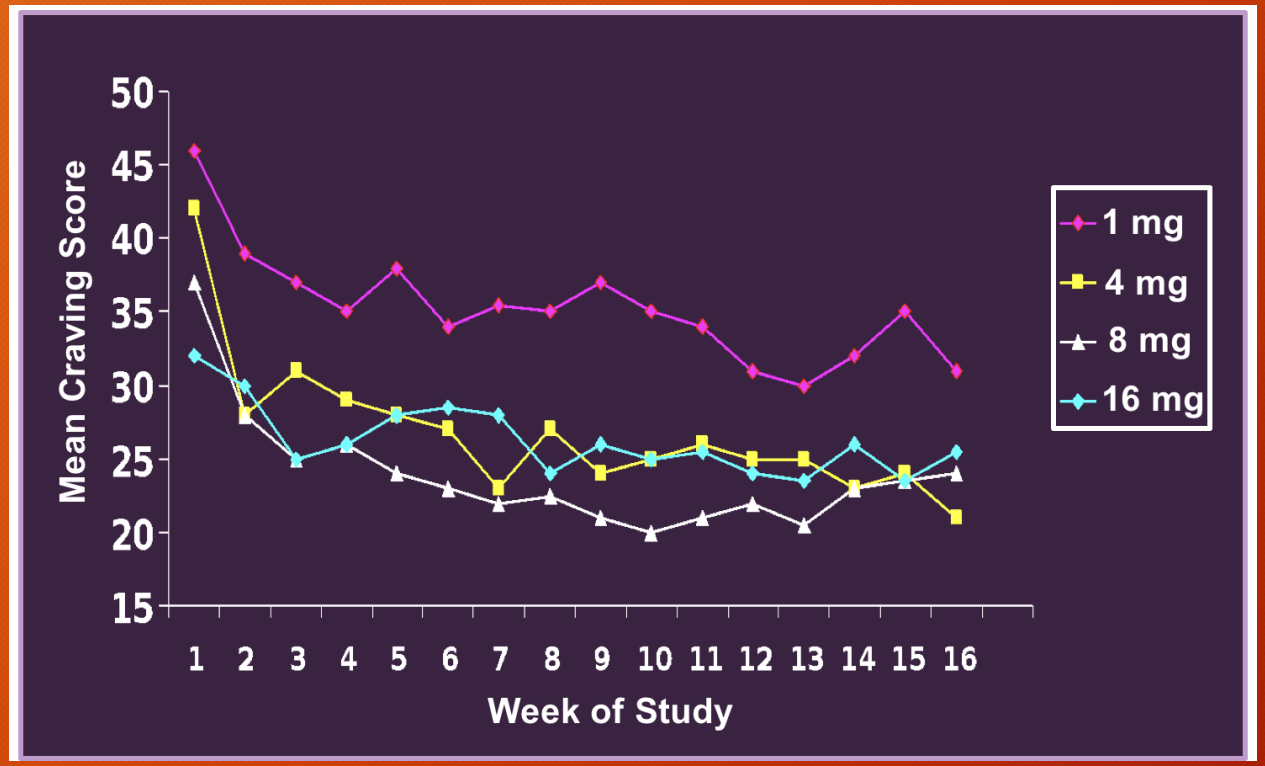
Mello NK. Journal of Pharmacology and Experimental Therapeutics. 1982, 223(1): 30-39.

