Buprenorphine Review

Kurt DeVine MD FASAM
Addiction Medicine
CentraCare

Collaborated Care Institute

Objectives

At the conclusion of this session, participants should be able to:

- Understand the options in MOUD
- Understand how buprenorphine differs from full agonists
- Describe the long term benefits
- Have a general understanding of the protocols for starting buprenorphine

Koob Definition of Addiction

Addiction is a chronic relapsing syndrome that moves from an impulse control disorder involving positive reinforcement to a compulsive disorder involving negative reinforcement.

Negative Reinforcement

"In negative reinforcement, a response or behavior is strengthened by stopping, removing, or avoiding a negative outcome or aversive stimulus" BF Skinner

What is MOUD

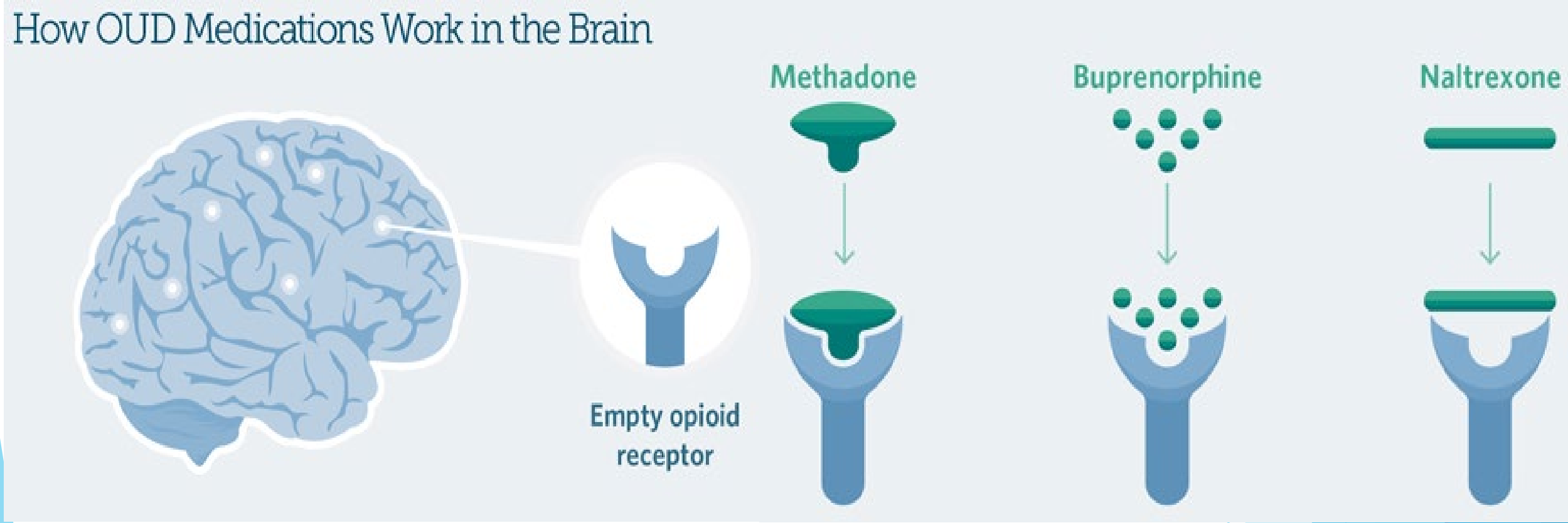
- MOUD stands for Medications for OUD
  - Methadone
  - Buprenorphine Products
  - Naltrexone/Vivitrol

Medication Assisted Treatment has been used previously but may be applied to any SUD

History of MOUD

- Reduction in:
  - HIV infection,
  - Hepatitis C
  - Crime
- Increases employment
- Improved participation in treatment
- Decreases all cause mortality

