Buprenorphine for NTP's

Friday, August 7th, 2020

Speaker Intro

- Dr. Candy Stockton-Joreteg, MD, FASAM;
  - CMO, Humboldt Independent Practice Association
- I have no relevant disclosures
- The slides used for today's presentation are adapted from the PCSS MAT Waiver Eligibility Training (*my own additions are italicized*)

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Overview:
Opioid Use Disorder Treatment with Buprenorphine/Naloxone

History of Opioids

- Utilized throughout the world for various uses for thousands of years
- 1800's:
  - Morphine and Heroin were marketed commercially as medications for pain, anxiety, respiratory problems
  - Invention of Hypodermic syringe allowed for rapid delivery to the brain

Pivotal Milestones in Treatment

Year	Milestone
1970 1973	Methadone is approved by the FDA for *detoxification* Methadone is approved by the FDA for *maintenance*
1974	Opioid Treatment Programs (OTP's) able to dispense Methadone for maintenance treatment
1984	Oral Naltrexone is approved by the FDA
2000	Drug Addiction Treatment Act of 2000 (DATA 2000) allowed qualified physicians to offer Office Based Opioid Treatment (OBOT)
2002	Buprenorphine is approved by the FDA
2010	Extended-release injectable naltrexone is approved by the FDA
2016	Comprehensive Addiction and Recovery Act (CARA) - Allows Nurse Practitioners and Physician Assistants to become eligible to prescribe buprenorphine for treatment of opioid use disorder

Treatment Goals

- Range of treatment goals

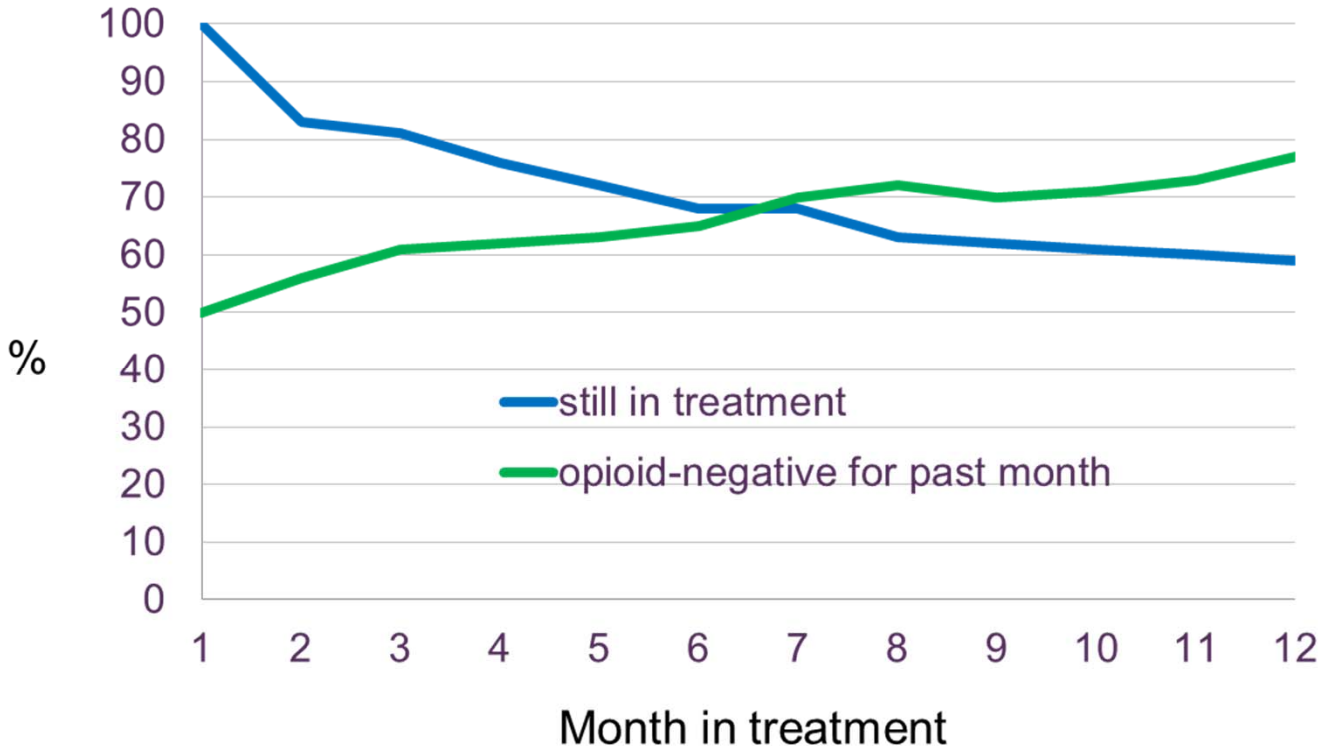
Minimization of harms from ongoing use

Sustained recovery with abstinence from all substances

- Treatment Options; Federations of State Medical Boards 2013
  - Partial Agonist (Buprenorphine) at the mu-receptor – OBOT/OTP
  - Agonist (Methadone) at the mu-receptor - OTP
  - Antagonists (Naltrexone) at the mu-receptor
  - Simple detoxification and no other treatment
  - Counseling and/or peer support without MAT
  - Referral to short or long term residential treatment

Treatment Retention and Decreased Illicit Opioid Use on MAT

- Buprenorphine promotes retention, and those who remain in treatment become more likely over time to abstain from other opioids



Kakko et al, 2003
Soeffing et al., 2009

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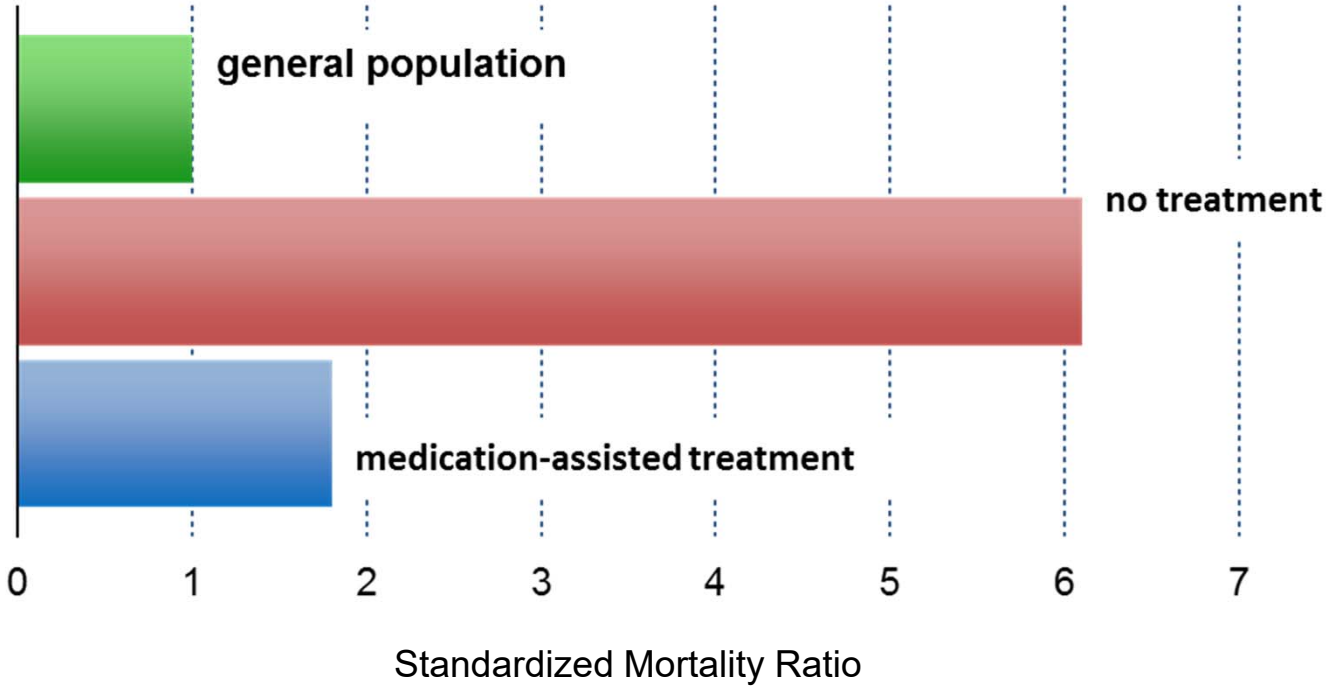
Benefits of MAT: Decreased Mortality