Opiate Free Screens with Buprenorphine Dosing



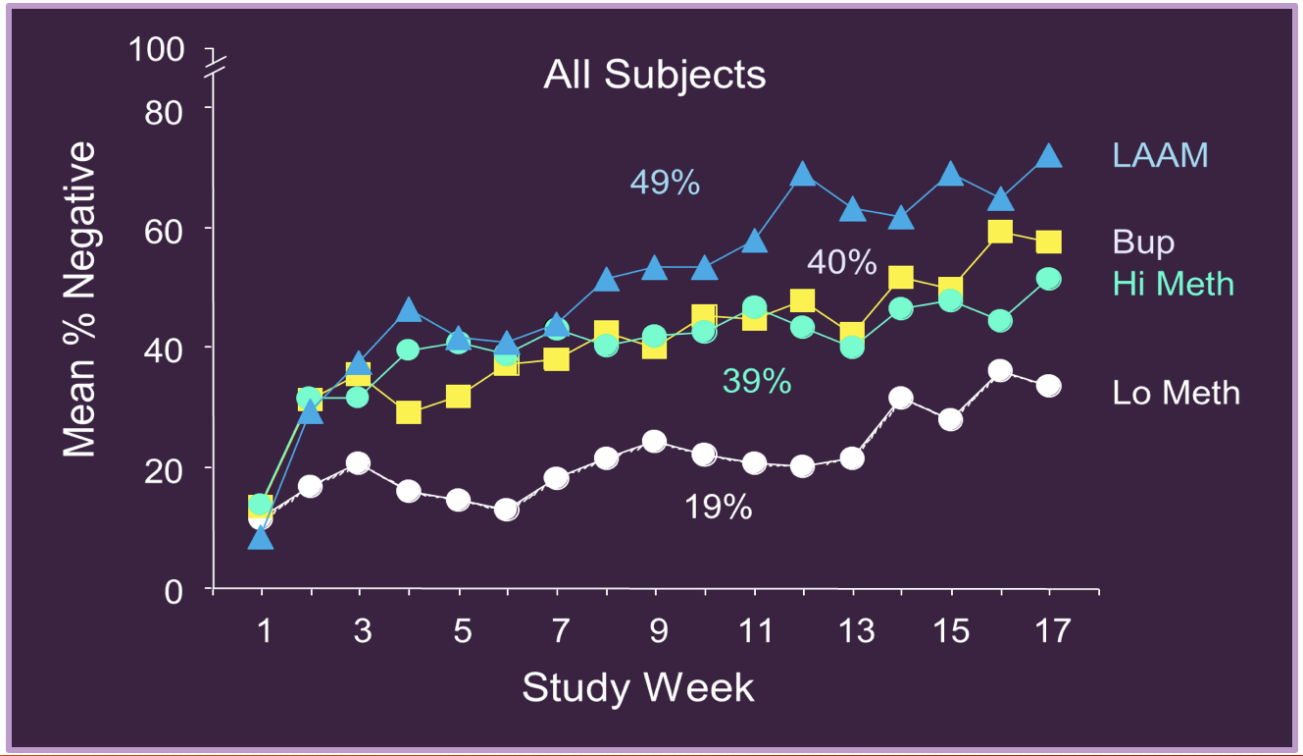
Ling W. Addiction. 1998, 93(4): 475-486.

Mean Heroin Craving Declines with Buprenorphine Maintenance



Ling W. Addiction. 1998, 93(4): 475-486.

Opioid Negative Urines Are Comparable with Buprenorphine and Methadone Maintenance



Johnson RE. NE Journal of Medicine. 2000, 343(18): 1290-1297.

Submucosal Buprenorphine Products

- Buprenorphine sublingual tablet (generic)
- Buprenorphine/naloxone sublingual tablets (generic, Zubsolv)
- Buprenorphine/naloxone sublingual films (Suboxone)
- Buprenorphine/naloxone buccal films (Bunavil)