Medications Approved for the Treatment of OUD



Full agonist
- Generous effect
- Only at federally regulated clinic

Partial agonist
- Generates limited effect
- Any waivered provider

Antagonist
- Blocks effect
- Available but expensive

Buprenorphine Overview

- Developed in 1970s by Reckitt and Coleman as an analgesic.
- Further investigated at Addiction Research Center in Lexington, KY (Narcotic Farm)
- results in landmark paper by Jasinski ET al. Predicting it had potential as a drug to treat UTI due to unique pharmacology

Buprenorphine Overview

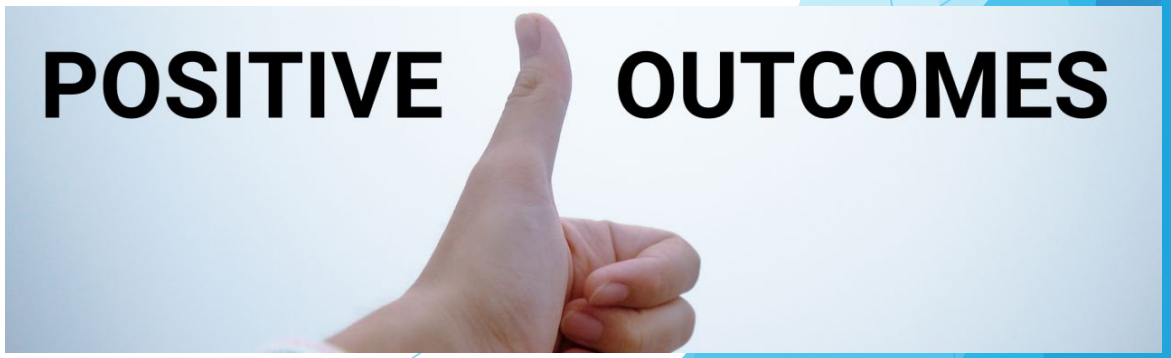
- Despite this, not approved to treat OUD until 2002 (parenteral form for analgesia was approved in 1989)
- Was being used abroad for a long time prior to approval in US.

Buprenorphine Overview

- In 2000, Data Act passed to allow waivers
- Sublingual formulations were schedule 3 drugs
- Multiple formulations have been developed: sublingual films and tablets, six-month implants, subcutaneous depot and more types in development.

Buprenorphine Overview

- Associated with positive outcomes
- France study showed patients who discontinued buprenorphine were 29x more likely to die (Dupouy et al)
- Buprenorphine associated with
  - Decreased crime
  - Decreased HIV, HCV



Buprenorphine Pharmacology

- MU receptor partial agonist
- Binds delta receptors
- Antagonist at Kappa opioid receptor
- Low incidence of respiratory depression-Ceiling effect
- The contribution of these interactions in OUD is unknown, but likely minimal.

Buprenorphine Pharmacology

- Because of Delta and Kappa involvement, buprenorphine is being investigated for:
  - Depression treatment (Karp et al, 2014)
  - Depression pathophysiology (Crowley and Kash, 2015)

Buprenorphine Pharmacology

- High affinity for MU receptor
- Comparison
  - 1.7 times stronger than hydromorphone
  - 6.2 times higher than fentanyl
  - 5.4 times higher than morphine
  - 120 times higher than Oxycodone
- (Volkow et al 2011)

Buprenorphine Disassociation from MU Receptor

- Buprenorphine stays attached to MU receptor for a long period of time, which contributes to long duration of action ad potential for
  - Daily dosing
  - Every other day dosing
  - 3x per week dosing
- Studies show minimal withdrawal and similar rates of drug use compared to daily dosing

Buprenorphine Disassociation

- Of note- in studies using dose ranging from 8-32mg, withdrawal symptoms were generally mild, increased over time after last dose, but severity was NOT related to dose

Buprenorphine Pharmacokinetics

Variability from patient to patient using transmucosal buprenorphine is high with estimates of bioavailability differing up to 3-fold after both acute and chronic administration

The amount of parent drug to reach systemic circulation

Buprenorphine Pharmacokinetics

- Differences may be due to individual variability in absorption
- IV and subcutaneous bioavailability is high with less variability

