Providers Clinical Support System

MAT Waiver Eligibility Training *(Live Session)*

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The Half and Half Course Agenda

- Overview: Opioid Use Disorder Treatment with Buprenorphine/Naloxone -
- Patient Evaluation
- Specialty Topics
- Case Study
- Medication Assisted Treatment Clinical Application
- Case Study
- Urine Drug Testing
- Case Study
- Overview of Clinical Tools
- Completing the Notification of Intent Waiver Form

Speaker Intro

Overview:
Opioid Use Disorder Treatment with Buprenorphine/Naloxone

Target Audience

The overarching goal of PCSS is to train a diverse range of healthcare professionals in the safe and effective prescribing of opioid medications for the treatment of pain, as well as the treatment of substance use disorders, particularly opioid use disorders, with medication-assisted treatments.

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

DATA 2000 – Practitioners Requirements

- ✓ Licensed provider with DEA Registration
- ✓ Subspecialty training in addictions or completion of an 8-hour course
- ✓ Registration with SAMHSA and DEA
- ✓ Must affirm the capacity to refer patients for appropriate counseling and ancillary services
- ✓ Must adhere to patient panel size limits
  - 30 during the first year
  - Eligible to apply for increase to 100 after the first year
  - May apply to increase to 275 after being at 100 for a year and meeting specific criteria.

Drug Addiction Treatment Act (DATA 2000)

Permitted physicians who met certain qualifications to treat opioid addiction with:

- Schedule III, IV, and V narcotic medications that had been specifically approved by the FDA or combination of such drugs for the treatment of opioid dependence
- In treatment settings other than the traditional Opioid Treatment Program ("methadone clinic") settings

DEA Enforcement of DATA 2000

- The Drug Enforcement Administration (DEA) is responsible for ensuring that physicians who are registered with DEA pursuant to the DATA 2000 are in compliance with the Controlled Substance Act.
- The primary purpose of the inspection is to ensure compliance with the recordkeeping and appropriate prescribing of controlled substances under CSA and DATA 2000.
- You must keep a log of patients who are treated with buprenorphine,
- If you have this information easily accessible, the inspection should be fairly rapid and non-onerous.

TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, Chapter 6, pp 79-85;

Treatment Goals

- Range of treatment goals

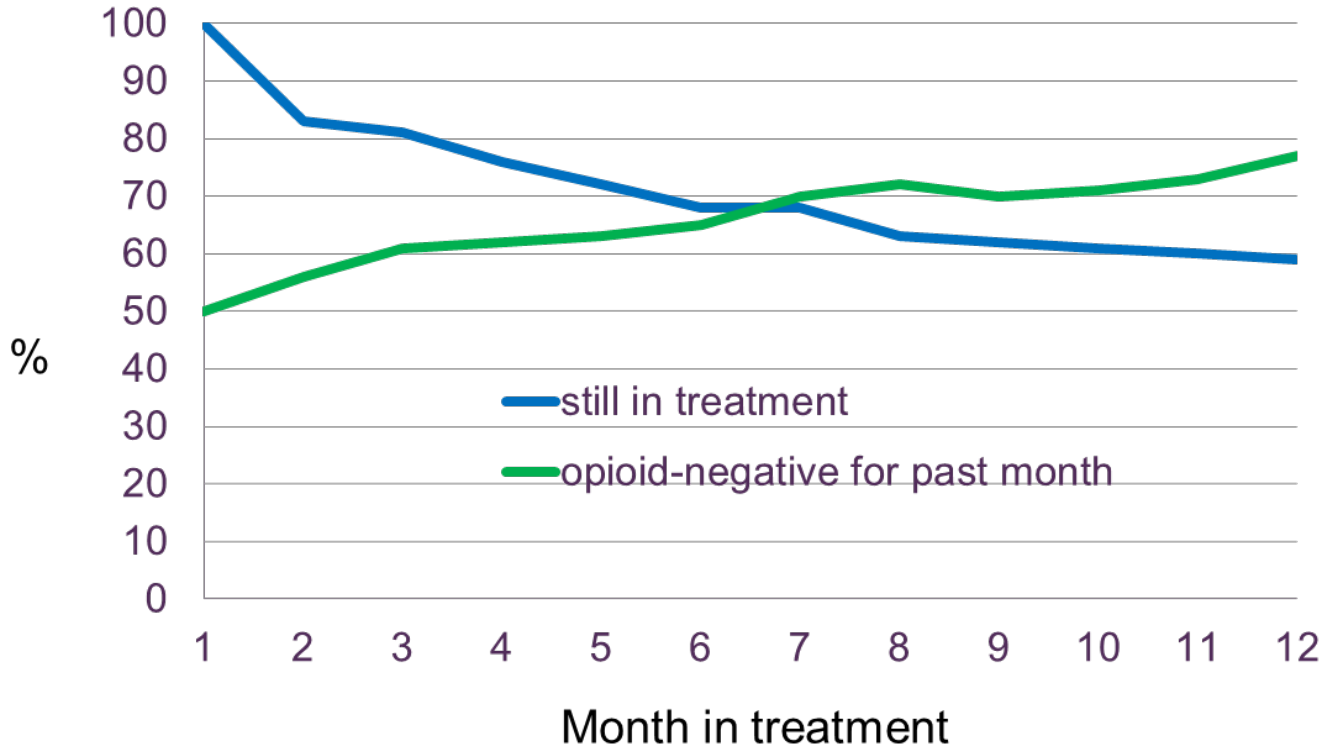
Minimization of harms from ongoing use

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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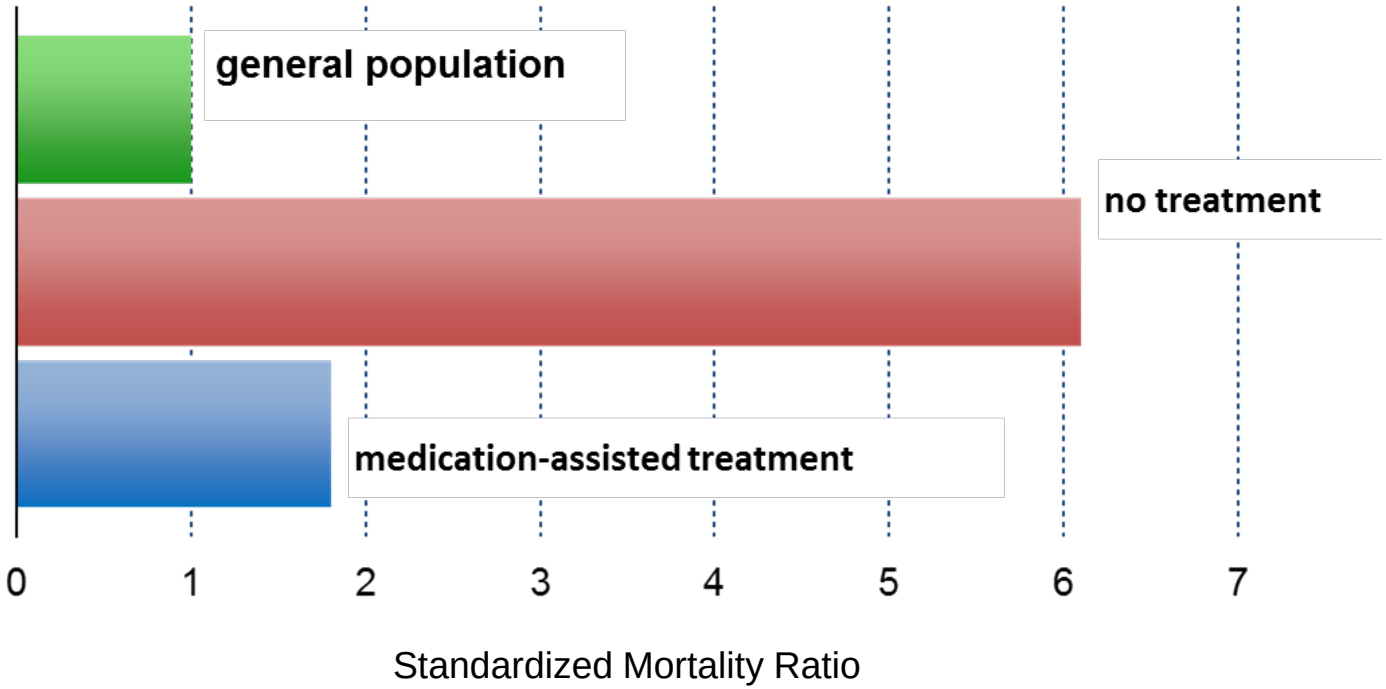
Benefits of MAT: Decreased Mortality

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
- DATA 2000 allows for the treatment of opioid use disorder to be treated outside of an Opioid Treatment Program with schedule III, IV, or V medications approved by the FDA.
- 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

References

- American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. Arlington, VA: American Psychiatric Association.
- American Society of Addiction Medicine (ASAM). 2011: https://www.asam.org/resources/definition-of-addiction (Accessed 11/2017).
- Centers for Disease Control and Prevention. Wide-ranging OnLine Data for Epidemiologic Research (WONDER) http://wonder.cdc.gov/mcd.html. Accessed 05/20/17.
- CSAT Buprenorphine Information Center. *Drug Addiction Treatment Act of 2000.* Available online at http://buprenorphine.samhsa.gov/data.html
- Dupouy J, Palmaro A, Fatséas M, et al. 2017. Mortality Associated With Time in and Out of Buprenorphine Treatment in French Office-Based General Practice: A 7-Year Cohort Study. *Ann Fam Med* 15(4): 355–358.
- Evans E, Li L, Min J, et al. 2015. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–2010. *Addiction* 110(6): 996–1005.
- Hunt WA, Barnett LW, Branch LG. 1971. Relapse rates in addiction programs. *Journal of Clinical Psychology* 27(4):455–456.
- Kakko J, Svanborg KD, Kreek MJ, and Heilig M. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 361:662–668.
- National Institute on Drug Abuse.2014: https://www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics (Accessed 11/2017).

References

- Soeffing JM, Martin LD, Fingerhood MI, et al. 2009. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. *Journal of Substance Abuse Treatment* 37(4):426–430.
- Sordo L, Barrio G, Bravo MJ, et al. 2017. Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *British Medical Journal* 357:j1550.
- Substance Abuse and Mental Health Services Administration. 2017. Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