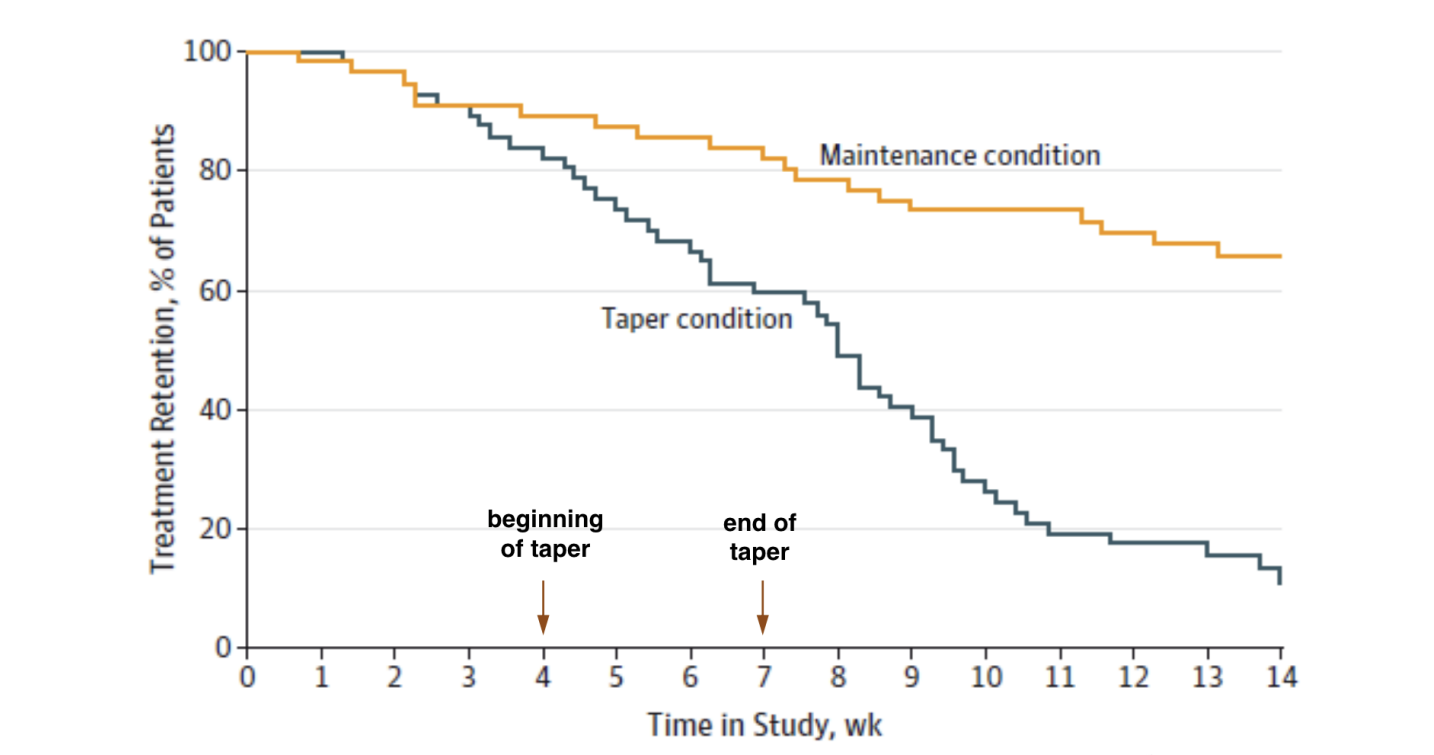
Buprenorphine implant

- Marketed as Probuphine
- No generic available
- Four 80 mg rods are implanted under the skin of the inner side of the upper arm
- Lasts for 6 months
- Requires training course for certification of use

Buprenorphine Extended-Release Injection

- Marketed as Sublocade
- No generic available
- Administered subcutaneously in the abdomen every 4 weeks by health care professionals after at least a 7 day induction period with sublingual buprenorphine
- Recommended dosage is 300 mg the first 2 months followed by 100 mg afterwards

Buprenorphine Taper vs Long-Term Maintenance



Fiellin DA. JAMA Internal Medicine. 2014, 174(12): 1947-1954.