Buprenorphine Metabolism

- Buprenorphine CPY450 Metabolism ----> Norbuprenorphine
- This is first pass metabolism in the liver which happens in Buccal/SL use
- Norbuprenorphine is also an active metabolite at MU receptor

Buprenorphine Metabolism

- Other metabolites of buprenorphine are considered inactive
- Results from glucuronidation of buprenorphine and norbuprenorphine

Buprenorphine Metabolism Fun Facts

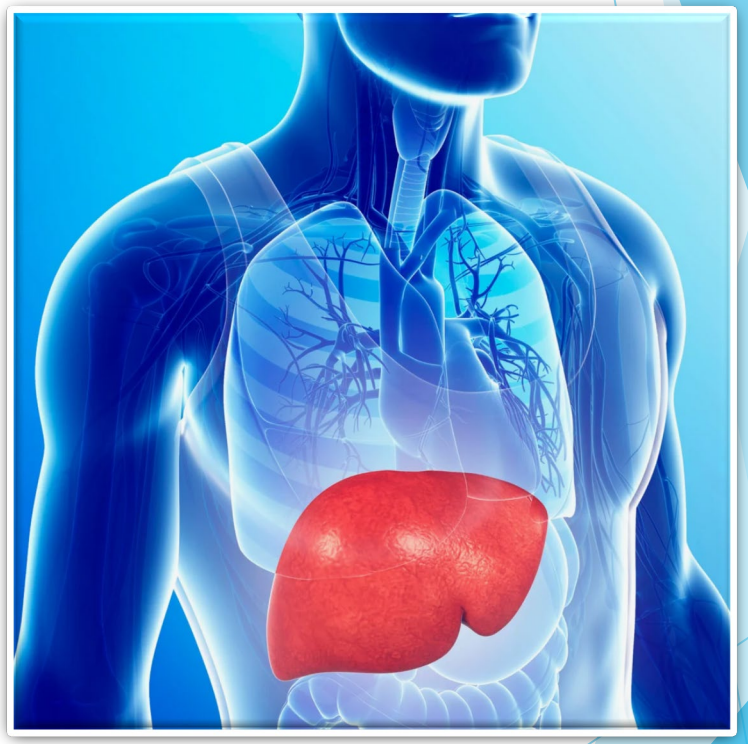
- Although norbuprenorphine is active, it has low concentrations in the brain, suggesting it may not contribute to the clinical effects of buprenorphine
- Norbuprenorphine is found in high concentrations in the urine

Buprenorphine- The Liver

- Study by Suxon et al 2013 (by NIDA)
- Enrolled patients with:
  - AST and ALT < 5x normal
  - ALK Phos < 3x normal

Buprenorphine- The Liver

- Randomized patients to methadone or buprenorphine
- Monitored liver functions over time



Buprenorphine- The Liver

- Results
  - No evidence of induced liver damage up to doses of 32mg daily sublingual
  - Extreme increases in liver function tests were uncommon
  - If LFTs increased it was due to seroconversion to Hep B or C or illicit drug use