Death rates:



Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017

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Summary

- A number of legislative initiatives have been passed to improve access to treatment for opioid use disorders
- MAT for opioid use disorder has several benefits including:
  - Decrease in the number of fatal overdoses
  - Increase patients' retention in treatment, and improved social functioning
- *People with any form of chronic disease deserve to be offered the full range of reasonable treatment options available and allowed to participate in treatment decisions*

Pharmacology

Major Features of Methadone

***Full Agonist* at mu receptor**

Long acting

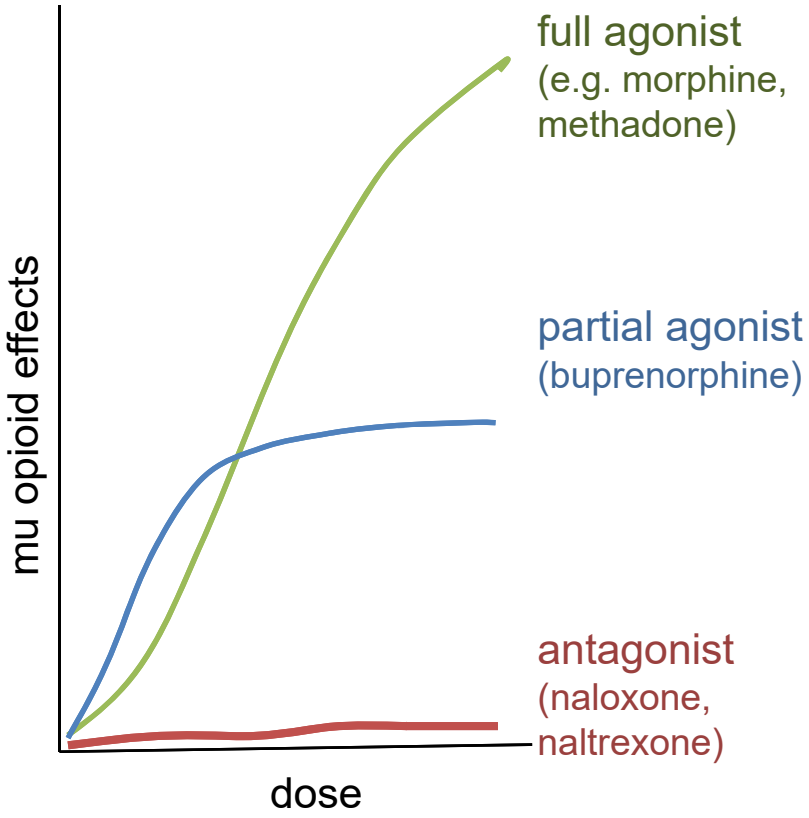
- Half-life ~ 15-60 Hours

Weak affinity for mu receptor

- *Can be displaced by partial agonists (e,g. burprenorphine) and antagonists (e.g.naloxone, naltrexone),* which can both precipitate withdrawal

Monitoring

- Significant respiratory suppression and potential respiratory arrest in overdose
- QT prolongation



CSAT, 2005

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Major Features of Naltrexone

Full Antagonist at mu receptor

- Competitive binding at mu receptor

Long acting

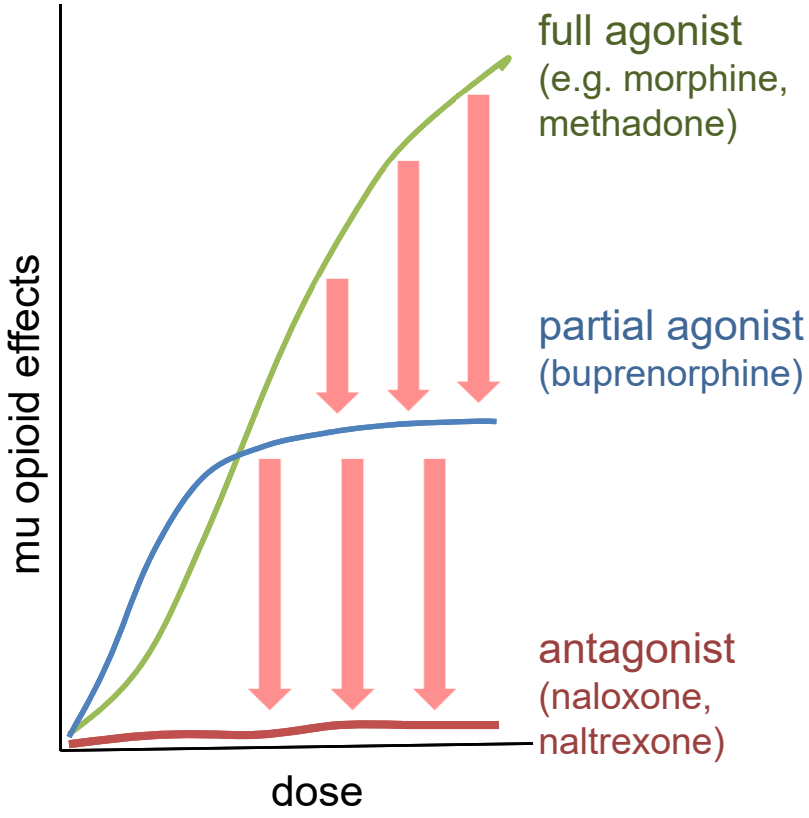
- Half-life:
  - Oral ~ 4 Hours
  - IM ~ 5-10 days

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids
  - Can precipitate withdrawal

Formulations

- *Tablets: Revia®: FDA approved in 1984*
- *Extended-Release intramuscular injection: Vivitrol®: FDA approved in 2010*



SAMHSA, 2018

Major Features of Buprenorphine

Partial agonist at mu receptor

- Comparatively minimal respiratory suppression and no respiratory arrest when used as prescribed

Long acting

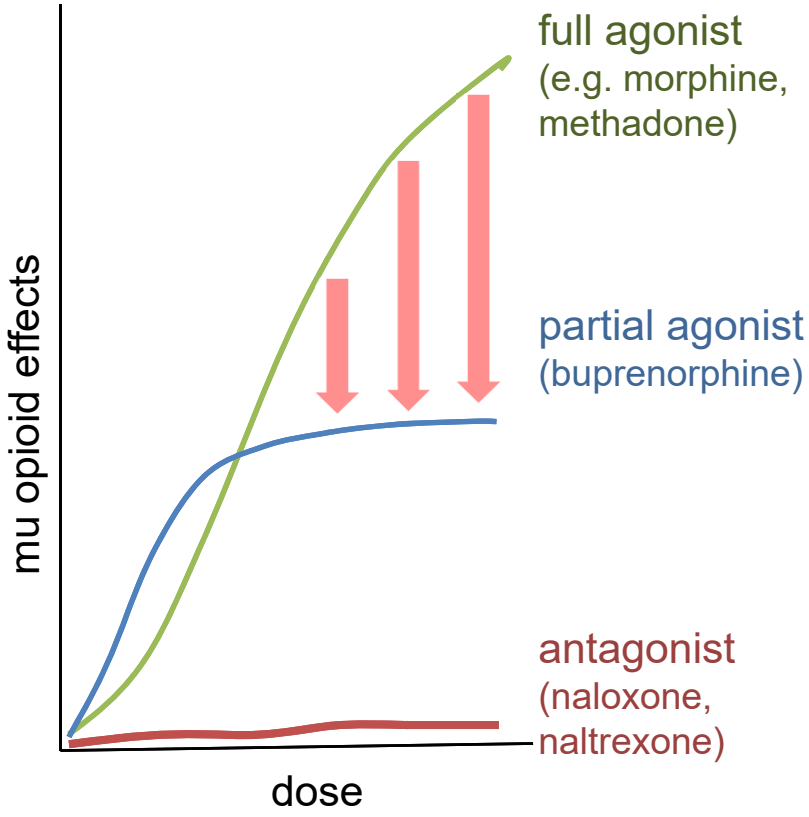
- Half-life ~ 24-36 Hours

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids
  - Can precipitate withdrawal

Slow dissociation from mu receptor

- *Stays on receptor for a long time*



SAMHSA, 2018
Orman & Keating, 2009

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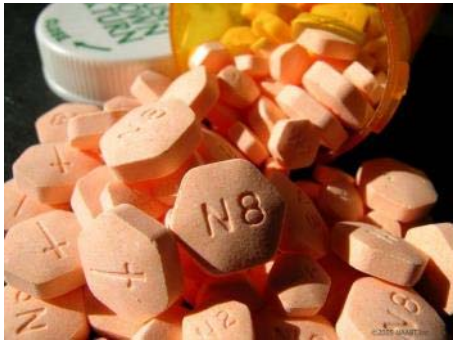
Buprenorphine