Extended-Release Naltrexone

- Naltrexone is an antagonist of the mu opioid receptor
- Naltrexone has a high mu receptor affinity
  - Therefore, it will displace most full mu agonists
- Extended-release naltrexone deposits in the muscle and has a long half-life
  - Therefore, it will continuously occupy mu receptors and prevent binding of full mu agonists
  - Has no analgesic effects

Ries RK. ASAM Principles of Addiction Medicine, 5th Ed. 2014.

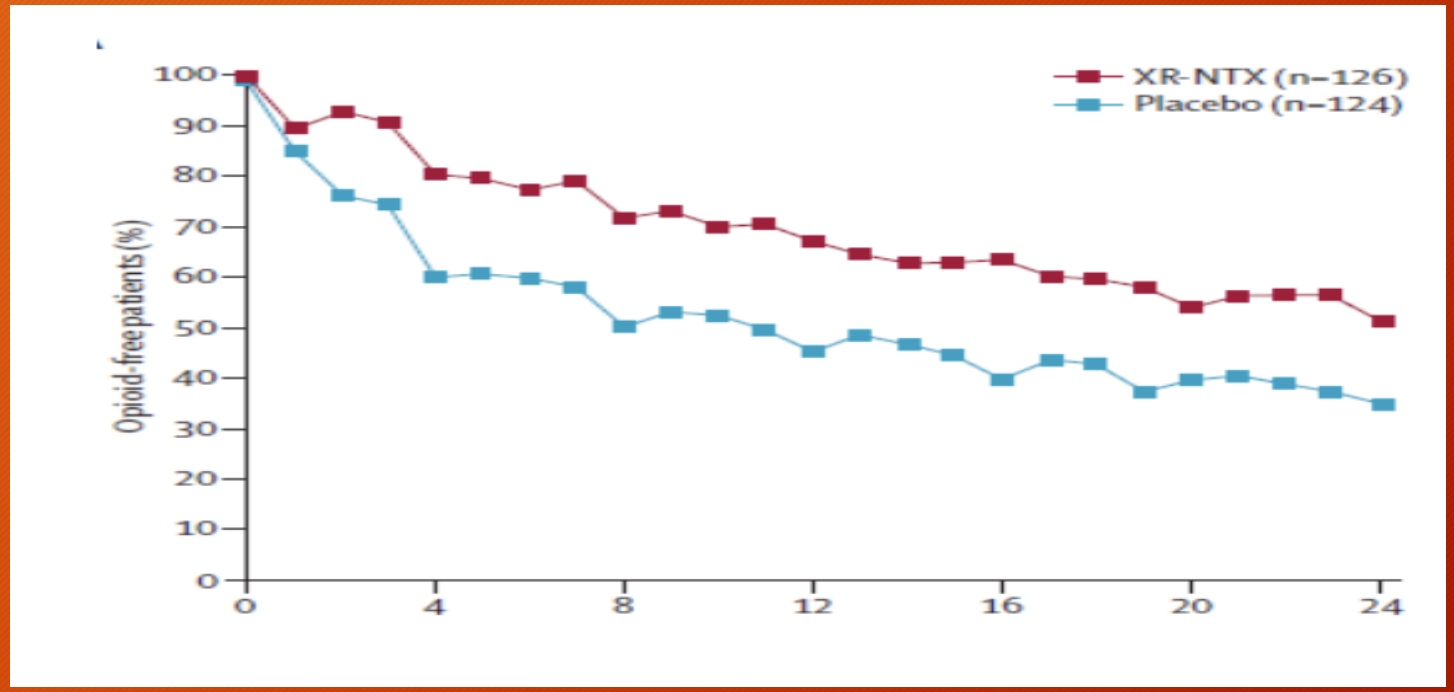
Benefits of Extended-Release Naltrexone

- Prevents opioid overdose by blockading the mu opioid receptor
- Improves treatment retention
- Reduces opioid cravings and number of positive opioid screens
- Administered once monthly to improve medication compliance
- Can be a useful option in individuals who are opioid free for an extended period of time but remain concerned about relapse
- No withdrawal from medication unlike methadone and buprenorphine
- Can be utilized in professions that do not allow use of agonist or partial agonist maintenance
- Also approved for treatment of alcohol addiction