Pharmacology

Major Features of Methadone

***Full Agonist* at mu receptor**

Long acting

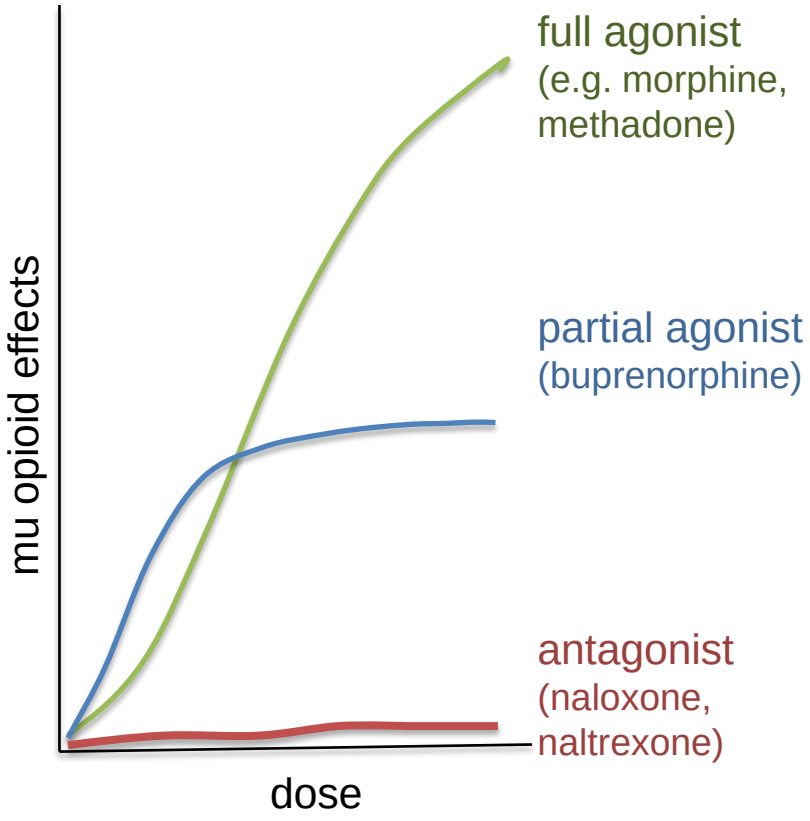
- Half-life ~ 15-60 Hours

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

Major Features of Buprenorphine

Partial agonist at mu receptor

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

Long acting

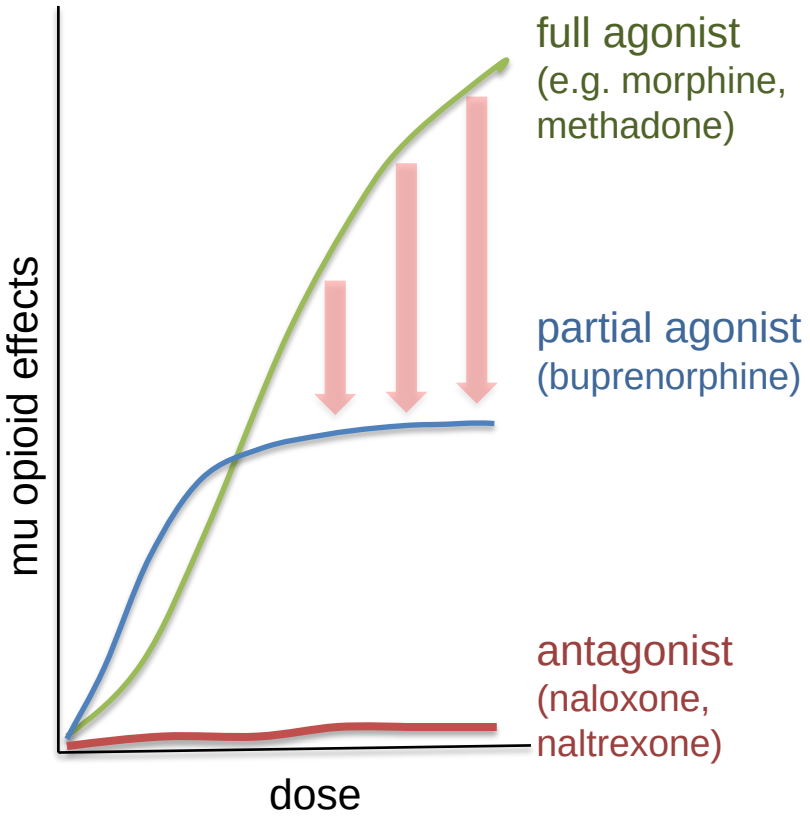
- Half-life ~ 24-36 Hours

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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Major Features of Naltrexone

Full Antagonist at mu receptor

- Competitive binding at mu receptor

Long acting

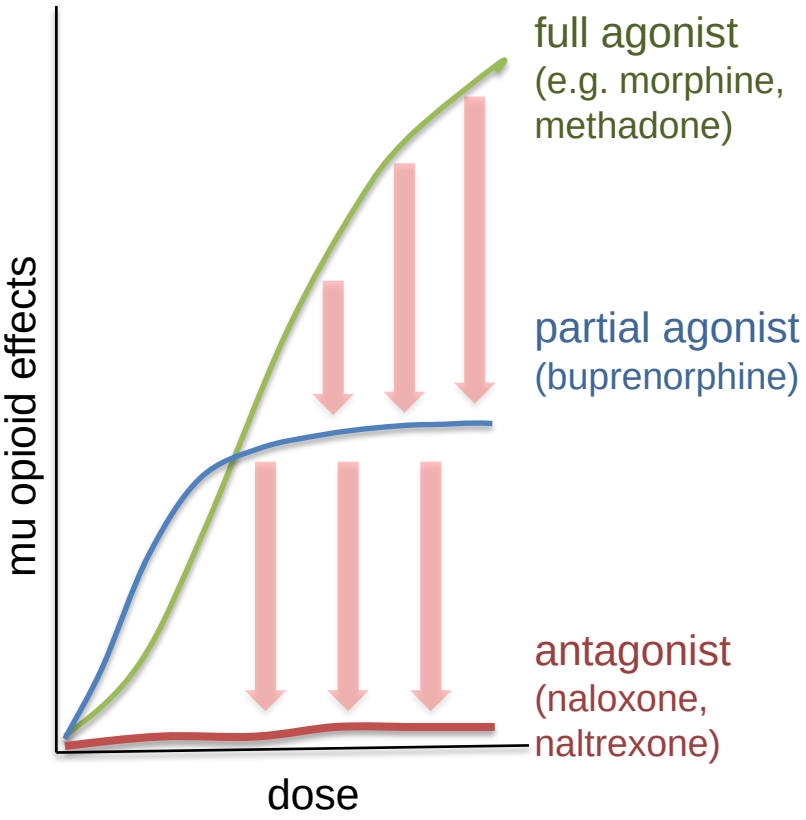
- Half-life:
  - Oral ~ 4 Hours
  - IM ~ 5-10 days

High affinity for mu receptor

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

Formulations

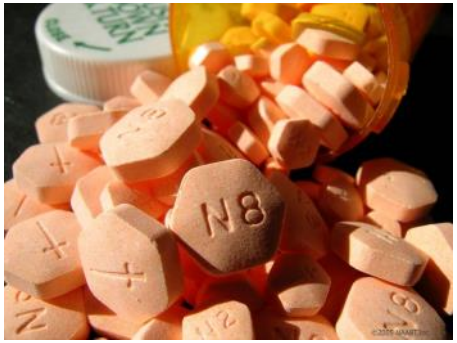
- *Tablets: Revia®: FDA approved in 1984*
- *Extended-Release intramuscular injection: Vivitrol®: FDA approved in 2010*



SAMHSA, 2018

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%

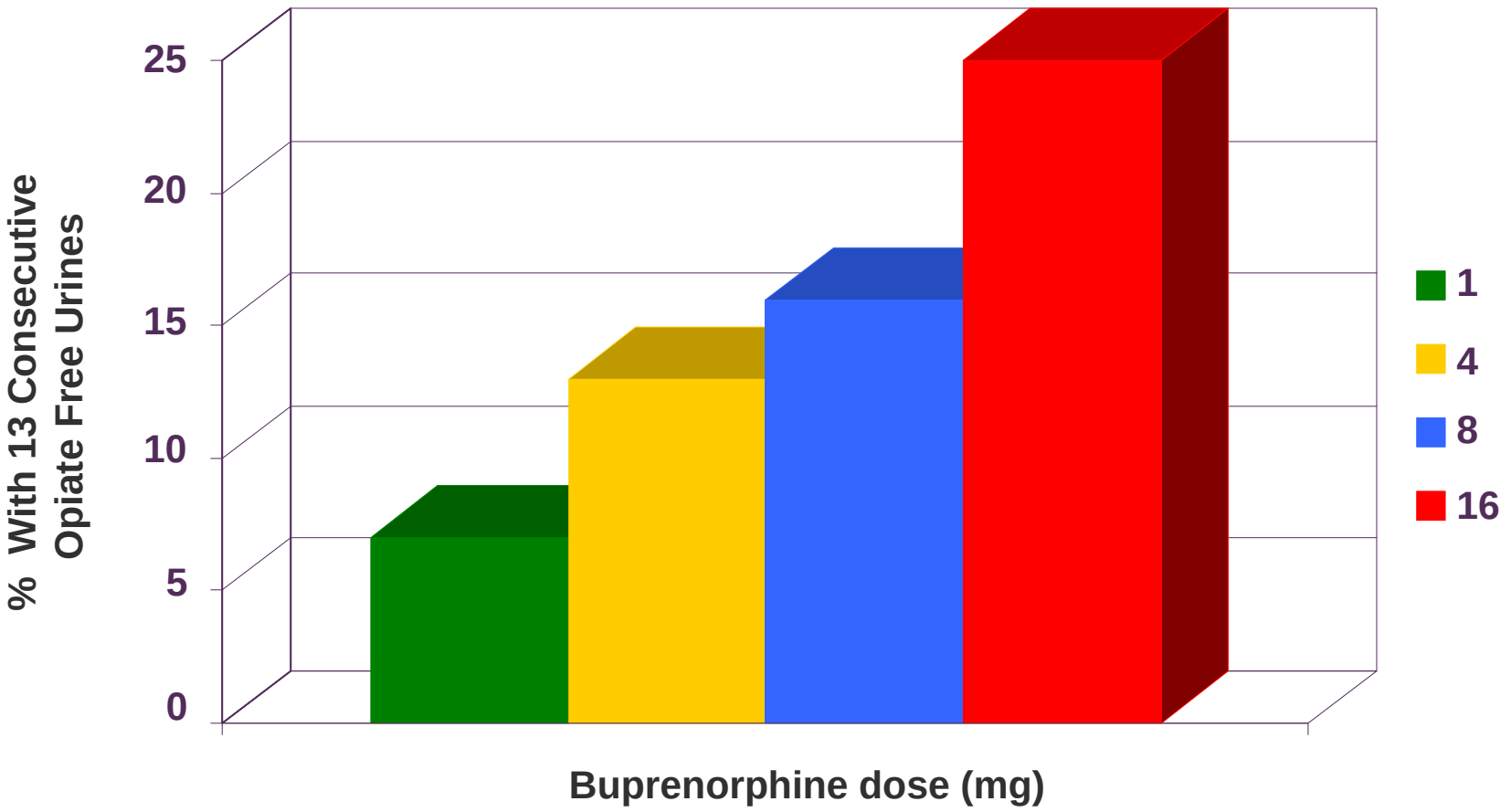
Mendelson et al., 1997
SAMHSA, 2016, 2016
SAMHSA, 2018