- Semi-synthetic analogue of thebaine
- Approved by the FDA in 2002 as a Schedule III medication for the treatment of opioid use disorder
- Metabolized in the liver, mainly by cytochrome P450 3A4 (CYP3A4), and has a less-active metabolite, norbuprenorphine



- Most buprenorphine is ultimately excreted into the biliary tract, but small fractions enter the urine and are detectable in urine drug tests
- Because of extensive first-pass metabolism, buprenorphine has poor oral bioavailability when swallowed (<5%), and all therapeutic formulations use other routes
- Sublingual administration bypasses first-pass metabolism and allows bioavailability around 30%

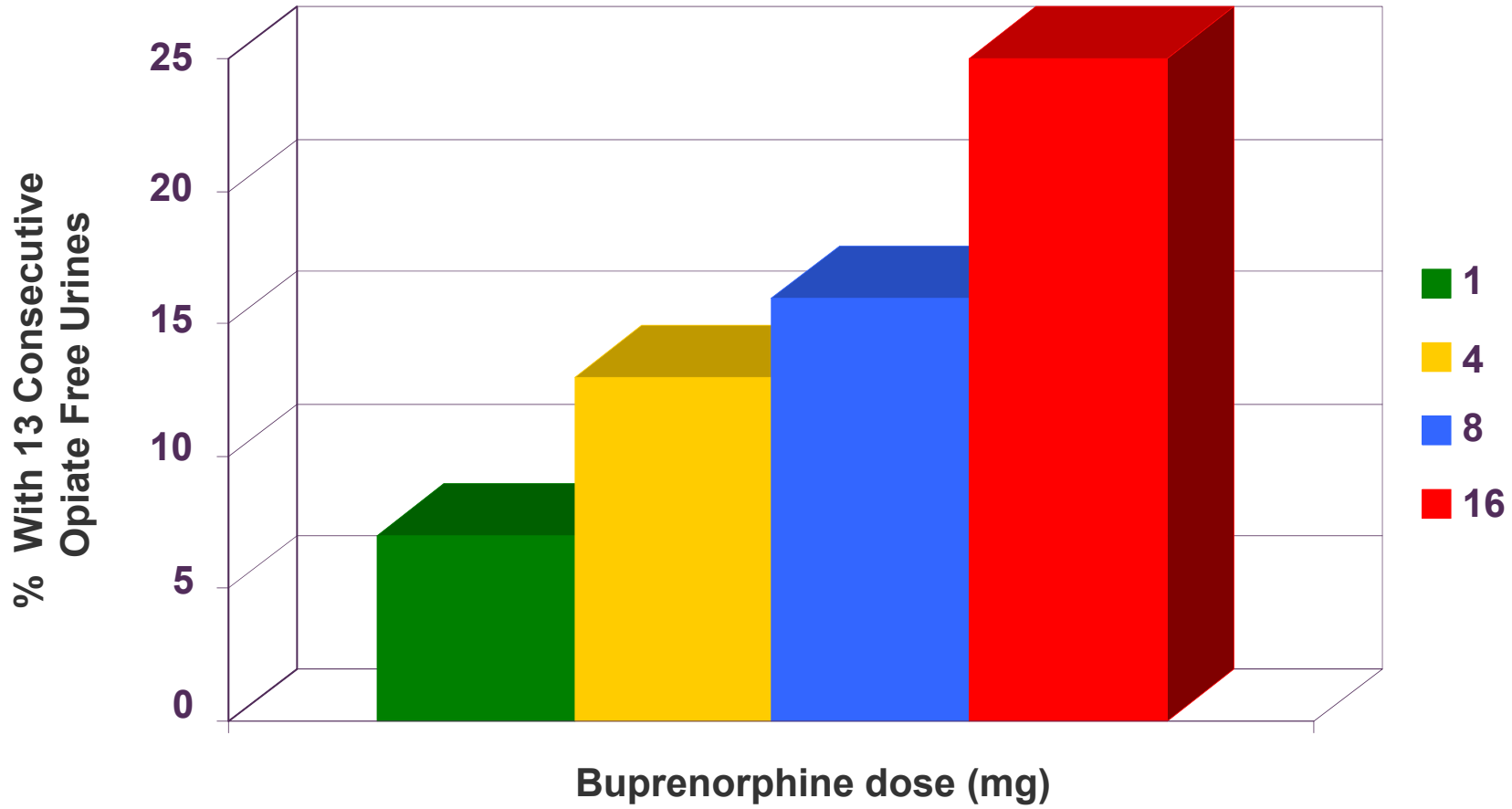
Mendelson et al., 1997
SAMHSA, 2016, 2016
SAMHSA, 2018

How Does Buprenorphine Work?

- AFFINITY is the strength with which a drug physically binds to a receptor
  - Buprenorphine has strong affinity; will displace full mu receptor agonists like heroin and methadone
  - Receptor binding strength, is NOT the same as receptor activation
- DISSOCIATION is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine dissociates slowly
  - Buprenorphine stays on the receptor a long time and blocks heroin, methadone and other opioids from binding to those receptors

NOTE: It is unlikely to block *all* effects from an opioid taken after initiation of buprenorphine treatment. Because binding to mu receptors is a dynamic process; while effects may be less, they are not likely to be completely eliminated.

Buprenorphine Dosing: Efficacy



Ling et al., 1998

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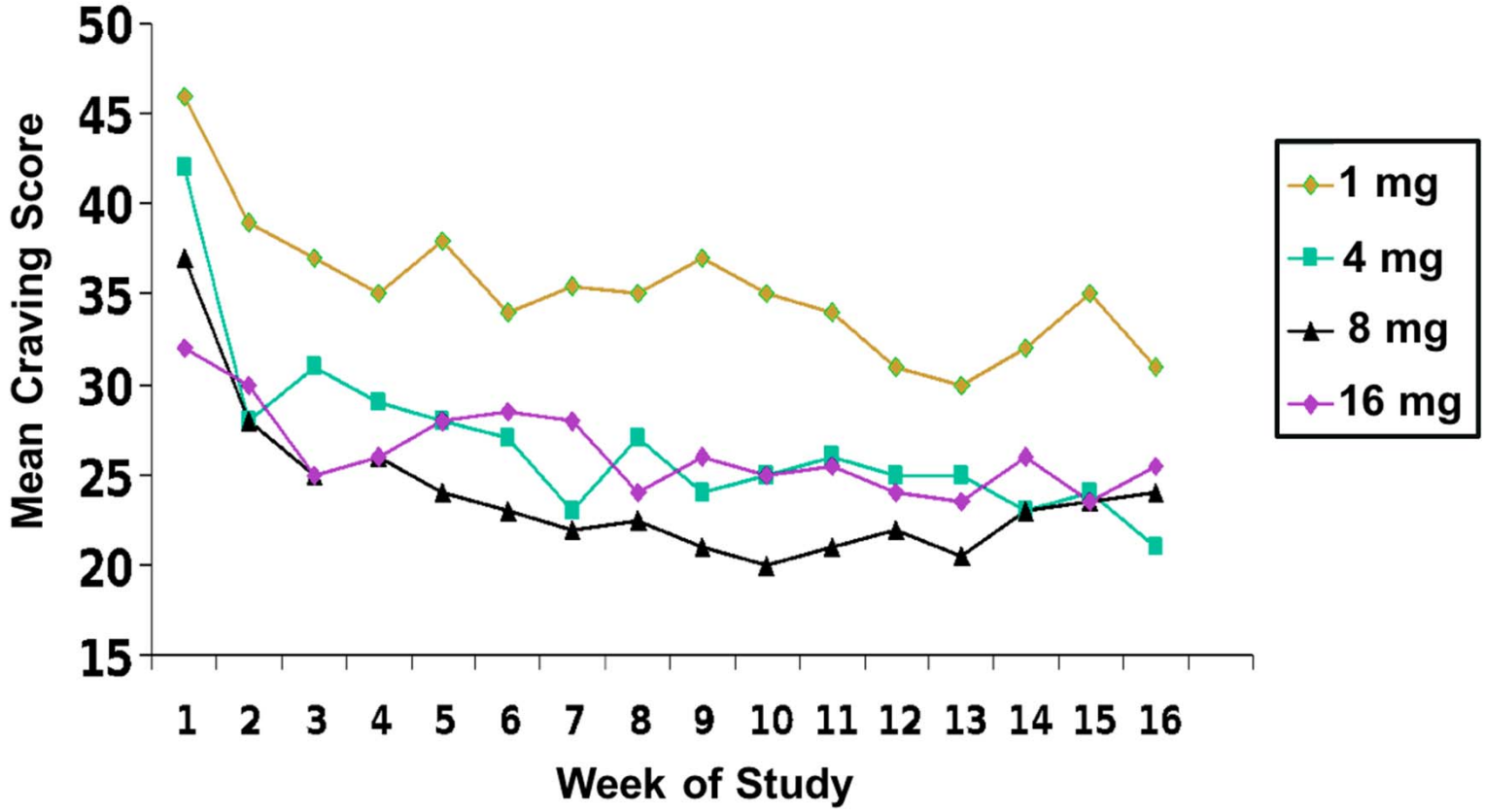
Mean Heroin Craving: 16 Week Completers: Reduced Craving with Therapeutic Buprenorphine Doses