Disadvantages of Extended-Release Naltrexone

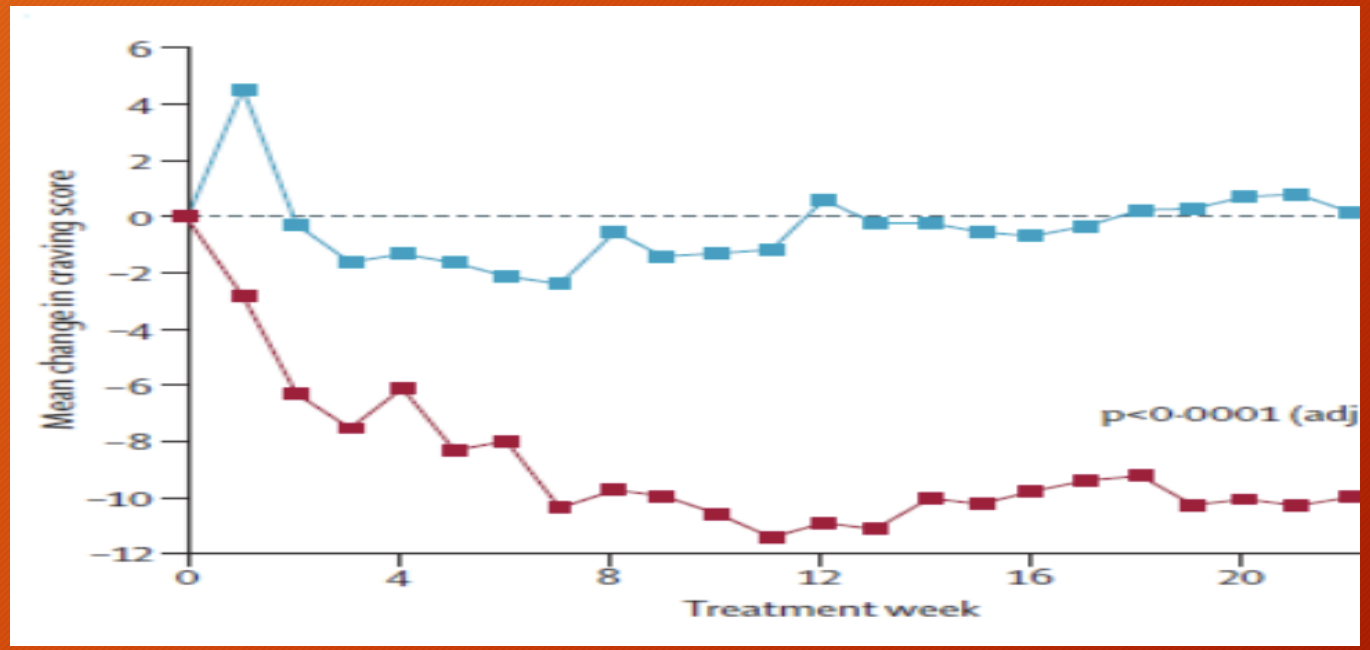
- Must be opioid free for 7-10 days prior to starting medication
- Takes longer to reduce opioid cravings compared to buprenorphine and methadone
- Does not improve pain
- More expensive than either methadone or buprenorphine (~$1100 per month)