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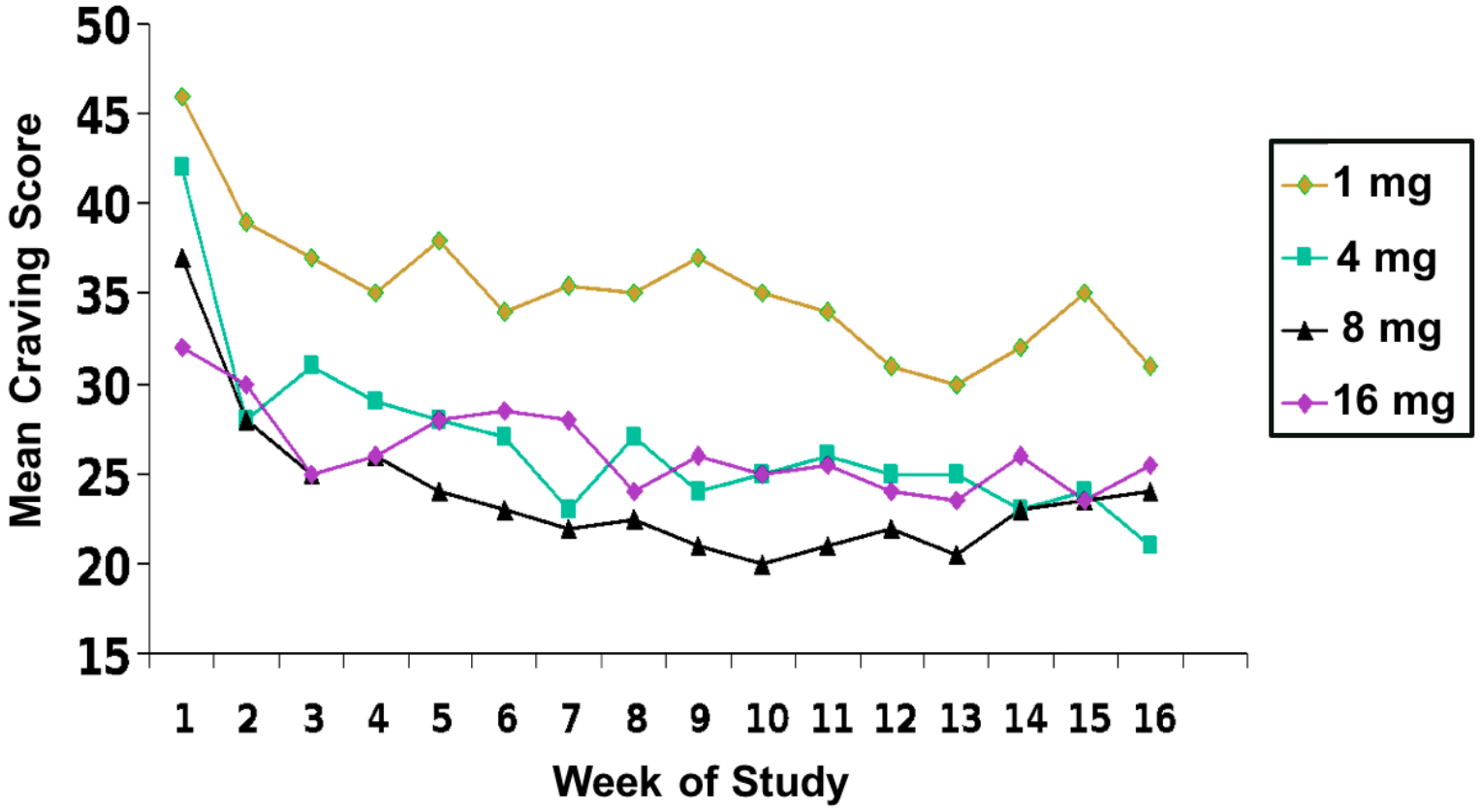
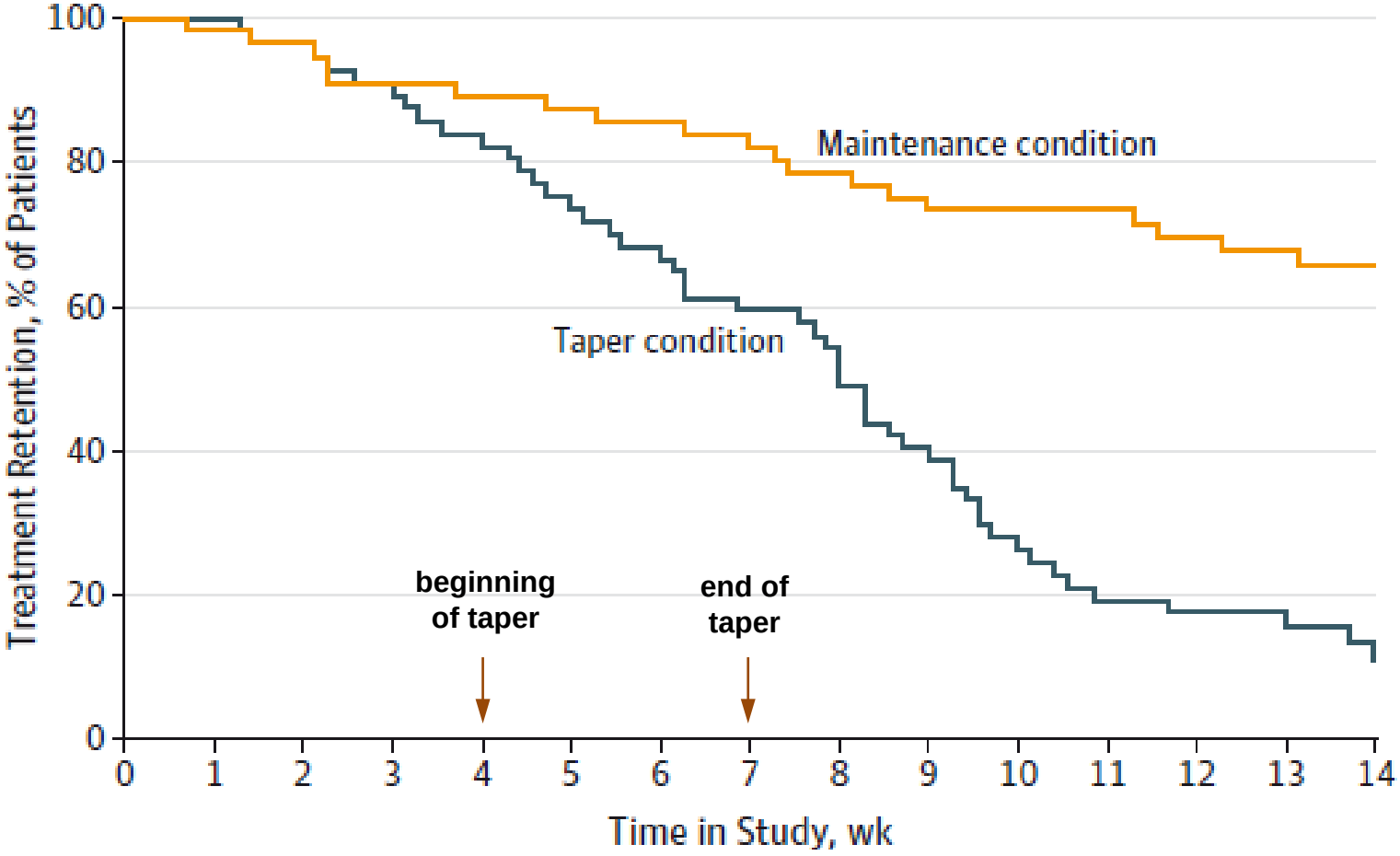
Mean Heroin Craving: 16 Week Completers: Reduced Craving with Therapeutic Buprenorphine Doses



Ling et al., 1998

Buprenorphine: Maintenance vs. Taper



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Fiellin et al., 2014

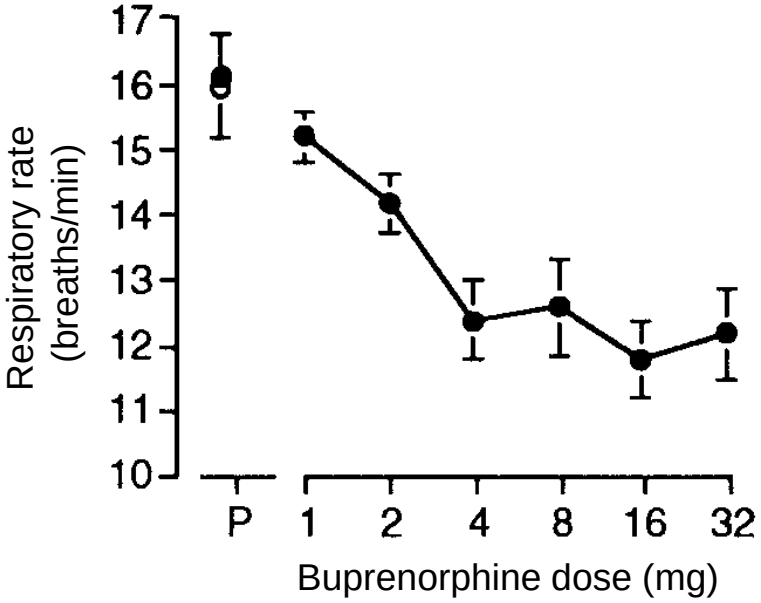
Common Adverse Effects of Buprenorphine

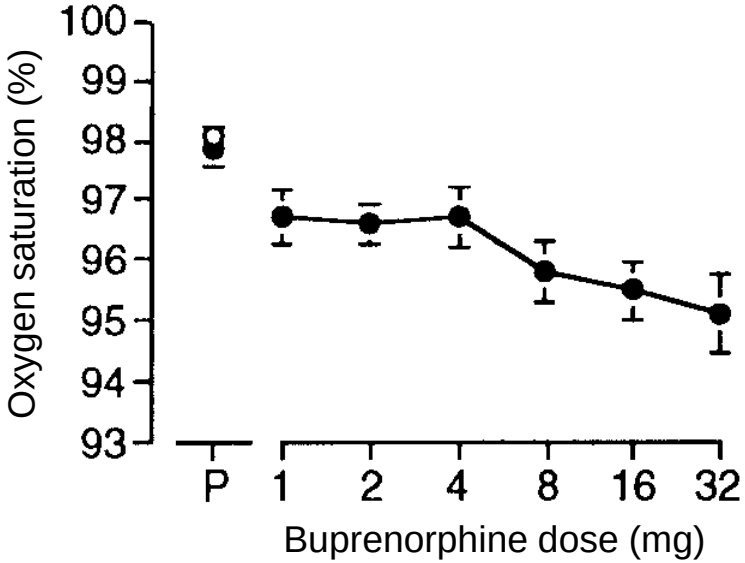
- Headaches
  - Management: aspirin, ibuprofen, acetaminophen (if there are no contra-indications)
- Nausea
  - Management: Consider spitting the saliva out after adequate absorption instead of swallowing.
- Constipation
  - Management: Stay well-hydrated, Consume high-fiber diet, Consider stool softeners, 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

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

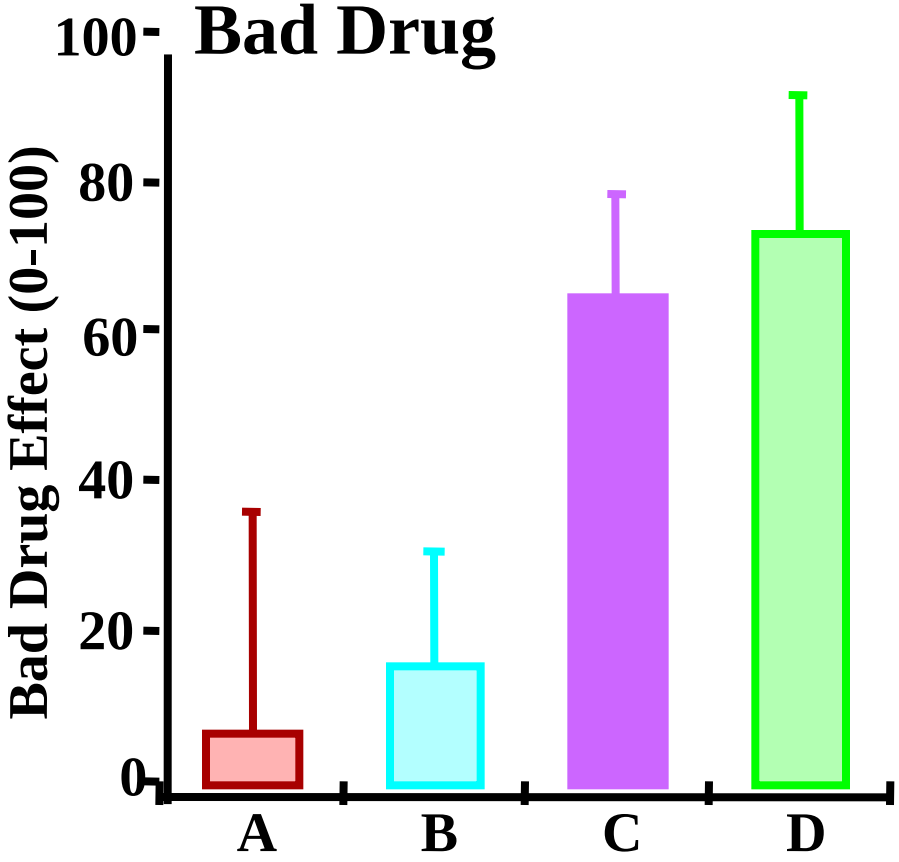
Rationale for the Combination of Buprenorphine with Naloxone

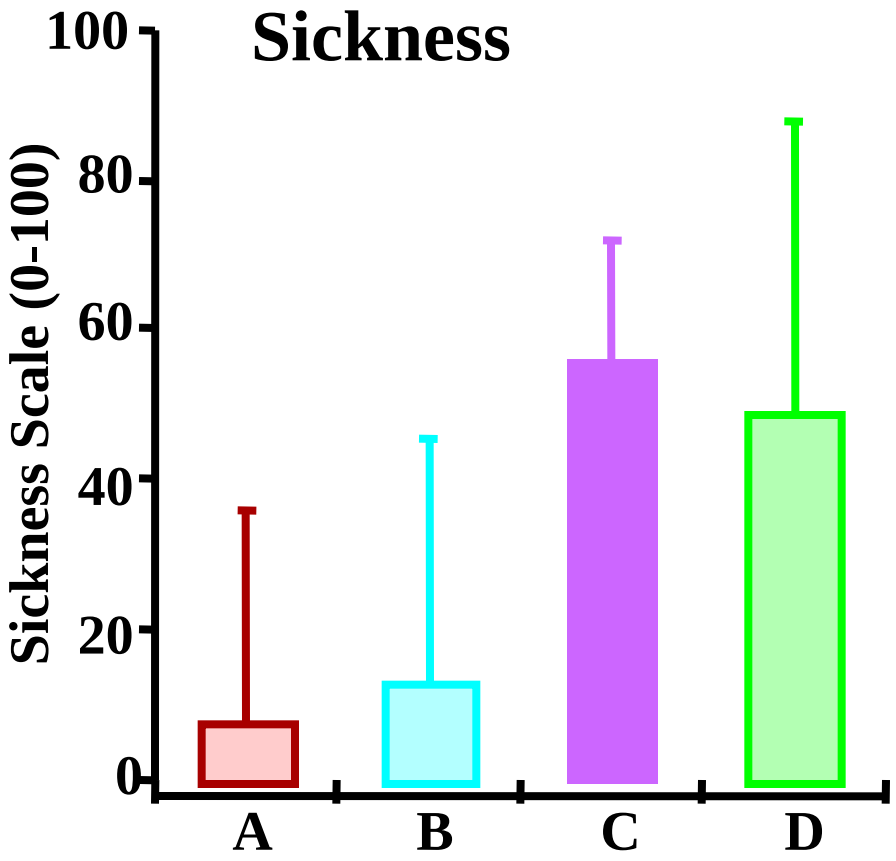
- When used as prescribed (sublingual or buccal administration), there is minimal bioavailability of naloxone
- Compared to buprenorphine alone, the buprenorphine/naloxone combination:
  - was developed to decrease IV misuse
  - is more likely to precipitate a withdrawal effect if injected by a current 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