Ling et al., 1998

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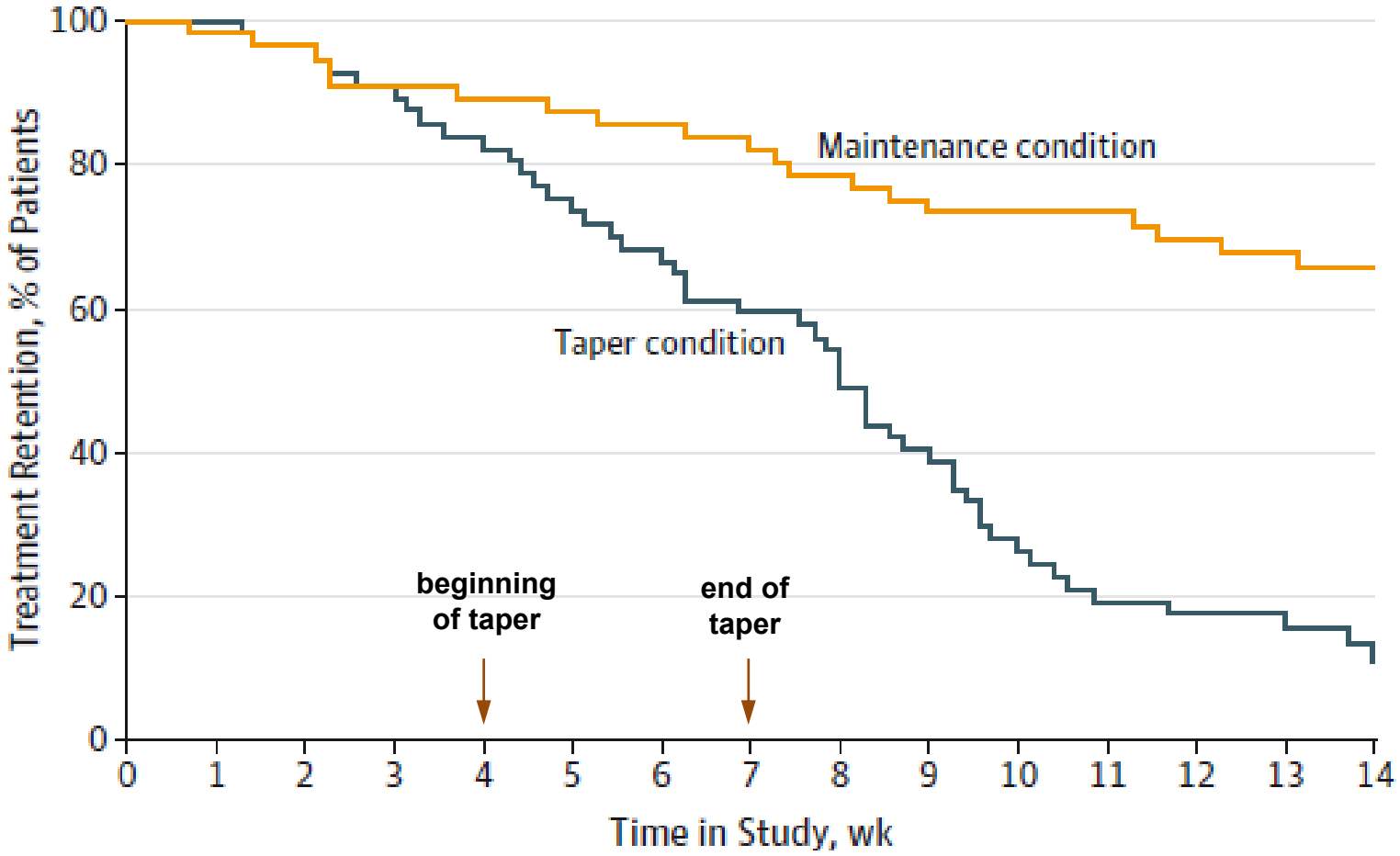
Buprenorphine: Maintenance vs. Taper



Fiellin et al., 2014

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Common Adverse Effects of Buprenorphine

- Headaches
  - Management: aspirin, ibuprofen, acetaminophen (if there are no contra-indications)
- Nausea
  - Management: Consider spitting the saliva out after adequate absorption instead of swallowing.
- Constipation
  - Management: Stay well-hydrated, Consume high-fiber diet, Consider stool softeners, laxatives, naloxegol
- Xerostomia (Dry mouth) – side effect of ALL opioids
  - Complications: Gingivitis, Periodontitis
  - Management: Stay well-hydrated, Maintain good oral hygiene

SAMHSA, 2018
Wald, 2016

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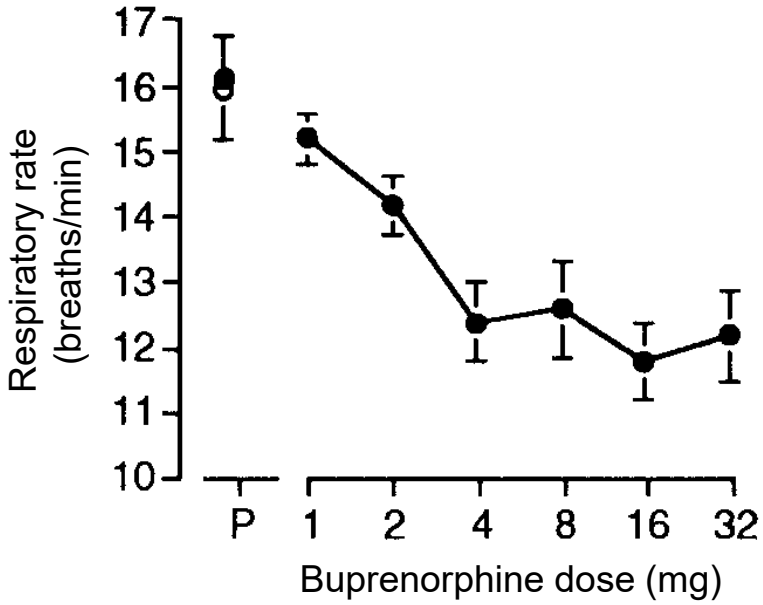
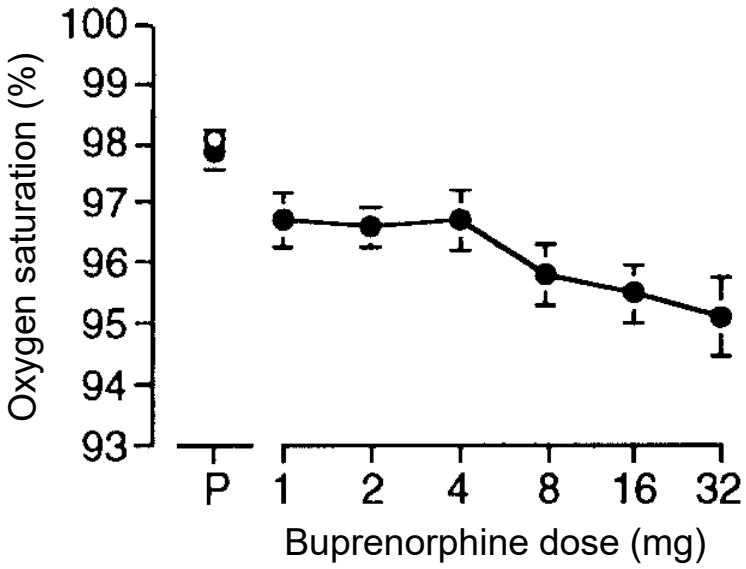
Buprenorphine Dosing: Safety

- Cognitive and psychomotor effects appear to be negligible.
- Respiratory rate slowed but has as a plateau effect in adults.