Buprenorphine Naloxone Products

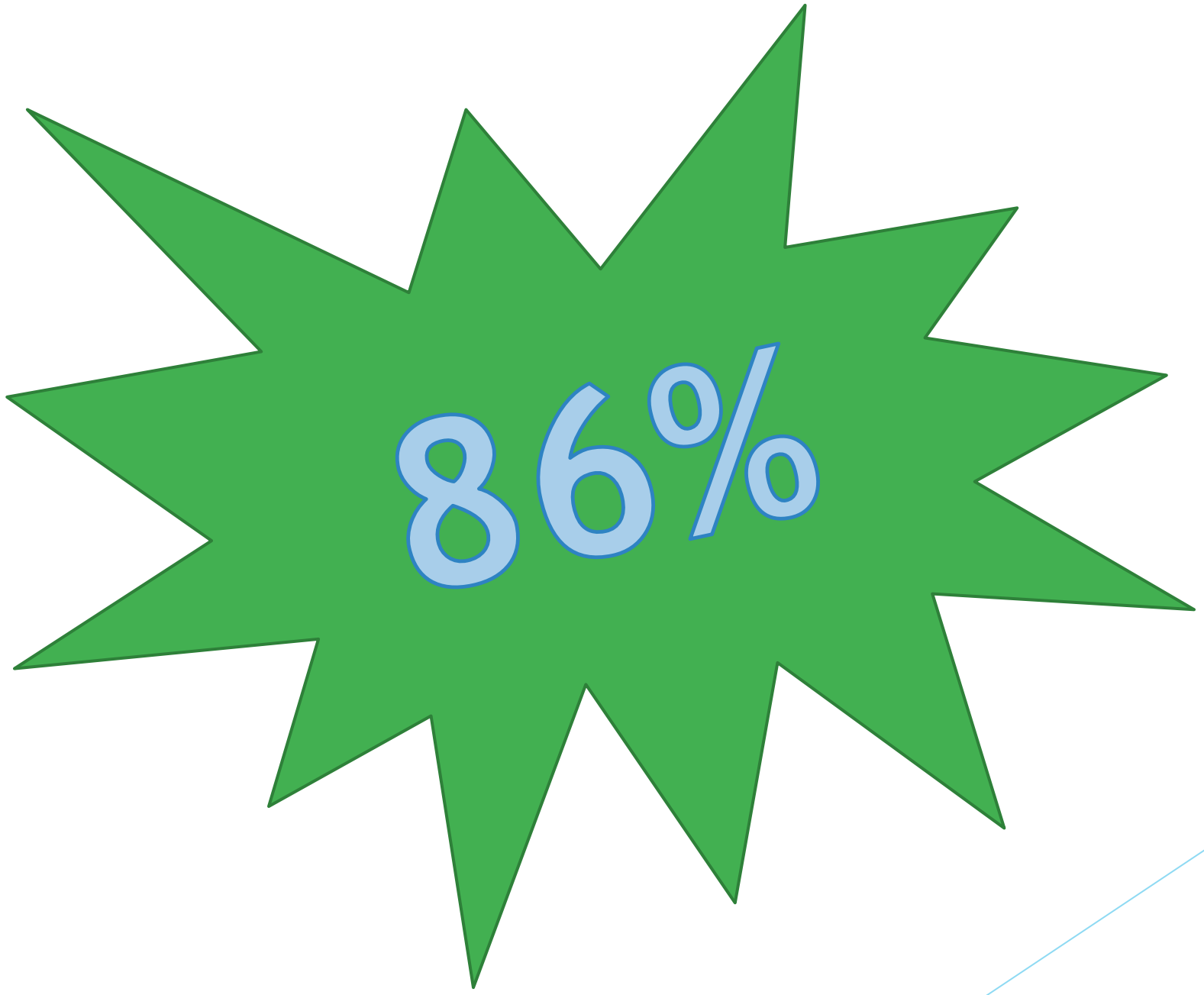
- Naloxone- MU antagonist, increases affinity
  - Inert, mostly in oral/sublingual preparations
  - Naloxone IV is 100% bioavailable and “snorted” 30% bioavailable
  - Sublingual bioavailability is about 3%

Buprenorphine Injectable

- FDA approved 2017
- 300 mg started dose, 100 mg maintenance
- Normal regimen, 300 mg, followed by monthly 100 mg doses
- Some suggest that two months of 300 mg injections might be more efficacious for IV drug user
- Expensive -1400 dollars per month

Buprenorphine and Pregnancy

- Buprenorphine vs. Bup/Naloxone
- Is there a place for injectable Sublocade? Limited data and contains a known teratogen in nonhuman animals. Brixadi (competitor) does not contain
- Dosing changes during Pregnancy
- Inductions during pregnancy-Low dose vs Macro
- Management of Pain-delivery vs C-Section