Opioid Free Urines with Extended-Release Naltrexone



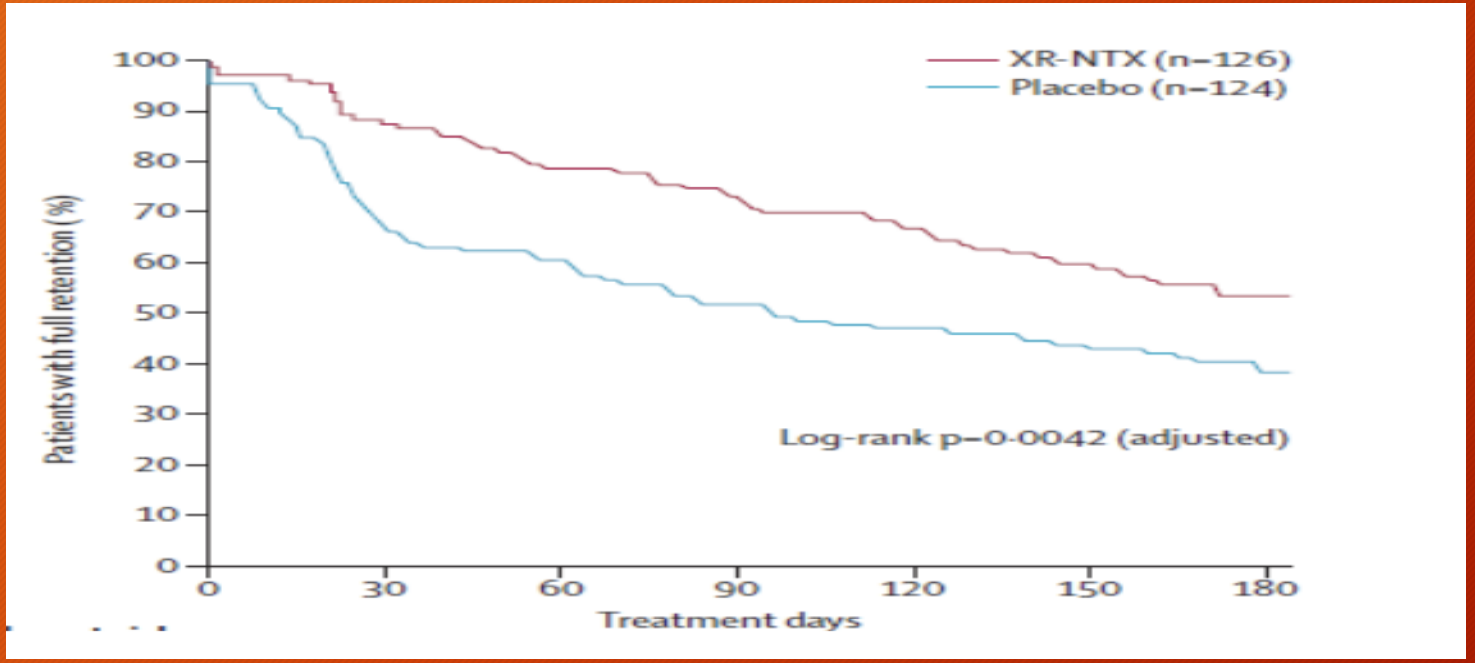
Krupitsky E. Lancet. 2011, 377(9776): 1506-1513.

Craving Reduction with Extended-Release Naltrexone



Krupitsky E. Lancet. 2011, 377(9776): 1506-1513.

Treatment Retention with Extended-Release Naltrexone



Krupitsky E. Lancet. 2011, 377(9776): 1506-1513.

Extended-Release Naltrexone vs Buprenorphine/Naloxone

- 24 week open label randomized controlled trial on 570 adult opioid addicts across 8 U.S. sites compared effectiveness of extended-release naltrexone vs buprenorphine/naloxone
- Conclusions
  - Higher level of difficulty initiating extended-release naltrexone (28% dropped out prior to initiation vs 6% with buprenorphine/naloxone)
  - Nearly all induction failures lead to relapse
  - Both had favorable outcomes in relapse rate, retention in treatment, negative urine assays, days of opioid abstinence, and days of opioid cravings once individuals were successfully inducted on the medications

Lee JD. Lancet. 2018; 391(10118): 309-318.

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