- Nearly all fatal poisonings involve multiple substances

Hakkinen et al., 2012
Walsh et al., 1994

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Rationale for the Combination of Buprenorphine with Naloxone

- When used as prescribed (sublingual or buccal administration), there is minimal bioavailability of naloxone
- Compared to buprenorphine alone, the buprenorphine/naloxone combination:
  - was developed to decrease IV misuse
  - is more likely to precipitate a withdrawal effect if injected by a current opioid user.
  - produces a slowed onset effect when injected or insufflated in those who are physically dependent buprenorphine.
  - per prescription, is less likely to be diverted

Comer et al., 2010
Jones et al., 2015
Stoller et al., 2001

Buprenorphine vs Placebo vs Methadone maintenance for opioid dependence

- Cochrane Review of 31 trials with over 5,400 participants found:
  - Buprenorphine is an effective medication for retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials
  - Buprenorphine appears to be less effective than methadone in retaining people in treatment, if prescribed in a flexible dose regimen or at a fixed and low dose (2 - 6 mg per day)
  - However, Buprenorphine prescribed at fixed doses (above 7 mg per day) was not different from methadone prescribed at fixed doses (40 mg or more per day) in retaining people in treatment or in suppression of illicit opioid use

Mattick et al., 2014

Buprenorphine and Benzodiazepines

- Benzodiazepines are present in most fatal poisonings involving buprenorphine

Human studies	Minimal effects on respiration when both are taken at therapeutic doses
Animal studies	May remove the protective "ceiling effect" and allow buprenorphine to produce fatal respiratory suppression in overdose

- Used as prescribed benzodiazepines in combination with buprenorphine have been associated with more accidental injuries, but not with other safety or treatment outcomes

Bardy et al., 2015
Jones et al., 2012
Nielsen & Taylor, 2005
Schuman-Olivier et al., 2013

Changes in FDA Recommendations

08/2016	09/2017
▪ Boxed Warning for combined use of opioid medicines with benzodiazepines or other CNS Depressants (e.g. Alcohol) ▪ Risks of slowed or difficult breathing; Sedation; Death	▪ 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.

FDA, 2016, 2017

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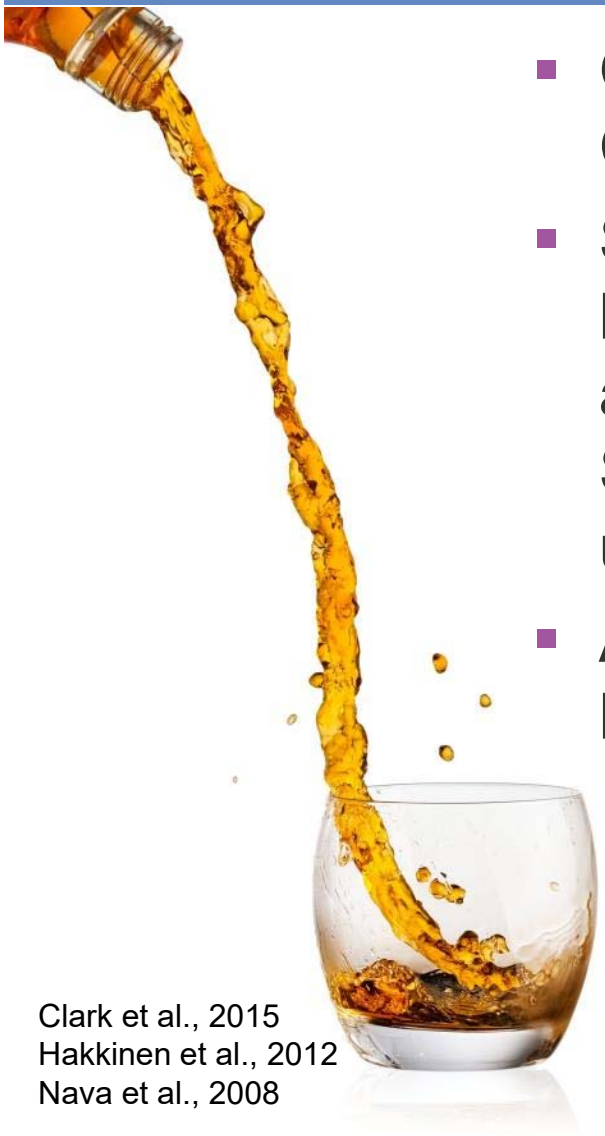
Buprenorphine and Alcohol



- Overall recommendation is to generally avoid CNS depressants with buprenorphine
- Some evidence that treatment with buprenorphine can help decrease craving for alcohol, ethanol intake and the Addiction Severity Index (ASI) subscale of alcohol use score
- Alcohol use disorder is associated with higher rates of relapse to opioid use

Clark et al., 2015
Hakkinen et al., 2012
Nava et al., 2008

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Diversion of Buprenorphine

- Has intravenous misuse potential
- Most estimates suggest that, per dose, tablets are more likely to be diverted than films, and mono product tablets more likely than combined buprenorphine/naloxone
- In a survey of more than 4,000 patients in treatment programs in the United States, relative rates of diversion per prescribed dose were:
  - **buprenorphine/naloxone film: 1** (reference)
  - **buprenorphine/naloxone tablet: 2.2**
  - **buprenorphine tablet: 6.5**
- Combination product is therefore the standard of care for general use

Comer et al., 2010
Jones et al., 2015
Larancea et al., 2014
Lavonas et al., 2014

Medication-Assisted Treatment (MAT)

	Methadone	Buprenorphine (Oral)	Naltrexone (IM)
Mechanism of Action	Full Agonist on Opioid Receptor	Partial Agonist on Opioid Receptor	Antagonist on Opioid Receptor
Dosing	80mg-100mg (Usual Dose)	4-32mg	380mg Depot Injection
Advantages	▪ Provided in a highly structured supervised setting where additional services can be provided on-site and diversion is unlikely ▪ Maybe effective for individuals who have not benefited sufficiently from partial agonists or antagonists	▪ Improved safety due to partial agonism ▪ Availability in office-based settings	▪ No addictive potential or diversion risk ▪ Available in office-based settings ▪ Option for individuals seeking to avoid any opioids

Schuckit, 2016

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Summary

- MAT is comprised of:
  - Methadone: A full agonist that activates the mu-receptor
  - Buprenorphine: A partial agonist that activates the mu-receptor at lower levels
  - Naltrexone: An antagonist that occupies the mu-receptor without activating it
- Ongoing treatment with MAT is effective at improving retention in treatment and decreasing use of illicit opioids. In contrast, short-term treatment where MAT is tapered after a brief period of stabilization have proven ineffective.
- Pharmacodynamically, combination of methadone or buprenorphine with other central nervous system depressants may increase the risk of sedation or respiratory depression and overdose. This risk is most clearly shown with benzodiazepines, particularly with intravenous use.