PEAK EFFECTS – MEAN (±SD)

Mendelson J., et.al. Biol Psychiatry 1997;41:1095-1101





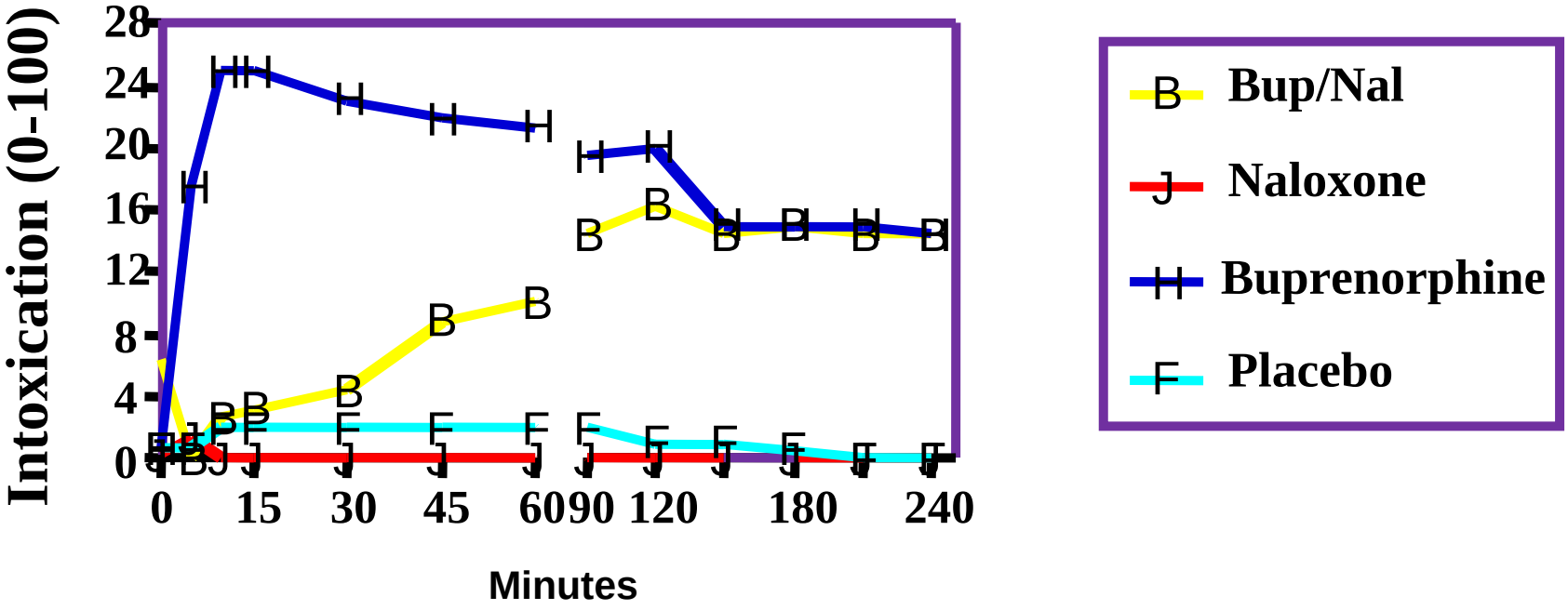
Buprenorphine placebo, Naloxone placebo

Buprenorphine placebo, Naloxone 0.1 mg

Buprenorphine 0.2 mg, Naloxone placebo

Buprenorphine 0.2 mg, Naloxone 0.1 mg

Effect of IDU diversion of Buprenorphine and buprenorphine/naloxone combination



Mendelson J., et.al. Biol Psychiatry 1997;41:1095-11

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.

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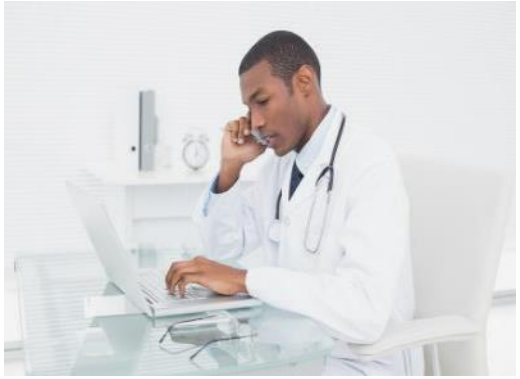
FDA, 2016, 2017

FDA Guidance for Health Care Professionals

- Take several actions and precautions and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants:



  - Educate patients about the serious risks; poss. death
  - Taper the benzodiazepine or CNS depressant to discontinuation if possible.
  - Verify the diagnosis for anxiety or insomnia and consider other treatment
  - Recognize that patients may require MAT medications indefinitely and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
  - Coordinate care to ensure other prescribers are aware of the patient's buprenorphine or methadone treatment.
  - Monitor for illicit drug use, including urine or blood screening

FDA, 2017

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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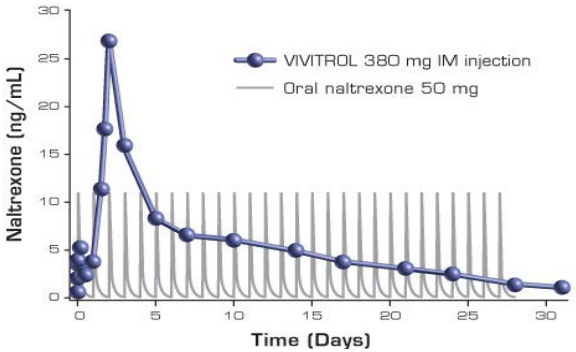
Diversion of Buprenorphine

- 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

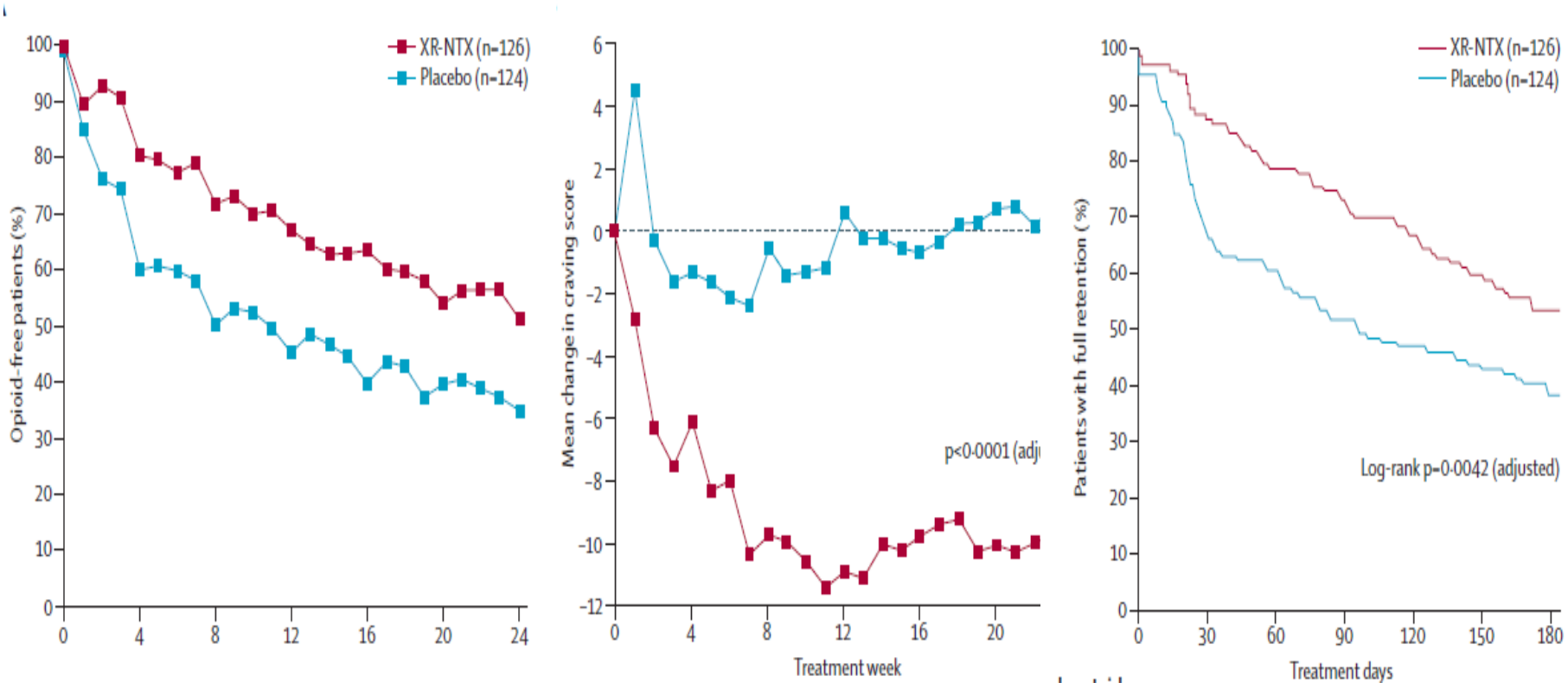
Comer et al., 2010
Jones et al., 2015
Larancea et al., 2014
Lavonas et al., 2014

Naltrexone Treatment

- Naltrexone is a long-acting, high affinity, competitive opioid receptor antagonist with an active metabolite (6-β-naltrexol) which is also an antagonist
- In sufficient plasma concentrations (>2 ng/ml) naltrexone fully blocks all opioid effects
- Naltrexone tablet is approved for the treatment of OUD; associated with poor daily adherence
- Naltrexone (extended release) monthly injection is approved for the treatment of OUD; better compliance
- Appealing choice for patients who prefer not be on any opioids



Naltrexone: Efficacy



Krupitsky et al., 2011

There may also be a higher proportion of opioid, cocaine, benzodiazepine, cannabinoids, amphetamine - free patients.
Comer et.al.,2011

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Naltrexone Treatment: Mechanism

There are two possible mechanisms of therapeutic effect:

- **Behavioral mechanism:** blockade of the reinforcing effects of heroin leads to gradual extinction of drug seeking and craving
  - Patients who use opioids while on naltrexone experience no effect of exogenous opioids and often stop using them
- **Pharmacological mechanism:** naltrexone decreases reactivity to drug-conditioned cues and decreases craving thereby minimizing pathological responses contributing to relapse

As naltrexone has a different mechanism of action than methadone or buprenorphine, it may be acceptable to, or effective for different subgroups of patients, thus helping to attract more patients into effective treatment overall.

Effectiveness of Buprenorphine vs. Injection Naltrexone

- Two randomized comparative effectiveness trials in Norway and US

- Overall Findings:
  - Once initiated, both medications appear comparably effective, although buprenorphine doses may not have been maximized in the trials
  - Naltrexone is more difficult to initiate due to the need to get a patient through medically supervised withdrawal

Lee et al., 2018
Tanum et al., 2017

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Naltrexone Considerations: Initiation

- Official prescribing information recommends that patients be opioid-free followed by a wait-period of 7-10 days before treatment can be initiated, to avoid precipitated withdrawal
  - Can be challenging due to need to tolerate withdrawal symptoms, and remain abstinent over 7 to 10 days
  - Non opioid medications for withdrawal (e.g. clonidine) can be helpful
  - Inpatient/residential treatment programs, where detoxification can be accomplished is an ideal setting for initiating naltrexone, but reduced access to such programs due to limited third party reimbursement
  - More rapid methods for naltrexone initiation are under development

Williams et al., 2017

Naltrexone Considerations: Adherence

- Treatment adherence can be challenging but this is better with long acting injectable formulation

  - Oral naltrexone generally not recommended for treatment of opioid use disorder, due to risk of non-adherence, relapse, and subsequent overdose
  - Long-acting injection naltrexone is preferred
  - Some patients experience subacute withdrawal symptoms after the first naltrexone injection.
    - Typically only occurs with the first injection and resolves within two weeks.
  - The treatment should include on going counseling, anticipatory guidance, motivational techniques emphasizing on adherence.
  - Involvement of a significant other may be helpful to support adherence.
  - Other than soreness at injection site, few other common side effects
  - Main safety concern is risk of relapse when injections are discontinued.