86%

MOUD Treatment Options

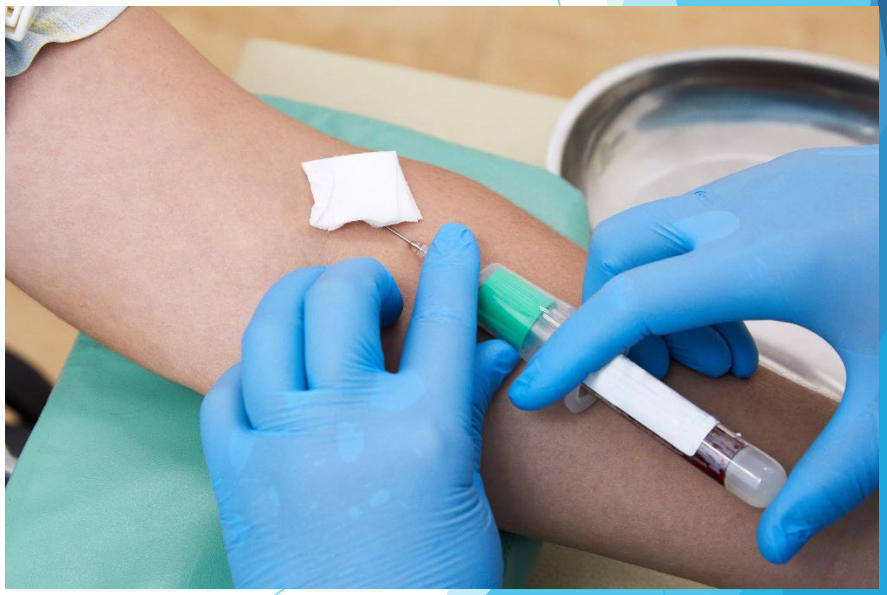
- Methadone
  - First discovered and marketed in Germany in 1939 as a pain medication
  - Used in the US in the 1950s for heroin detox
  - Not approved to treat addiction until 1972

MOUD Treatment Options cont.

- Methadone is different from other opiates in the following ways
  - Methadone patients generally do not develop tolerance
    - Meaning that once the patient reaches stabilization (pain is controlled or cravings subside) no dose increases are generally necessary

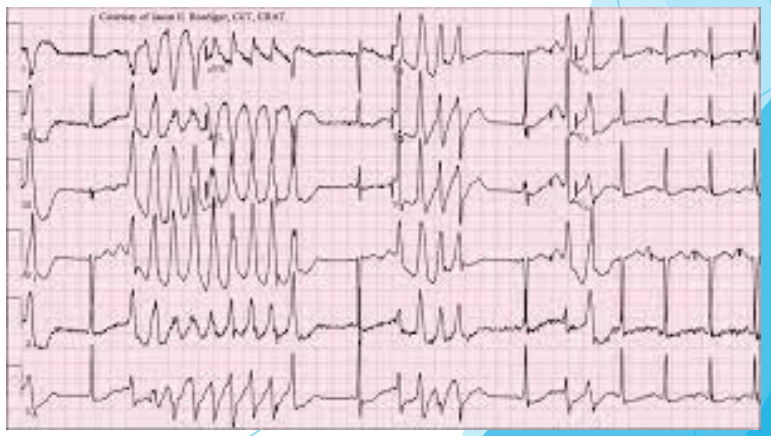
MOUD Treatment Options cont.

- Methadone dosing and schedule
  - Generally started at 5-10mg/day
  - Dose increases every 3-5 days
  - Serum levels can be checked, generally, <200 Ng/ml is considered subtherapeutic



MOUD Treatment Options cont.

- Methadone Side Effects/Risks
  - Disproportionate risk of overdose and deaths in relation to number of scripts written
  - Minor side effects like other opioids- nausea, constipation, insomnia, anxiety, and so on…
  - QT prolongation may cause fatal cardiac rhythm including torsade de pointes



MOUD Treatment Options cont.

- Naltrexone History
  - First synthesized in 1963 by Endo Laboratories (they were bought by Dupont)
  - No future work was done on this drug for several years
  - In 1972 Congress passed the Drug Abuse Office and Treatment Act, which encouraged the development of non addiction (non agonist) opioid addiction treatments
  - At that time, methadone was the only approved treatment

MOUD Treatment Options cont.