Concurrent Substance Use and OBOT Suitability

- Alcohol:
  - Sedative-hypnotic
  - Patients should be cautioned to avoid alcohol while taking buprenorphine. Persons with active or current alcohol use disorders may require residential treatment prior to starting OBOT

  - Note: Essential to assess for use, intoxication, and withdrawal from sedative-hypnotics. If a patient is at risk for withdrawal seizures from alcohol or sedative-hypnotic use, buprenorphine will not control seizures

- Use of other drugs (e.g. marijuana or cocaine):
  - Not an absolute contraindication to buprenorphine treatment
  - Important to explore the reasons for continued use, willingness to abstain and document the discussion

Specialty Topics

Factors to Consider in treating OUD in the Pregnant Patient

- Pregnancy:
  - If patient elects to start or to stay on buprenorphine
    - Document informed consent for ongoing treatment with buprenorphine.
    - Obtain consent for release of information and inform patient's Ob/Gyn that patient is on buprenorphine.
    - Consider starting with or switching to equivalent dose of buprenorphine mono-product (available as a generic medication) *[Not required]*
  - If methadone is selected may start without a period of mild withdrawal.
  - *Treatment with Bup is less likely to require split dosing in pregnancy*

Use of Buprenorphine With or Without Naloxone in the Pregnant Patient

- Buprenorphine/Naloxone:
  - FDA designates naloxone as Pregnancy Category B (the formulation of buprenorphine-naloxone is Category C):
    - No known teratogenic effects in animals
    - Controlled studies have not been conducted in humans
  - Increasing evidence that buprenorphine-naloxone may be safe in pregnancy
  - However, buprenorphine *without* naloxone is recommended for pregnant, opioid-dependent women
- Postpartum:
  - Transition to original pre-pregnancy dose and formulation
  - Mothers taking buprenorphine are safe to breastfeed

Lund et al., 2013

Pregnancy and Methadone Treatment

- Formally first-line tx. Commonly used for pregnant women with OUD
- Titrate dose to effectively reduce cravings
- Medication changes:
  - Second and third trimester:
    - Doses may need to ***increased*** due to increased metabolism and circulating blood volume
    - Doses may need to be split
  - With advancing gestational age: Plasma levels of methadone progressively decrease and clearance increases
    - Increasing or splitting the methadone into 12-hour doses may produce less cravings and withdrawal

Kampman et al., 2015

Buprenorphine vs. Methadone in Pregnant Patients with OUD

Buprenorphine (Mono Product)	**Methadone**

▪ Similar efficacy as methadone
▪ Same rates of adverse events, NAS, as methadone
▪ Improvement over methadone:
  ▪ Lower risk of overdose
  ▪ Fewer drug interactions
  ▪ Milder withdrawal symptoms in NAS
  ▪ Reduced morphine dosing
  ▪ Significantly shorter hospital stay
	▪ More structure- better for patients in unstable situations
	  ▪ Decreased risk of diversion
	▪ More long-term data on outcomes

Fischer et al., 1998, 1999
Jones et al., 2010;
Kakko et al., 2008;
Kraft et al., 2017

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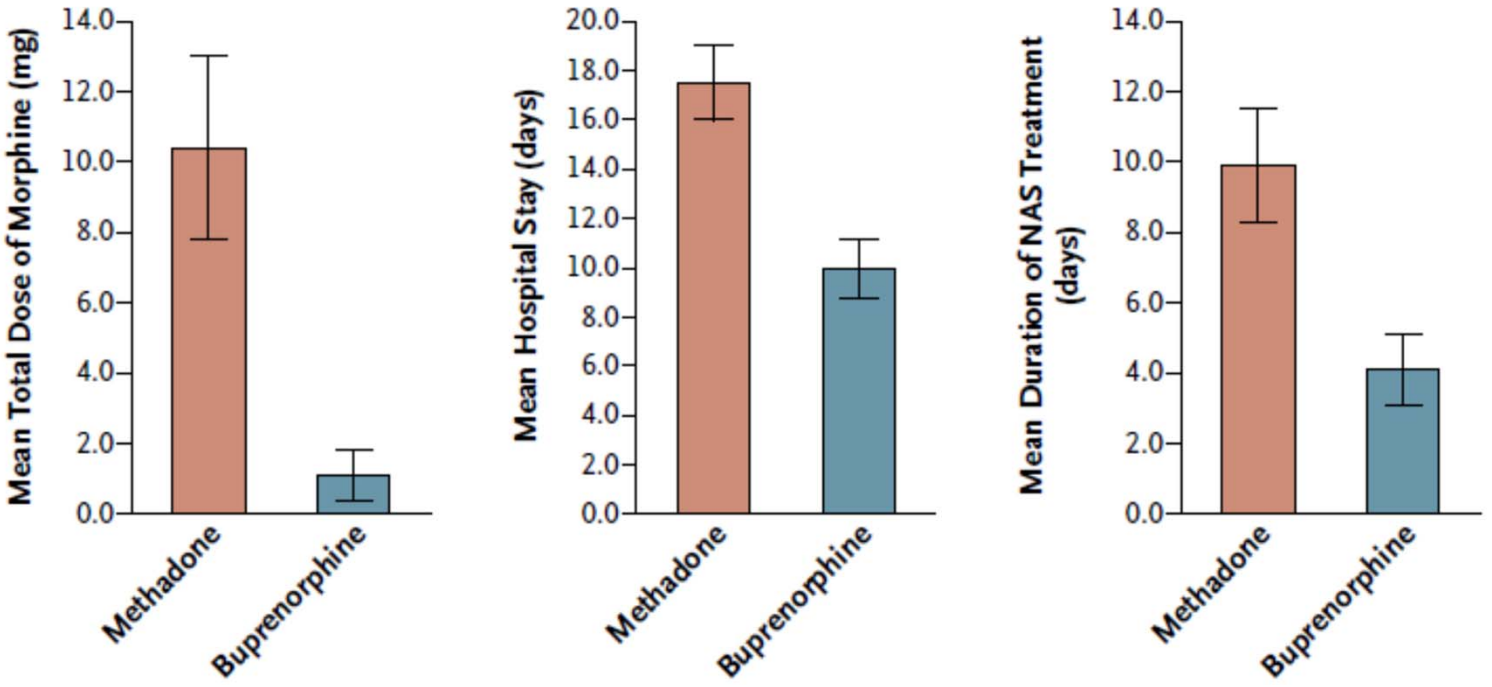
Maternal Opioid Treatment:
Human Experimental Research (MOTHER) Study



Jones et al., 2010

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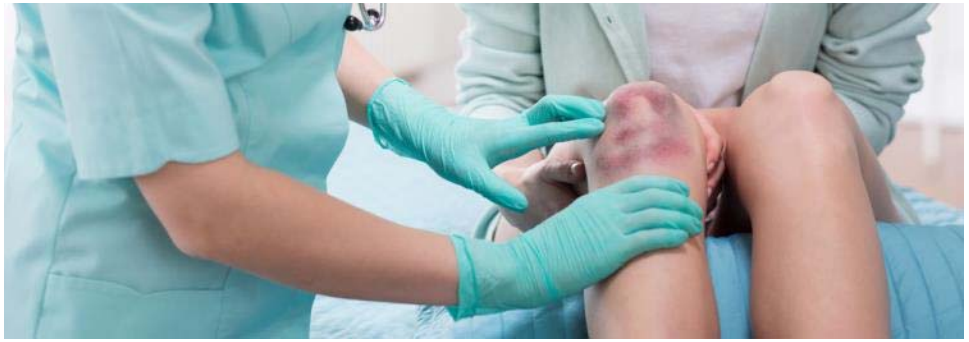
Factors to Consider in Treating the Adolescent OUD Patient

- The American Academy of Pediatrics (AAP) advocates for increasing resources to improve access to medication-assisted treatment of opioid-addicted adolescents and young adults.
  - Increase resources for medication-assisted treatment within primary care and access to developmentally appropriate substance use disorder counseling in community settings.
  - The AAP recommends that pediatricians consider offering medication-assisted treatment to their adolescent and young adult patients with severe opioid use disorders or discuss referrals to other providers for this service.
- Buprenorphine is approved for use in patients 16y/o and older.
- Naltrexone and methadone are approved for patients 18y/o and above.
- Protocols for initiation and treatment are similar to the adult.
- Encourage looking for adolescent based programs in the community.