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.

References

- Bardy G, Cathala P, Eiden C, et al., 2015. An unusual case of death probably triggered by the association of buprenorphine at therapeutic dose with ethanol and benzodiazepines and with very low norbuprenorphine level. *J Forensic Sci* 60 suppl 1:s269–s271.
- Clark RE, Baxter JD, Aweh G, et al., 2015. Risk factors for relapse and higher costs among medicaid members with opioid dependence or abuse: opioid agonists, comorbidities, and treatment history. *J Subst Abuse Treat* 57:75–80.
- Comer SD, Sullivan MA, Yu E, et al., 2006. Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence A Randomized, Placebo-Controlled Trial. *Arch Gen Psychiatry* 63:210–218.
- Comer SD, Sullivan MA, Vosburg SK, et al., 2010. Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. *Addiction* 105(4):709–718.
- Fareed A, Patil D, Scheinberg K, et al., 2013. Comparison of QTc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: a 5-year follow-up. *J Addict Dis* 32(3):244–251.
- Fiellin DA, Schottenfeld RS, Cutter CJ, et al., 2014. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Internal Medicine* 174(12):1947–1954.
- Food and Drug Administration. 2016: https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed 10/2017
- Food and Drug Administration. 2017: https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm. Accessed 10/2017

References

- Häkkinen M, Launiainen T, Vuori E, and Ojanperä I. 2012. Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning. *Eur J Clin Pharmacol* 68(3):301–309.
- Hser Y, Saxon AJ, Huang D et al., 2014. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*109(1):79–87.
- Isbister GK, Brown AL, Gill A, et al., 2017. QT interval prolongation in opioid agonist treatment: anlaysis of continuous 12-lead electrocardiogram recordings. *Br J Pharmacol* doi: 10.1111/bcp.13326.
- Jones JD, Mogali S, and Comer SD., 2012. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend* 125(1-2):8–18.
- Jones JD, Sullivan MA, Vosburg SK et al., 2015. Abuse potential of intranasal buprenorphine versus buprenorphine/naloxone in buprenorphine-maintained heroin users. *Addict Biol* 20(4):784–798.
- Larancea B, Lintzeris N, Ali R, et al., 2014. The diversion and injection of a buprenorphine-naloxone soluble film formulation. *Drug and Alcohol Dependence* 136: 21–27.
- Lavonas EJ, Severtson SG, Martinez EM, et al., 2014. Abuse and diversion of buprenorphine sublingual tablets and film. *J Subst Abuse Treat* 47(1):27–34.
- Lee JD, Nunes EV Jr, Novo P, et al., 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 391:309–318.
- Ling W, Charuvastra C, Collins JF, et al. 1998. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 93(4):475–486.

References

- Mattick RP, Breen C, Kimber J, and Davoli M. 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*, Issue 2. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub4.
- Mendelson J, Upton RA, Everhart ET, et al. 1997. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* Jan;37(1):31–37.
- Nava F, Manzato E, Leonardi C, and Lucchini A. 2008. Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence: Preliminary results of an open randomized study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 32:1867–1872.
- Nielsen S and Taylor DA. 2005. The effect of buprenorphine and benzodiazepines on respiration in the rat. *Drug Alcohol Depend* 79(1):95–101.
- Orman JS and Keating GM. 2009. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs* 69:577–607.
- Schuman-Olivier Z, Hoeppner BB, Weiss RD et al. 2013. Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. *Drug Alcohol Depend* 132(3):580–586.
- Schuckit MA. Treatment of Opioid-Use Disorders. 2016. *N Engl J Med*;375(4):357–368.
- Stoller KB, Bigelow GE, Walsh SL, Strain EC. 2001. Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology* (Berl) 154(3):230–242.
- Substance Abuse and Mental Health Services Administration (SAMHSA). 2016. Sublingual and transmucosal buprenorphine for opioid use disorder: review and update. *Advisory* 15(1).

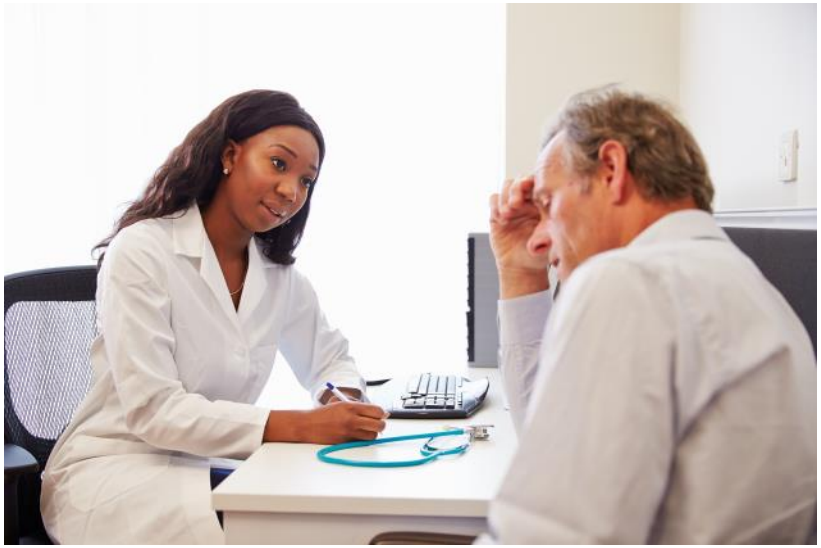
References

- Substance Abuse and Mental Health Services Administration. Medications To Treat Opioid Use Disorder. *Treatment Improvement Protocol (TIP)* Series 63, Full Document. HHS Publication No. (SMA) 18-5063FULLDOC. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.
- Substance Abuse and Mental Health Services Administration (SAMHSA). 2016. *Medication-Assisted Treatment of Opioid Use Disorder Pocket Guide.* Pub id: SMA16-4892PG. Washington, DC.
- Tanum L, Solli KK, Latif ZE, et al., 2017. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA Psychiatry* 74(12):1197–1205.
- Wald A. 2016. Constipation: advances in diagnosis and treatment. *JAMA* 315(2):185–191.
- Walsh SL, Preston KL, Stitzer ML, et al. 1994. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 55:569–580.
- Weiss RD, Potter JS, Fiellin DA, et al. 2011. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry* 68(12):1238–1246.
- Williams AR, Barbieri V, Mishlen K, et al. 2017. Long-Term Follow-Up Study of Community-Based Patients Receiving XR-NTX for Opioid Use Disorders. *The American Journal on Addictions* 26(4): 319–325.

Patient Evaluation

Building a Therapeutic Alliance

- Attitude
  - Non-judgmental, curious, empathetic
- Respectful
  - Recognize adversity
  - Recognize strengths
  - Use the non-stigmatizing language
- Honesty
- Shared goals
  - Why is the patient seeking treatment?
  - Provider treatment team concerns



- Reassurance
  - Assure patient your objective is concern for his or her health
  - Confidentiality (with qualifiers)
    - Safety of self, well-being of other (especially children)

Miller WR, Rollnick S, Motivational Interviewing, Guilford Press, NY NY, Third Ed., 2013, page 22.

Goals Prior to Visit or During Visit

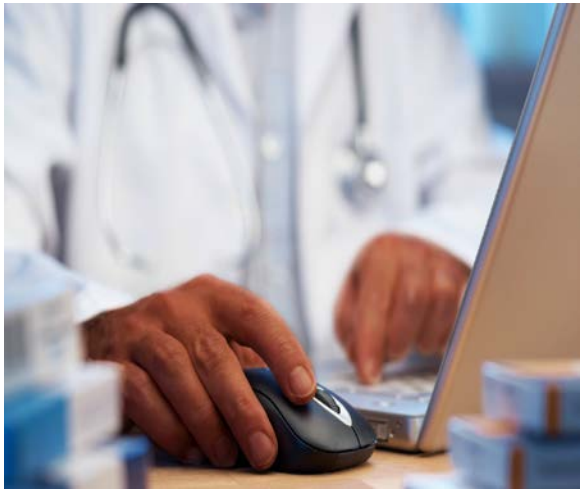
- Review Prescription Drug Monitoring Program (PDMP)
- Signed Forms:
  - Consent for treatment
  - Multi-Party Release, obtaining/releasing collateral information from/to all current or prior treatment teams
  - Treatment agreement
- Examples can be found at:
  - https://pcssnow.org/resources/clinical-tools/

Initial Urine Drug Screening for BUP/MAT Patients

- Point of care testing
  - Screening for:
    - Opiates
    - Marijuana
    - Cocaine
    - Amphetamines
    - Benzodiazepine
    - Alcohol bio-markers *
- Confirmation
  - On all new patients
  - On positive POC
- Adjunctive Testing
  - Pregnancy?
  - Fentanyl?

Medical History

- Review of current symptoms
- Review Medical History/Chronic Medical Problems
- Relationship of medical symptoms to substance use
- Treatments and response:
  - Medical/Surgical
- Obstetrics/Gynecology:
  - Pregnancies/Menstrual Status/Birth Control
- Dental care
- Medications:
  - Present/Past
  - Response/Side Effects
- Review of Labs, ECG



Psychiatric History

- Review of symptoms
- Relationship of psychiatric symptoms to substance use – establish temporality
- Prior diagnosis
- Trauma History
- Treatments and response:
  - Inpatient/Residential
  - Intensive Outpatient Programs (IOPs)/ Partial Hospitalization Programs (PHPs)
  - Outpatient
- Psychotropic medications
  - Present/Past
  - Response/Side Effects

Social and Family History

- Social history:
  - Birth and early development
  - Education:
    - Completing high school on time
  - Current employment status and prior occupations
  - Marital status, children, close supports
  - Living situation
  - Legal status? (No longer part of Dx)
  - Current Stressors, e.g. Housing/finance
- Family history:
  - Substance use disorders
  - Other psychiatric conditions
  - Other medical disorders

Substance Use History: Patterns

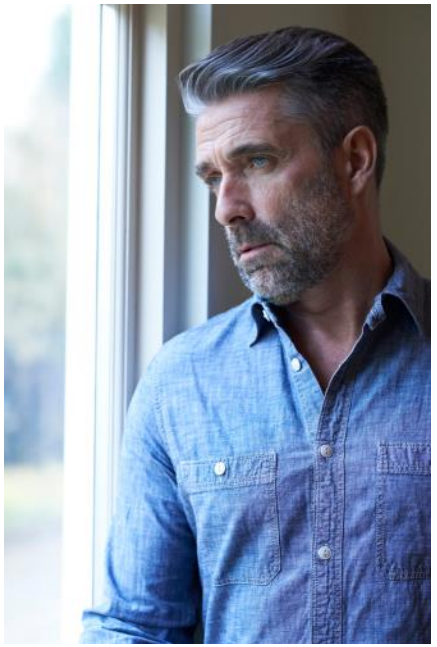
- Substance use history:
  - Ask about all substances:
    - Nicotine
    - Opioids: prescription opioids, non-prescribed opioids, heroin
    - Alcohol, marijuana
    - Hallucinogens, sedative/hypnotics, stimulants, other

Substance Use History: Patterns

- Substance use history:
  - Age at first use
  - Determine patterns of use over time:
    - Frequency
    - Amount
    - Route
  - Assess recent use (past several weeks)
  - Cravings and control:
    - Assess temporality and circumstances
    - Determine if patient sees loss of control over use

Substance Use History: Relapse/Treatment

- Relapse/attempts to abstain:
  - Determine if the patient has tried to abstain
    - What happened?
    - What helped?
  - Longest period of abstinence
  - Identify triggers to relapse



- Treatment episodes:
  - Response to treatment
  - Attitudes towards various treatment settings and mutual support groups (AA, NA etc.)
  - Length of abstinence

Substance Use History: Effects and Consequences

- Tolerance, intoxication, withdrawal:
  - Explain what is meant by tolerance
  - Determine the patient's tolerance and withdrawal history
  - Ask about complications associated with intoxication and withdrawal
- Consequences of use:
  - Determine current vs past levels of functioning
  - Aberrant behaviors (e.g. sedation, deterioration in function)
  - Identify consequences:
    - Medical
    - Legal
    - Family
    - Psychiatric
    - Employment
    - Other

DSM V Criteria

- Loss of Control
  - Larger amounts, longer time
  - Inability to cutback
  - More time spent, getting, using, recovering
  - Activities given up to use.
  - Craving
- Physiologic
  - Tolerance
  - Withdrawal
- Consequences
  - Hazardous use
  - Social or interpersonal problems related to use
  - Neglected major roles to use
  - Continued use after significant problems.