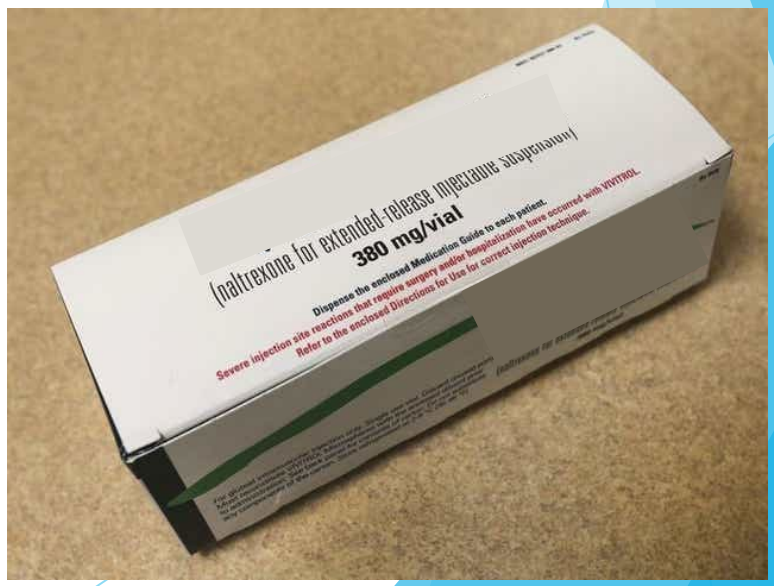
- Naltrexone History
  - Interest in Naltrexone was reignited for several reasons
    - Non sedating
    - Non addictive
    - No potentially fatal side effects of methadone

MOUD Treatment Options cont.

- Naltrexone History
  - In 1974 studies were done to facilitate FDA approval
  - Studies were promising, but compliance of an oral daily dose was problematic
  - Noncompliance led to relapse
  - Regardless, the FDA approved in 1984 noting some of these issues in labeling

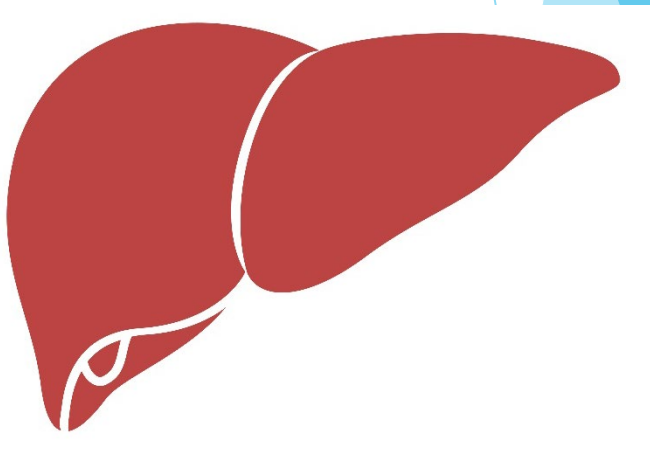
MOUD Treatment Options cont.

- Naltrexone History
  - Vivitrol (monthly injectable Naltrexone) showed markedly improved compliance
  - FDA approvals
    - AUD 2006
    - OUD 2010



MOUD Treatment Options cont.

- Advantages of injectable Naltrexone over oral MOUD treatments
  1. No first pass liver metabolism
  2. Total monthly dose less (due to #1)
  3. Compliance generally better



MOUD Treatment Options cont.

- Advantages of injectable Naltrexone over oral MOUD treatments
  - Can be treatment for both AUD and OUD
  - Compliance improved over oral meds
  - Can be initiated while patient continues to drink EtOH but not opioids

MOUD Treatment Options cont.