Acute Pain Management in Buprenorphine Maintained Patients

- **Different Approaches:**
  - Initially try non-opioid analgesics (ketorolac or NSAIDs)



  - Continue Same buprenorphine maintenance dose but add non-opioid analgesics
  - Use split dose for concurrent pain and dependence
    - Buprenorphine's analgesic duration is only a few hours
  - Stop buprenorphine and initiate full agonist therapy

Perioperative Management

- General:
  - Patients fear mistreatment, Providers fear deception
  - Lack of consensus in the field – often based on the preference of the surgical/anesthesia teams

- Pre-Op:
  - Confirm Multi-Party Consent and Coordination of care with providers
  - If patient is already on Partial Agonist:
    - Take last Buprenorphine maintenance dose 24-hours prior to surgery
    - Higher dosing of short-acting opioids may be required post-surgical

Merrill et al., 2002
Wenzel et al., 2016

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Post Op Options for Patients already on Buprenorphine

Options	Considerations
▪ Continue Full Agonist and then ▪ Transition to Partial Agonist:	▪ Consider using Extended Release/Long Acting with Immediate Release/Short Acting for breakthrough pain ▪ Discussions about risks of relapse ▪ Medication security
▪ Continue Partial Agonist with:	▪ More frequent dosing ▪ Consideration for Increased total dosage ▪ Have a clear and detailed discussion with patient about a return to baseline dosing – specify timeline of changes for clarity

Merrill et al., 2002
Wenzel et al., 2016

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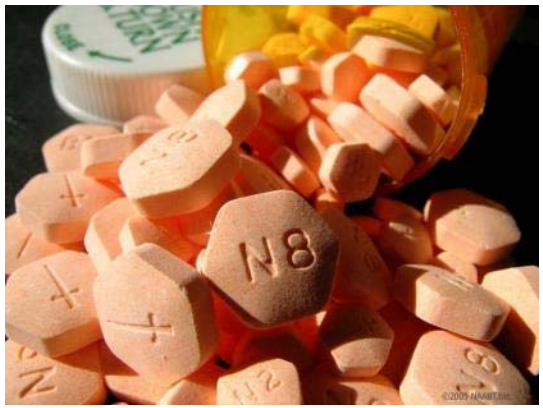
HIV – Positive Patients

- CYP 3A4 is the primary hepatic enzyme involved in metabolism Of both methadone and buprenorphine
- Many anti-retrovirals affect buprenorphine or Methadone levels and in some cases buprenorphine or Methadone levels affect anti-retrovirals levels
- There are markedly fewer drug/drug interactions with buprenorphine and anti-retrovirals as compared to methadone and little or no interactions with naltrexone
- Providers should consider referral to specialized HIV treatment programs and services – if available

CSAT, 2004
McCance-Katz et al., 2010
Moatti et al., 2000
Montoya et al., 1995

Patients with Renal Failure

- Suitable to use buprenorphine in patients with renal failure
- No significant difference in kinetics of buprenorphine in patients with renal failure versus healthy controls



- No significant side effects in patients with renal failure
- Buprenorphine and methadone can be prescribed to patients undergoing hemodialysis

Patients with Compromised Hepatic Function

- Buprenorphine undergoes hepatic metabolism, primarily by the CYP450 3A4 system
- Patients with compromised hepatic function could have reduced metabolism of buprenorphine, with resultant higher blood levels of the medication
- No specific hepatotoxicity has been demonstrated for either methadone or buprenorphine
- Patients with impairments in hepatic function should be monitored closely
  - Moderately elevated levels (>3times the upper limit of normal) should be monitored.

Summary

- Peri-operative pain management practices for patients with OUD are variable and require close coordination with surgical team.
- There are markedly fewer drug/drug interactions with Buprenorphine and antiretrovirals as compared to methadone.
- Buprenorphine is suitable to use in patients with renal failure.
- Unless the patient has acute hepatitis, pharmacotherapy with methadone or buprenorphine is not contraindicated on the basis of mildly elevated liver enzymes.

Medication Assisted Treatment Clinical Application

Clinical Uses of Buprenorphine

- Induction
- Stabilization and Maintenance
- Withdrawal

Buprenorphine Induction
Rationale

- Goals of buprenorphine initiation:
  - Identify dose of buprenorphine at which the patient:
    - Discontinues or markedly reduces use of other opioids
    - Significantly decreased or absent withdrawal symptoms
    - Has minimal/no side effects
    - Experiences decreased cravings

SAMHSA, 2004

Buprenorphine Formulations

- Choice of formulations is based on:
  - Insurance/Third party payer considerations
  - Patient preferences
  - Safety
  - Decreased Diversion potential
- Formulations:
  - Buccal film; Sublingual films
  - Tablets
  - Subdermal implants
  - Depot formulation given as a subcutaneous injection
- All of the approved forms have demonstrated similar efficacy for treating opioid use disorder
- Buprenorphine for transdermal (via patch) and intravenous (via injection) use are available for analgesic use. They were tested but not approved for treating opioid use disorder

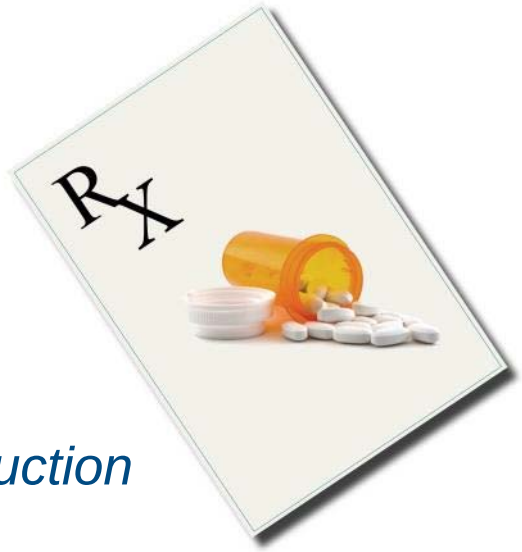
SAMHSA, 2016, 2016

Buprenorphine Formulations for Opioid Use Disorder

Content	Route	Products	Available Doses	Equivalent Dose to 8mg Buprenorphine
With Naloxone	Sublingual	Film (suboxone)	2mg Bup/0.5mg Nx 4mg Bup/1mg Nx 8mg Bup/2mg Nx 12mg Bup/3mg Nx	8mg
		Tablet - Generic	2mg Bup/0.5mg Nx 8mg Bup/2mg Nx	
	Sublingual	Tablet - (Zubsolv®)	1.4mg Bup / 0.36mg Nx 2.9mg Bup / 0.7mg Nx 5.7mg Bup / 1.4mg Nx 8.6mg Bup / 2.1mg Nx 11.4mg Bup / 2.6mg Nx	5.7 mg
	Buccal	Film (Bunavail®)	2.1mg Bup / 0.3mg Nx 4.2mg Bup / 0.7mg Nx 6.3mg Bup / 1mg Nx	4.2mg
Mono-product	Sublingual	Tablet - Generic	2mg Bup 8mg Bup	8mg
	Implant	probuphine	74.2mg (Four implants for six-months in one arm)	74.2 mg
	Injection	sublocade	100mg, 300mg (Once-monthly injection)	300 mg: First dose 100mg: Steady state dose

Buprenorphine Induction
First Prescription

- Logistical Factors/Considerations
  - *Confirm formulation covered by Insurance*
  - *Confirm access to pharmacy*
- Location
  - Office Induction:
    - *Allows for direct observation & instruction*
  - Home Induction:
    - *May reduce the risk of precipitated withdrawal and increase the likelihood of follow through*



Buprenorphine Induction
Common Problems

- *Subjective v. Objective signs of withdrawal*
- *Don't eat, drink, or talk while waiting for medication to dissolve*
- *Don't chew or swallow the strip/tablet*
- *Spit out any residual saliva*
- *Schedule adequate time*
- *Specifically ask about last methadone use before induction*
- *Don't use the term induction when talking to their OB doctor*

PCSS Providers Clinical Support System

Clinical Opiate Withdrawal Scale (COWS)

- Resting Pulse
- Sweating
- Restlessness
- GI Upset
- Tremor

- Pupil Size
- Bone or Joint Aches
- Yawning
- Anxiety or Irritability
- Gooseflesh
- Runny Nose or Tearing Eyes

Wesson and Ling, 2003

PCSS Providers Clinical Support System

Clinical Opiate Withdrawal Scale (COWS)

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time _____/_____/_____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

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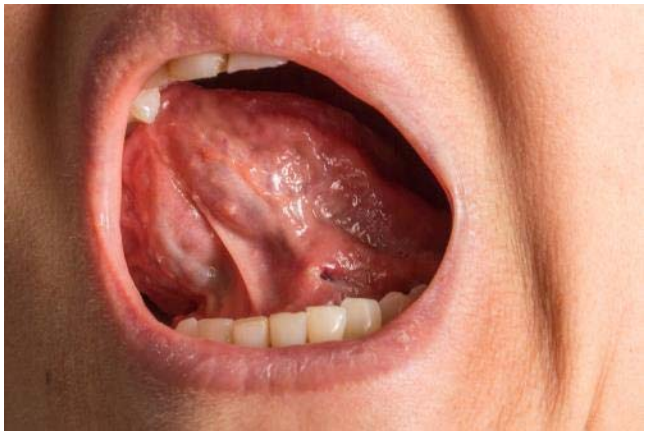
Buprenorphine Induction
Patient Education

- Sublingual tablets and films must be held under the tongue several minutes to dissolve
- Buccal delivery films take fewer minutes to dissolve and are stuck to the buccal mucosa



- **Instruct to:**
  - ❑ Start with a moist mouth, avoid acidic drinks (coffee or fruit juice)
  - ❑ Avoid using nicotine products as this interferes with absorption
  - ❑ Avoid speaking with the sublingual medication
  - ❑ Keep dissolving medicine under tongue
  - ❑ After medication is completely disolved, leave in mouth an additional 5 min before swallowing or spitting remaining saliva

Buprenorphine Induction

- Instruct the patient to abstain from any opioid use for a minimum of:
  - 12-16 hours for short-acting opioids
  - 24 hours for sustained-release opioid medications
  - 36 hours for methadone

- Observe and document Mild vs. Moderate withdrawal (COWS >8):
  - **NOTE:** Be aware of **Fentanyl;** do not induce unless moderate withdrawal (COWS 13 to 15) is observed

Buprenorphine Induction

- If opioid withdrawal appears shortly after the first dose buprenorphine may have precipitated a withdrawal syndrome

- Greatest severity of buprenorphine-related precipitated withdrawal in the first few hours (1-4) after a dose, with a decreasing (but still present) set of withdrawal symptoms over subsequent hours

Precipitated Withdrawal Management

- If a patient has precipitated withdrawal consider:
  - Giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal

OR

  - Stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day

Since the latter risks losing the patient, the first option is preferred.