- A substance use disorder is defined as having 2 or more of these symptoms in the past year
- Tolerance and withdrawal alone don't necessarily imply a disorder.
- Severity is related by the number of symptoms.

2-3 = mild
4-5 = moderate
6+ = severe

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Physical Examination

System	Findings
Dermatologic	Abscesses, rashes, cellulitis, thrombosed veins, jaundice, scars, track marks, pock marks from skin popping
Ear, nose, throat, and eyes	Pupils pinpoint or dilated, yellow sclera, conjunctivitis, ruptured eardrums, otitis media, discharge from ears, rhinorrhea, rhinitis, excoriation or perforation of nasal septum, epistaxis, sinusitis, hoarseness, or laryngitis
Mouth	Poor dentition, gum disease, abscesses
Cardiovascular	Murmurs, arrhythmias
Respiratory	Asthma, dyspnea, rales, chronic cough, hematemesis
Musculoskeletal and extremities	Pitting edema, broken bones, traumatic amputations, burns on fingers
Gastrointestinal	Hepatomegaly, hernias

SAMHSA, 2018
Kampman et al., 2015

Laboratory Testing

Baseline Labs	Recommended Labs (Case-by-Case and Provider Preference)
Pregnancy test (for women of child-bearing age)	Complete Blood Count (with differential) and platelet count
Urine Drug Screen	Serum Electrolytes
	Hepatitis C&A, HIV
	Liver Function Tests (GGT, AST, ALT, PT or INR, albumin)

SAMHSA, 2018
Kampman et al., 2015

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Factors to Consider in Determining OBOT Suitability

- Can the patient adhere with treatment requirements?
- Are the psychosocial circumstances of the patient stable and supportive?
- Is the patient taking other medications that may interact with buprenorphine, such as naltrexone, benzodiazepines, or other sedative-hypnotics?
- Are there resources available in the office to provide appropriate treatment? On-call coverage?
- Are there treatment programs available that will accept referral for more intensive levels of service if needed?

Chou et al., 2016
Korthuis et al., 2017

General Principles: Prior to starting OBOT

- First meeting/assessment can also be used to give the individual information about medication-assisted treatment:
  - Appropriate use of the medication; no sharing or diversion
  - The need to avoid continued drug and alcohol misuse
  - The need to inform physician if other medications are prescribed for any purpose
  - The need to store the medication safely; how will the patient do that?

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

OBOT and Concurrent SUDs and Non-prescribed Medication Use

- Other concurrent substance use disorders:
  - May benefit from completion of more intensive treatment such as Intensive Outpatient Programs or Residential Treatment prior to re-establishing care at OBOT

- Other Substance Use:
  - Buprenorphine is a treatment for opioid use disorder, not other drug use disorders. Does not directly impact cocaine/amphetamine use, cannabis use, alcohol use [though reductions may occur indirectly as a result of participating in monitored treatment]
  - Misuse of other drugs (such as stimulants or sedatives) can be prevalent among opioid-addicted persons and may interfere with overall treatment adherence
  - Also assess for misuse/overuse of other prescribed medications e.g. gabapentin

Treatment Agreement

- Before getting started with treatment:
  - Make goals of treatment and expectations clear to patients
  - Consider Obtaining multi-disciplinary Release
- Use Treatment Agreements that outline terms of treatment:
  - What the patient can expect from you and from treatment
  - What you will expect/require from the patient
  - Information for patients about buprenorphine and its safe use
  - Informed consent (see Clinical Tools at www.pcssNOW.org)
  - Know referral sources in the community if patients are unable to follow the treatment agreement and need more intensive care
  - Example Agreement can be found in TIP(s) - 40 and 63:
    - https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf

SAMHSA, 2018

Treatment Agreements – Example of Key Components

- Arriving at appointments punctually
- Courteous in the office
- Refrain from arriving intoxicated or under the influence of drugs
- Agree not to sell, share, give any medication to others

- Agree not to deal, steal or conduct other illegal or disruptive activities
- Medications will be provided during scheduled office visits
- Responsible safe storage of medications
- Agree not to obtain medications from other providers, physicians, pharmacies, or other sources without informing my treating provider
- Agree to follow the prescription instructions

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Review of the Initial Evaluation

Goals	Details
Therapeutic Alliance	▪ Non-judgmental, understanding, respectful ▪ Use Language of recovery ▪ Shared goal-setting
Collateral Information	▪ Prescription Monitoring Programs ▪ Other Treatment Providers
Comprehensive Assessment	▪ Medical, Psychiatric, Review/Perform Lab Tests, Physical Exam
Signs of Withdrawal	▪ Clinical Opioid Withdrawal Scale (COWS)
Diagnostic Clarification of Substance Use Disorder	▪ DSM-Criteria with: - Descriptor: Use Disorder; Intoxication; Withdrawal - Specifiers: In Early remission; In Sustained remission; In a controlled environment - Severity: Mild, Moderate, Severe
Risk Assessment	▪ Active Suicidal Ideation; Homicidal Ideation; Overdose
Assessment of Appropriateness	▪ Buprenorphine Treatment (any contraindications) ▪ Is OBOT appropriate for patient at this time
Plan	▪ MAT; Therapy; Referrals; Safety Measures

ASAM, 2014
SAMHSA, 2018

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Summary

- The initial evaluation is comprised of building a therapeutic alliance, obtaining data for treatment planning and initiation.
- Important components include History of medical, psychiatric and substance use disorders. There is great variability in practice and providers and clinics may have their own policies, protocols and preferences regarding the evaluation and documentation.
- Comprehensive physical exam can identify current state of health and areas for further evaluation and treatment.
- Office-Based Opioid Treatment (OBOT) can be appropriate for patients that are able to receive the level of care that can be provided in an outpatient setting. Some patients may benefit from stabilization offered by higher levels of care before engaging in office-based care.
- Methadone or Naltrexone-ER are other options for MAT and may be more suitable for patients who prefer either of these option or for whom OBOT is not effective or appropriate.

References

- American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA. American Psychiatric Association.
- American Society on Addiction Medicine. 2014. The ASAM Standards of Care for the Addiction Specialist Physician. Available at: http://www.asam.org/docs/default-source/practice-support/quality-improvement/asam-standards-of-care.pdf?sfvrsn=10.
- Babor TF, Higgins-Biddle JC, Saunders JB & Monteiro MG. The Alcohol Use Disorder Identification Test: Guidelines for Use in Primary Care, Second Edition. World Health Organization, 2001. Available at: http://whqlibdoc.who.int/hq/2001/who_msd_msb_ 01.6a.pdf.
- Bass F, Naish B, Buwembo I. 2013. Front-office staff can improve clinical tobacco intervention Health coordinator pilot project. *Can Fam Physician* 59:e499-506.
- Center for Behavioral Health Statistics and Quality (CBHSQ). 2016. Key substance use and mental health indicators in the United States: results from the 2015 National Survey on Drug Use and Health. *HHS Publication SMA 16-4984, NSDUH Series H-51.* Retrieved from http://www.samhsa.gov/data.
- Chou R, Korthuis PT, Weimer M, et al. 2016. Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings. Technical Brief No. 28. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 16(17)-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

References

- Kampman K, Comer S, Cunningham C, et al., 2015. National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Chevy Chase, MD: American Society of Addiction Medicine.
- Korthuis PT, McCarty D, Weimer M, et al., 2017. Primary Care–Based Models for the Treatment of Opioid Use Disorder - A Scoping Review. *Ann Intern Med* 166(4):268-278.
- Merlino JI, Raman A. 2013. Health Care's Service Fanatics. *Harv Bus Rev* 91(5):108-16.
- Substance Abuse and Mental Health Services Administration. Medications To Treat Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 18-5063FULLDOC. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018

Case Study #1: The Lawyer

Lawyer, beginning to use daily Clinical Management

Mr. Smith is a forty–year-old man who comes to your office asking to be treated with buprenorphine. He is a criminal defense attorney in private practice, and he knows about buprenorphine because you are treating some of his clients. His goal is to use buprenorphine during the week and occasionally use heroin (by snorting) on the weekend. He has used heroin for the past 5 years.

For the past 6 months, he has used heroin primarily on the weekend, but he is concerned now because he has begun to use small amounts of heroin daily. If he doesn't use heroin, he gets loose stools, is irritable, and has difficulty getting and staying asleep. He has no desire to completely stop heroin use, but he doesn't want to use it during the week.

His passion is playing jazz and he has organized a band. He says that heroin use is common in the club where his band plays. All the members of the band use heroin and many of his friends who come to the club also snort or inject heroin. He rarely buys heroin, as his friends usually give it to him.

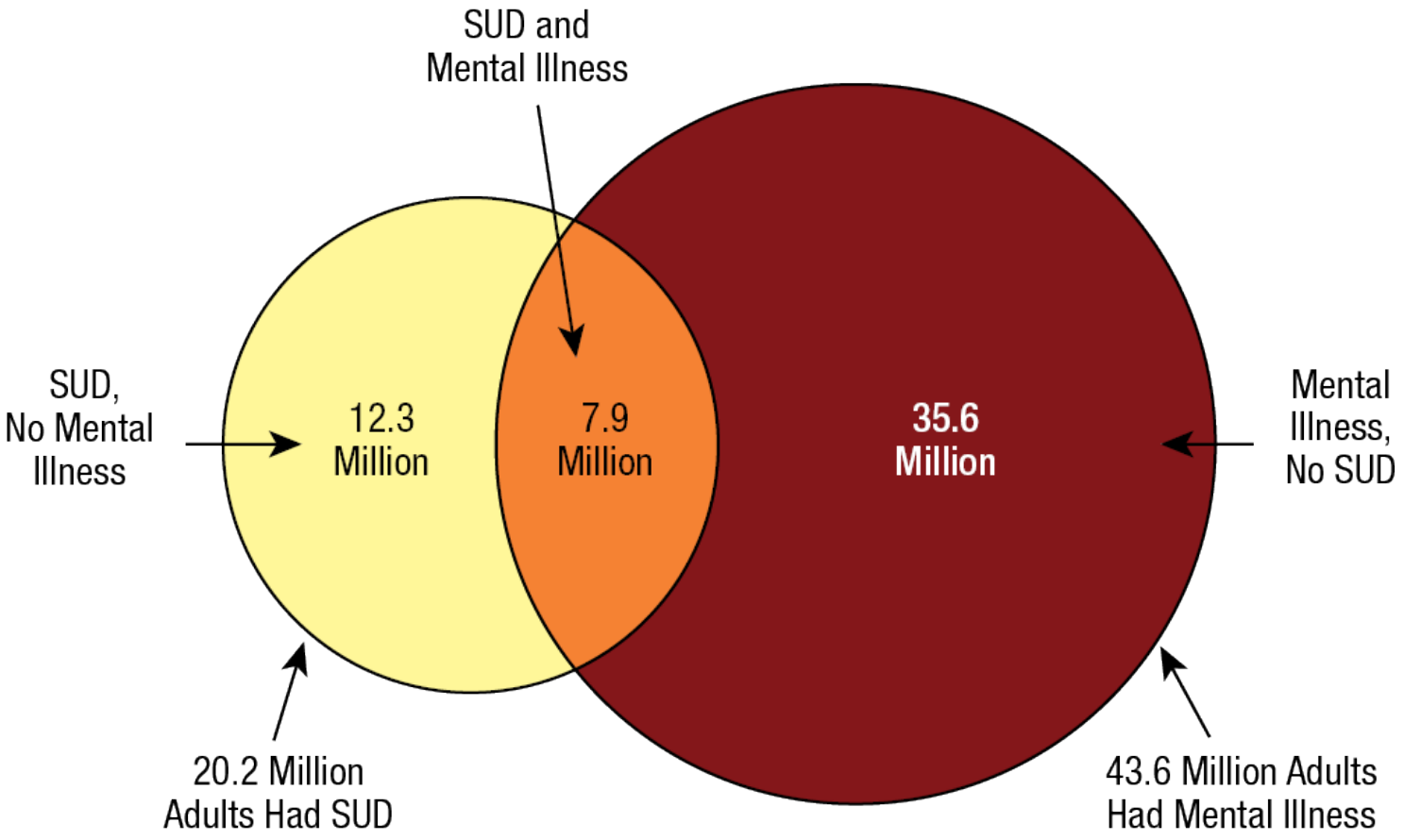
Case #1 Lawyer, beginning to use daily cont.