- Disadvantages of injectable Naltrexone over oral MOUD treatments
  - Pain control in the event of a significant injury will be challenging potentially for weeks
  - Neither form of naltrexone will induce tolerance which can be an issue if patient stops naltrexone and relapses
  - Patient must go through withdrawal prior to starting (28% relapse rate)
  - Cost about 1,400 dollars per month

MOUD Treatment Options cont.

- Naltrexone Risks
  - Precipitated withdrawal
  - NO addiction risk
  - Loss of opioid tolerance
  - Poor survival data compared to Bup/Methadone

Some Induction Basics

- Things to consider prior to induction
- Low Dose inductions
- Macro Inductions

What To Consider Prior To Induction

- What are they using? “Real Rx med” vs. Street
- Do we really know how much they using?
- Is what they use contaminated with other substances
- How long have they used opioid
- Have they had precipitated WD and how much Bup did it take
- How long ago was there last use

What To Consider Prior To Induction

- Have they been trying to taper or used less in the last few days and been in prolonged WD
- What route
- What form? Powder, Dirty 30’s
- How do other medications affect the Cows score? Pulse, pupils, symptoms,
- How accurate do you think the information they give you is?

Low Dose inductions

- I consider Low Dose inductions starting in the range of .5 mg-2 mg of Buprenorphine
- Micro induction can be started lower by cutting 2 mg strips or using IV Bup.
- Often with Fentanyl, you can start at 12 hours if cows is sufficiently elevated
- If you start earlier, with a lower Cows score, start and stay at lower doses and consider less frequent dosing

Low Dose inductions

- Pregnant patients are a special group and should be carefully dosed to avoid significant WD symptoms. If they present in significant WD a quick thorough history of use should be taken to guide dosing which should be started as soon as able, and care should be taken to improve symptoms and avoid precipitated WD
- Pregnant patients on Kratom should be carefully induced as precipitated WD can be significant

Low Dose inductions

- There are many methods of Low dose induction, the reality is there are many ways to do it that work, and many dosing strategies that will give good results. There is not a proven most effective method
- Genetic factors may be in play that affect the potential for precipitated withdrawal.
- All though many use a standard dosing and interval between dosing for the first 72 hours, again history should be considered with how aggressive you are.

My Usual Low Dose Induction

- Take specific history as previously discussed
- Generally prescribe 2 mg strips and have patient cut them if needed
- By third day of induction I generally increase more quickly.
- I dose based on symptom resolution and symptom return…let me explain.
- Encourage patient to call if issues, daily check ins

How Can This Go Wrong

- Patient takes to little and WD gets worse
- Patient overtakes (common) and precipitates
- Patient uses on top of Buprenorphine (good or bad?)
- Prior auth issues

Things To Know

- Patients will use other substance to lessen WD symptoms. Meth improves symptoms, MJ improve nausea. Alcohol may help them sleep.
- Patients often are hard to contact and their voicemail are often full. They may not answer if they don’t feel well or are sleeping, get permission to call a friend or family member.

Macro-dosing

- There is no standard way to dose, everyone does it a little different
- Advantage is that if it works, patient will go home with out symptoms and is less likely to relapse
- Disadvantage is sometimes they get worse before they get better and dosing may go over 32 mg prior to going home.
- Probably not a great idea in pregnancy

Macro-dosing

- If I consider this, I pretreat with Zofran, clonidine, and sometime lorazepam in case they develop symptoms
- It is best if they have high Cows score, greater than 15 and have not used for 10-12 hours
- If they severely underreport their use, macro-dosing will likely be more difficult

Summary

- Buprenorphine has many advantages over other MOUD choice
- Inductions have become more challenging in the era of Fentanyl
- Buprenorphine improves outcomes for both pregnant and non-pregnant patients
- Cautious inductions in pregnancy are preferred.

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Questions?

- Join Wednesday SOAR Addiction ECHO every week at 12:15-1:15
  - Weekly education on topics related to addiction and substance use
  - One ***FREE*** hour of CME weekly
- Contact kstangl@stratishealth.org for more information

- Contact me for any question or help Kurt.devine@centracare.com
- Cell 320-630-2507