Buprenorphine Induction
Day #2 and Beyond

- Stabilization will occur for most patients between 8 to 16mg per day:
  - Most individuals do not need more than 16mg per day but occasionally higher doses may be needed for persistent symptoms/ongoing opioid use
    - Most insurance companies limit daily doses to 24 mg
    - Though there is approval for a maximum dose of 32mg, doses above 24mg may increase risk of diversion
  - Note – If there are concerns for diversion:
    - Consider more intensive monitoring [E.g. more frequent urine testing, shorter prescription durations, supervised dosing]

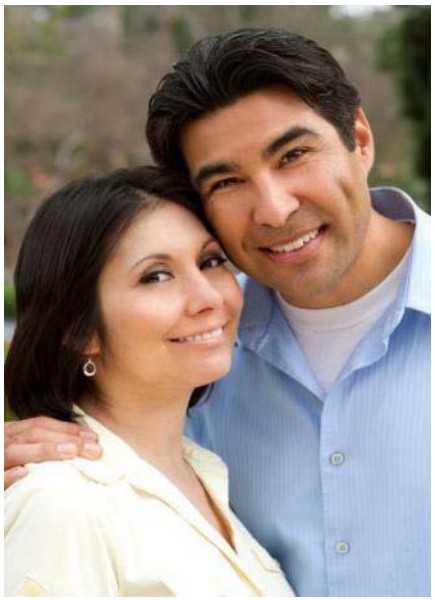
Stabilization and Maintenance

- Continue to reassess patient technique in medication administration:
  - Usual administration of buprenorphine/naloxone dosing is daily however preferably no more than twice-daily dosing
  - For proper absorption, no more than two film strips or two tablets should be taken at once

- Adjust daily dose by increments of 2-4 mg as needed:
  - Increase primarily for persistent cravings

How Long Should Buprenorphine Maintenance Be?

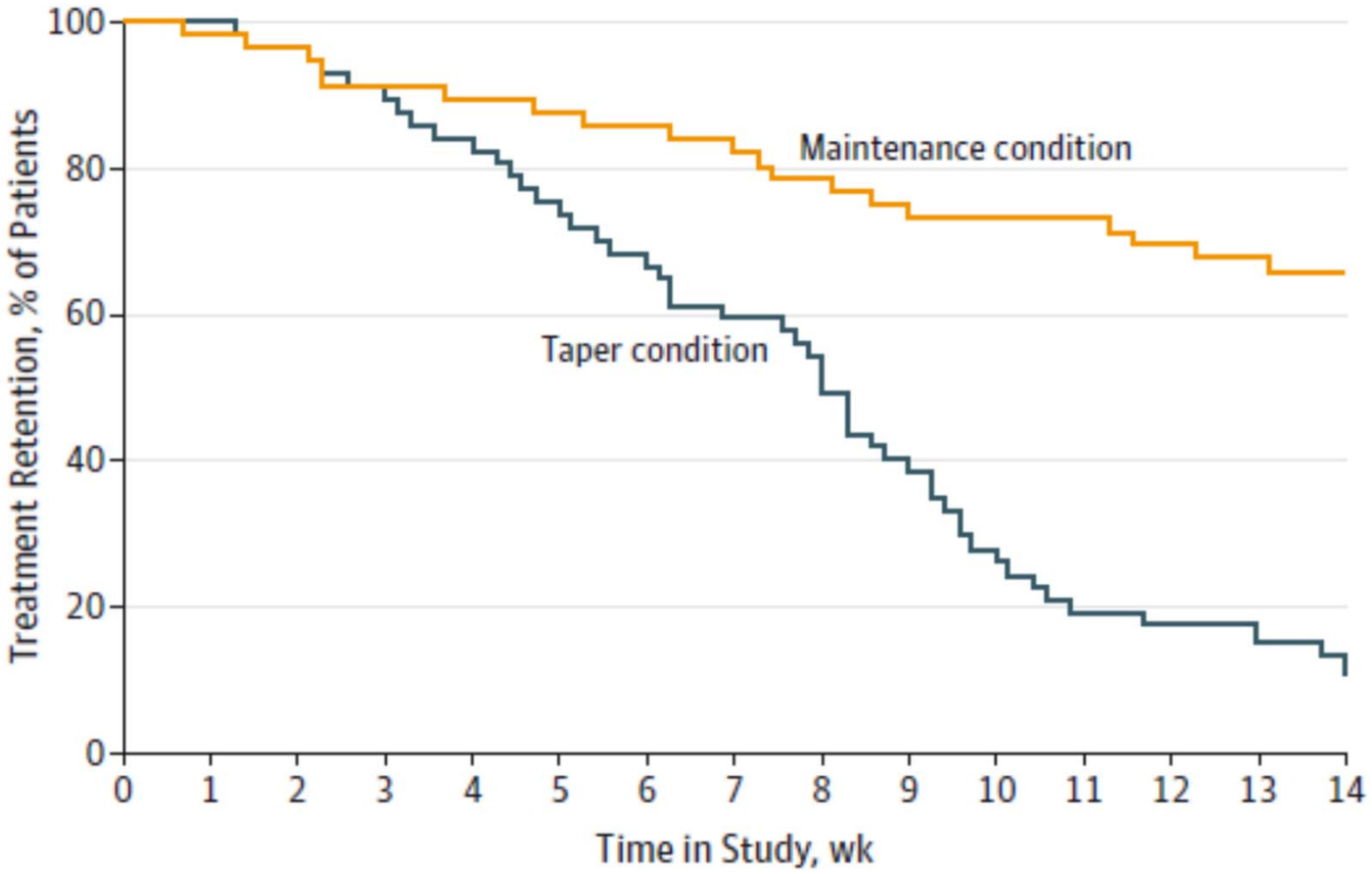
- Evidence is variable
  - Studies as long as 16 weeks show high relapse rates with medication withdrawal
  - Improved retention rates in treatment with extended buprenorphine maintenance



- Continue maintenance as long as patient is benefitting from treatment (decreased substance use, meeting employment, educational, relationships goals):
  - Note: Provider can have discussions regarding reduction in dose with improving stability or patient preference however:
    - Caution patients about discontinuing medication too early in treatment

Kakko et al., 2003
Weiss et al., 2011

Treatment Retention and Buprenorphine Dosage



Fiellin et al., 2014

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Acute Withdrawal Using Buprenorphine

- Buprenorphine suppresses opioid withdrawal symptoms
- Long-term efficacy of medical withdrawal with buprenorphine is not known.
- Studies of other withdrawal treatments have shown that brief withdrawal periods are unlikely to result in long-term abstinence unless one plans on initiating naltrexone.

Testing for Buprenorphine

- Testing for buprenorphine during MAT can be useful to monitor adherence and detect possible diversion
- Confirmatory testing will distinguish buprenorphine and its metabolite, norbuprenorphine, which is usually present in greater concentrations
- Individuals vary in the ratio of buprenorphine to norbuprenorphine due to individual metabolism and co-administered inducers or inhibitors of CYP3A4
- Buprenorphine with little or no metabolite (i.e. a ratio of norbuprenorphine:buprenorphine: < 0.02) suggests that buprenorphine was added to the urine

Sethi & Petrakis, 2013
Hull et al., 2008