His only other drug use is marijuana and alcohol (3-6 drinks/night on the weekend), again primarily used on the weekend. He has never been arrested or had significant medical consequences from his heroin use. He is not married. He has a 14-year-old son who he has supported and sees often.

- ***What is the diagnosis?***
- ***Is this patient a candidate for treatment with buprenorphine?***
- ***What are the treatment goals?***
- ***What is the initial treatment plan?***

Specialty Topics

Co-occurring Psychiatric Disorders



SAMHSA, 2017

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Comorbid Psychiatric Disorders

- Distinguish between substance-induced disorders versus independent psychiatric disorders:
  - Substance-induced:
    - Disorders related to the use of psychoactive substance; typically resolve with sustained abstinence
  - Independent:
    - Disorders which present during times of abstinence; symptoms not related to use of psychoactive substance

Note: There is no specific period of time used to differentiate these disorders

Substance-Induced Disorders

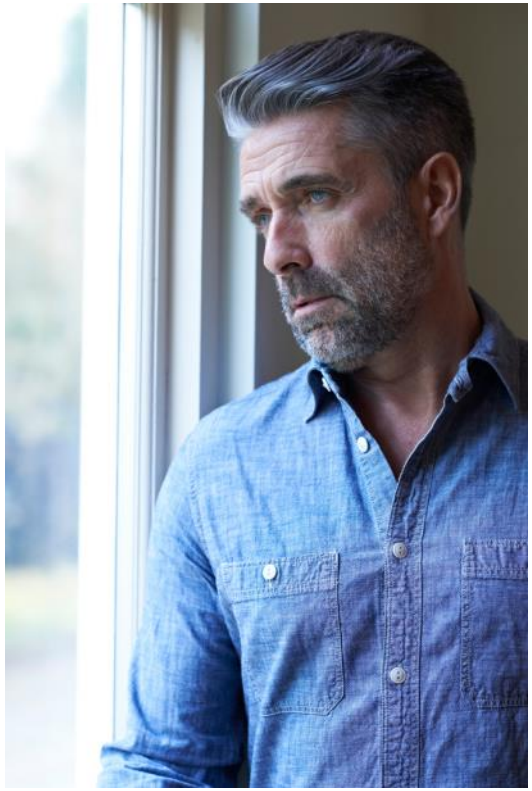
- Symptoms occur only when misusing drugs
- Symptoms are related to intoxication, withdrawal, or other aspects of active use
- Onset and/or offset of symptoms is preceded by increases or decreases in substance use
- Goals:
  - Sustained abstinence
  - Re-evaluation

Independent Disorders

- Symptoms occur when not using or misusing psychoactive substances, or with steady use without change in amount or type
- Family history may point to independent disorder if present in first degree relatives
- Goal:
  - Cessation of substance use, and treatment of psychiatric symptoms

Depressive and Anxiety Symptoms

- Depressive and anxiety symptoms are common at treatment entry
- Symptoms may resolve within few days of stable treatment
- Symptoms that persist beyond acute intoxication and withdrawal can be worthwhile targets for treatment:
  - For example, with Selective Serotonin Reuptake Inhibitors
- Patients treated with MAT respond to medications for depression and anxiety at rates similar to those without opioid use disorders



Treatment of Co-Occurring Psychiatric Disorders

- Avoid use of benzodiazepines
  - Risk of misuse
  - Interactions with buprenorphine possible
  - First-Line Treatments for anxiety and depression
    - Selective Serotonin reuptake inhibitors
    - Psychotherapy (e.g.: cognitive behavioral therapy)
- Stimulants
  - Obtain collateral information from Prescription Drug Monitoring Program, Psychiatric and/or Primary Care Provider
  - If there is concern for Attention Deficit Hyperactivity Disorder (ADHD), consider Adult ADHD Self-Report Scale (ASRS) or refer patient to a Psychiatric or Primary Care Provider for assessment
  - Continue stimulants if they have been legitimately prescribed by Psychiatric or Primary Care Provider

Chang et al., 2005
Kampman et al., 2015

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 in on buprenorphine.
    - Consider starting with or switching to equivalent dose of buprenorphine mono-product (available as a generic medication)
  - If methadone is selected refer to OTP and may start without a period of mild withdrawal.
    - Administer split dose (e.g.: 30 mg on day 1 in two divided doses, and increase as clinically indicated).

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

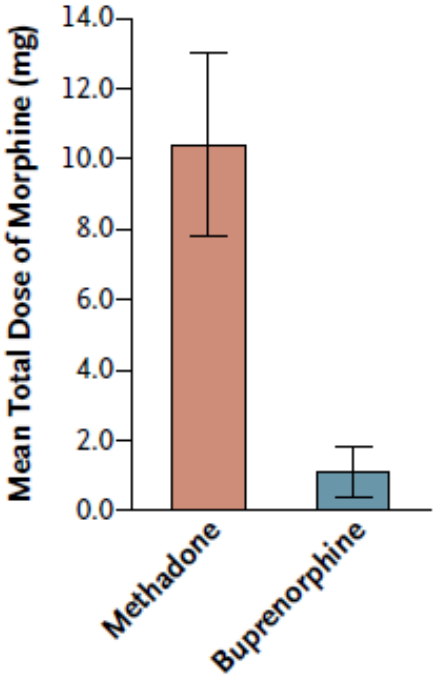
Buprenorphine vs. Methadone in Pregnant Patients with OUD

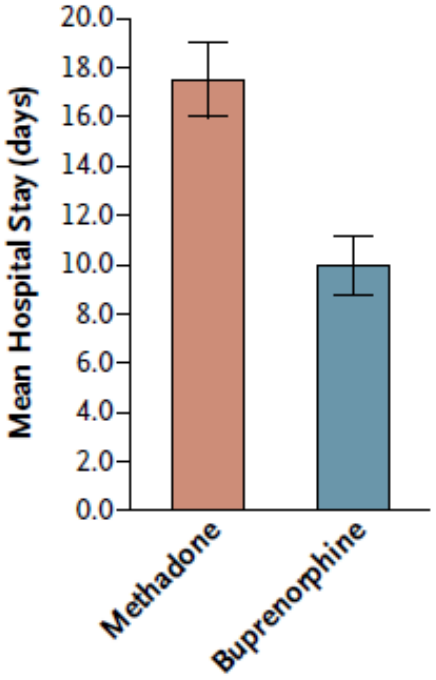
Buprenorphine (Mono Product)	**Methadone**

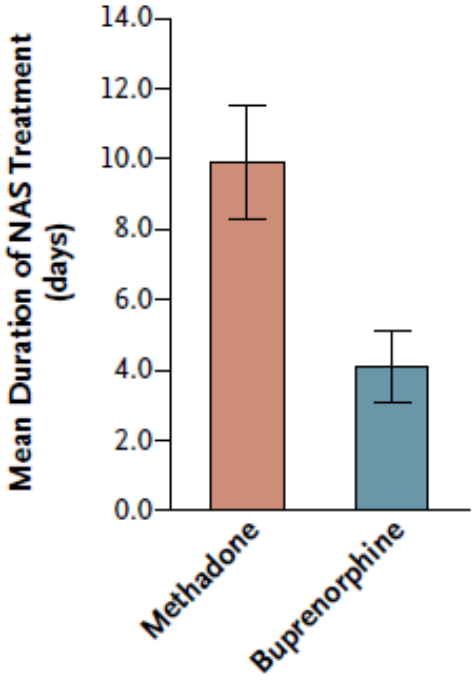
▪ Similar efficacy as methadone
▪ Same rates of adverse events, NAS, as methadone
▪ Improvement over methadone:
  ▪ Lower risk of overdose
  ▪ Fewer drug interactions
  ▪ Milder withdrawal symptoms in NAS
  ▪ Reduced morphine dosing
  ▪ Significantly shorter hospital stay
	▪ More structure- better for 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

Maternal Opioid Treatment:
Human Experimental Research (MOTHER) Study







Jones et al., 2010

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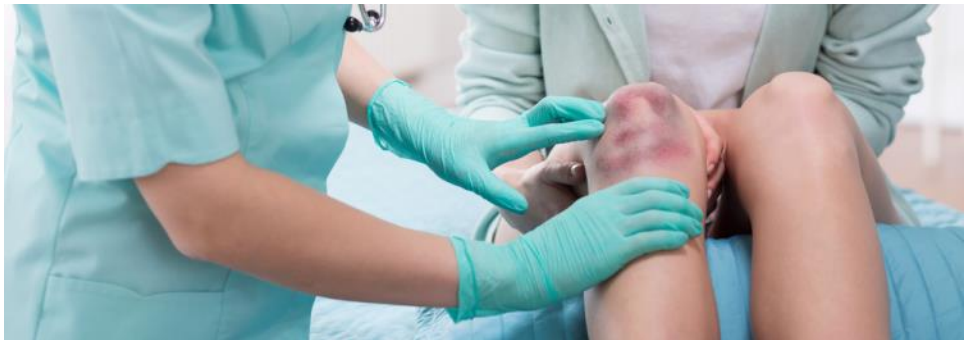
Factors to Consider in Treating the Adolescent OUD Patient

- 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

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

PCSS Providers Clinical Support System

Acute Pain Management for Patients currently on Naltrexone

Clinical Scenario	Management Options
Mild Pain	▪ Non-Opioid options e.g. Full doses of NSAIDs (e.g. ketorolac injection)
Elective Surgery	▪ Make a plan and schedule surgery. For patients on: • Oral Naltrexone: Discontinue at least 72 hours after last dose • Extended Release Naltrexone: At least four-weeks after receiving injection
Major Pain or Emergency	▪ Regional anesthesia ▪ Conscious sedation ▪ General anesthesia [Note: *High potency opioids like fentanyl can override blockade*]

Alford et al., 2006
CSAT, 2004
Kampman et al., 2015
WHO, 2009

Chronic Pain Patients

- Consider consulting a pain medicine specialist
- Consider Multidisciplinary Team Approach
- Try non-opioid and adjuvant analgesics
- Consider non-pharmacologic therapies

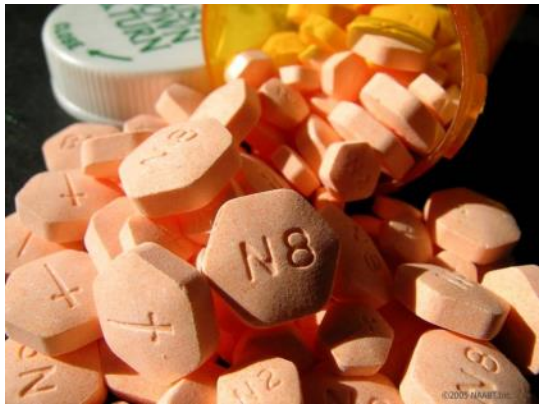
HIV – Positive Patients

- 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

- Approximately 40% of adults with SUD had a co-occurring psychiatric disorder. Diagnosis and Treatment of mental health issues can potentially have a positive impact on Opioid Use Disorder (OUD).
- Methadone has historically been considered first-line treatment of OUD in pregnant women. However, Increasing evidence is demonstrating that Buprenorphine without naloxone is well-tolerated and efficacious with potential benefits for the newborn.
- Although Buprenorphine is approved for individuals over 16 years of age and Methadone is approved for individuals over 18 years of age providers can consider Naltrexone ER in combination with psychosocial treatment options for adolescents with OUD.

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.

References

- AAP Committee on Substance Use and Prevention. 2016. Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. *Pediatrics* 138(3):e20161893.
- American College of Obstetricians and Gynecologists (ACOG) and American Society of Addiction Medicine (ASAM). Opioid Use and Opioid Use Disorder in Pregnancy. 2017 https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co711.pdf?dmc=1&ts=20171105T2029443754
- Carrieri MP, Vlahov D, Dellamonica P, et al., 2000. Use of buprenorphine in HIV-infected injection drug users: negligible impact on virologic response to HAART. The Manif-2000 Study Group. *Drug and Alcohol Dependence* 60(1): 51–54.
- Center for Substance Abuse Treatment (CSAT). 2004. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration.
- Center for Substance Abuse Treatment. Substance Abuse Treatment for Persons with HIV/AIDS. Treatment Improvement Protocol (TIP) Series, Number 37. Rockville, MD: Center for Substance Abuse Treatment, 2000.
- Chau DL, Walker V, Pai L, and Cho LM. 2008. Opiates and elderly: Use and side effects. *Clin Interv Aging* 3(2): 273–278.

References

- Chou R, Turner JA, Devine EB, et al., 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 162(4): 276–286.
- Drug Addiction Treatment Act of 2000 (DATA 2000). 2000. Public Law 106-310, Stat. 1223–1227.
- Fischer G, Etzerdorfer P, Eder H, et al.,1998., Buprenorphine maintenance in pregnant opiate addicts. *European Addiction Research* 4(Suppl 1): 32–36.
- Fischer G, Gombas W, Eder H, et al.,1999. Buprenorphine versus methadone maintenance for treatment of opioid dependence. *Addiction* 94(9): 1337–1347.
- Fishman MJ, Winstanley EL, Curran E, et al., 2010. Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: Preliminary case-series and feasibility. *Addiction* 105(9): 1669–1676.
- Hadland SE, Wharam JF, Schuster, et al., 2017. Trends in Receipt of Buprenorphine and Naltrexone for Opioid Use Disorder Among Adolescents and Young Adults, 2001-2014. *JAMA Pediatrics*. Published Online. Accessed 06/20/17.
- Holmes AV, Atwood EC, Whalen B, et al., 2016. Rooming-In to Treat Neonatal Abstinence Syndrome: Improved Family-Centered Care at Lower Cost. *Pediatrics* 137(6):e20152929.

References

- Hudak ML, Tan RC and the Committee on Drugs and the Committee on Fetus and Newborn. Neonatal Drug Withdrawal. 2012. *Pediatrics* 129(2);e540–560.
- Johnston LD, O'Malley PM, Miech RA, et al. 2016. Monitoring the Future national survey results on drug use, 1975-2015: Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan.
- Jones HE, Kaltenbach K, Heil SH, et al., 2010. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 363(24): 2320–2331.
- Kakko J, Heilig M, Sarman I. 2008. Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug and Alcohol Dependence* 96(1-2) 69–78.
- Kampman K, Comer S, Cunningham C, et al., 2015. National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Chevy Chase, MD: American Society of Addiction Medicine.
- Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al., 2017. Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome. *N Engl J Med* 376(24): 2341–2348.
- Lund IO, Fischer G, Welle-Strand GK, et al., 2013. A Comparison of Buprenorphine + Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes. *Subst Abuse* 7:61–74.
- Maree RD, Marcum ZA, Saghafi E et al., 2016. A Systematic Review of Opioid and Benzodiazepine Misuse in Older Adults. *Am J Geriatr Psychiatry* 24(11): 949–963.

References

- Mattson M, Lipari, RN, Hays C and Van Horn, SL. A day in the life of older adults: Substance use facts. The CBHSQ Report: May 11, 2017. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.
- McCance-Katz EF, Sullivan LS and Nallani S. 2010. Drug interactions of clinical importance between the opioids, methadone and buprenorphine, and frequently prescribed medications: A review. *American Journal of Addictions* 19(1): 4–16.
- Merrill J, Rhodes LA, Deyo RA et al., 2002. Mutual mistrust in the medical care of drug users: the keys to the "narc" cabinet. *J Gen Intern Med* 17(5): 327–333.
- Moatti JP, Carrieri MP, Spire B et al., 2000. Adherence to HAART in French HIV-infected injecting drug users: The contribution of buprenorphine drug maintenance treatment. *AIDS* 14(2): 151–155.
- Montoya ID, Umbricht A, and Preston KL.1995. Buprenorphine for human immunovirus-positive opiate-dependent patients. *Biological Psychiatry* 38(2): 135–136.
- Patrick SW, Davis MM, Lehmann CU and Cooper WO. 2015. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol* 35(8): 650–655.
- Roux P, Sullivan MA, Cohen J et al., 2013. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. *Pain* 154(8): 1442–1448.

References

- Sachs HC, MD and Committee on Drugs. 2013. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. *Pediatrics* 132(3):e796-809. doi: 10.1542/peds.2013-1985. Epub 2013 Aug 26.
- Smith, K. and Lipari, R.N. Women of childbearing age and opioids. The CBHSQ Report: January 17, 2017. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.
- Substance Abuse and Mental Health Services Administration. 2017. Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/ .
- U.S. National Archives and Records Administration.2017. *Code of federal regulations*. Title 10, Part 2. Confidentiality of substance use disorder patient records.
- Volkow ND, McLellan AT. 2016. Opioid abuse in chronic pain: misconceptions and mitigation strategies. *N Engl J Med* 374(13): 1253–1263.
- Volkow ND, McLellan TA. 2011. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA* 305(13): 1346–1347.

References

- Wenzel JT, Schwenk ES, Baratta JL and Viscusi ER. 2016. Managing opioid-tolerant patients in the perioperative surgical home. *Anesthesiol Clin* 4(2): 287–301.
- West NA, Severtson SG, Green JL and Darta RC. 2015. Trends in abuse and misuse of prescription opioids among older adults. *Drug and Alcohol Dependence* 149(1): 117–121.
- Woody GE, Poole SA, Subramaniam G et al., 2008. Extended vs. short-term buprenorphine-naloxone for treatment of opioid-addicted youth: A randomized trial. *JAMA* 300(17): 2003–2011.
- World Health Organization. 2009. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland: WHO Press.
- Wu L and Blazer DG. 2014. Substance use disorders and psychiatric comorbidity in mid and later life: a review. *Intern Journal of Epidem* 43(2): 304–317.

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

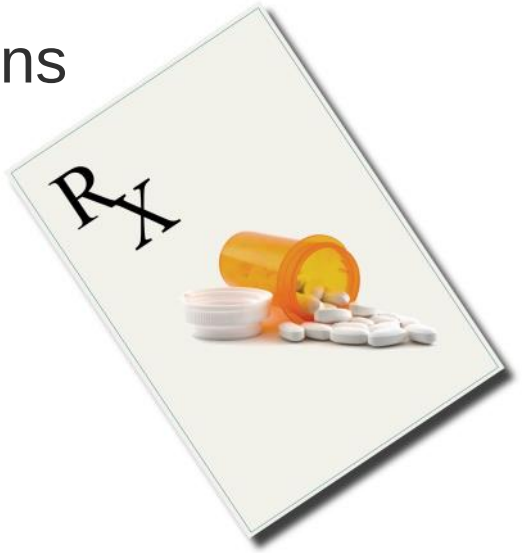
SAMHSA, 2016, 2016

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

- Many Logistical Factors/Considerations
  - Review that patient meets induction criteria
  - Insurance
  - Confirm access to pharmacy
  - Confirm access to urine drug testing



- Location
  - Office Induction:
    - Patient given prescription and brings medication to the office
  - Home Induction:
    - Patient goes home with instructions, follow-up appointment, and a prescription for medicine

Office Buprenorphine Induction
Day #1

- Timing
  - Some offices prefer inductions earlier in the week – Consider Monday, Tuesday and avoid Fridays
  - Consider scheduling office induction earlier in the day

- Decrease likelihood of precipitated withdrawal at induction by:
  - Ensuring mild to moderate withdrawal at the time of induction
    - Document using Clinical Opiate Withdrawal Scale (COWS)
  - Start with low dose: 2-4mg equivalents

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

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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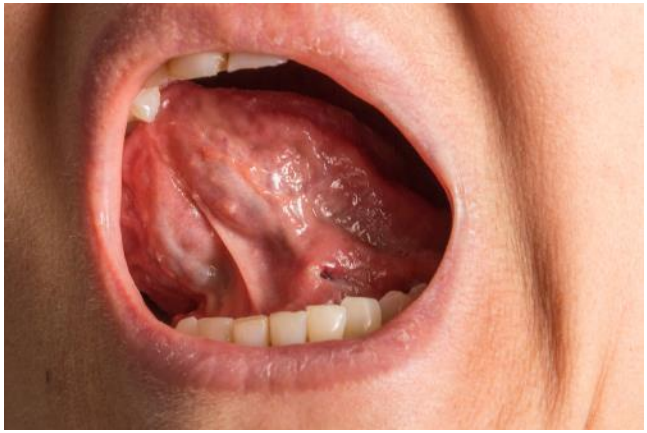
Office Buprenorphine Induction
Patient Education

- 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 sputum

Buprenorphine Induction
Day #1

If patient is not in opioid withdrawal on arrival in office:

- Assess and confirm time of last opioid use
- Have patient wait in the office until you see
  evidence of withdrawal

OR

- Consider home induction

Photo by: Wouterhagens

PCSS Providers Clinical Support System

Office Buprenorphine Induction
Day #1

- 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:
  - **NOTE:** Be aware of **Fentanyl;** do not induce unless moderate withdrawal (COWS 13 to 15) is observed

Office Buprenorphine Induction
Day #1 – Short Acting Opioids

- Patients dependent on short-acting opioids (e.g. heroin/oxycodone/ hydrocodone):
  - Instruct patient to abstain from any opioid use for 12 to 24 hours prior to induction visit:
    - Arrive in mild-moderate withdrawal at induction visit
  - Use opioid withdrawal scale (COWS > 8):
    - Document and assess severity of withdrawal
    - Track the patient's response to first day's dose

Office Buprenorphine Induction
Day #1 – **Methadone**

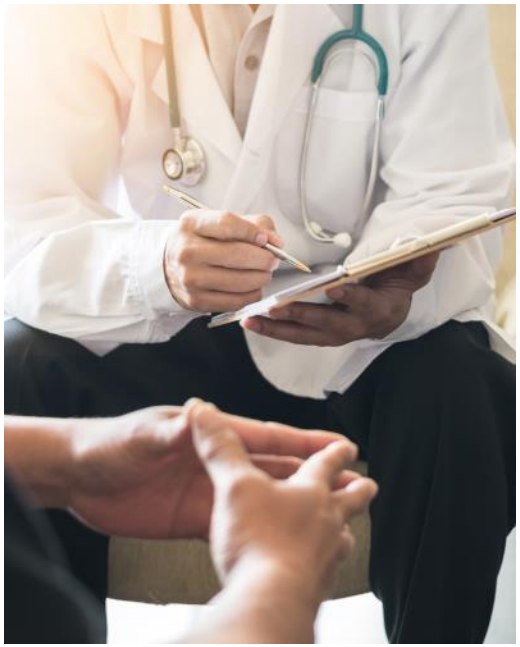
- **Do not start buprenorphine until the patient manifests signs of opioid withdrawal**
  - Waiting at least 36 hours reduces risk of precipitated withdrawal
  - Lower doses of buprenorphine/naloxone are less likely to precipitate methadone withdrawal.[328]
    - For example, once opioid withdrawal is verified, an initial dose of 2 mg/0.5 mg can be given. If patients continue to have unrelieved opioid withdrawal after the first 2 mg dose, administer another 2 mg/0.5 mg dose approximately every 2 hours as needed (holding for sedation)
  - Induction should be conducted slowly; consider treating unrelieved withdrawal symptoms with nonopioid therapies as needed
  - Be alert to any increase in withdrawal symptoms, as this may suggest precipitated withdrawal.

Buprenorphine Induction
Review

- First dose: 2-4 mg SL buprenorphine/naloxone
- Monitor in office for 2+ hours after first dose
  - Relief of opioid withdrawal symptoms should begin within 30-45 minutes after the first dose
- Re-dose every 2-4 hours, if opioid withdrawal subsides then reappears
- Stabilize at dose that eliminates craving; typical dose range from 8 mg to 16 mg
- Gradually increase dose after establishment of a steady state over as needed for continued craving.
  - Note: This can be increased more rapidly if the patient has a lot of craving.

Buprenorphine Induction
Day #1

- 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.

Home Induction
Multiple Approaches but Subtle Clinical Variance

- Similar outcomes noted for observed and home induction in terms of safety and efficacy
- Process:
  - Teach patient about how bup/nx works and how it is absorbed
  - Review typical withdrawal symptoms with patient
    - Start assessing withdrawal symptoms 12 hours after short-acting opioids and 24 - 36 hours after last illicit methadone use
    - Self administer 2mg bup/nx when experiencing withdrawal symptoms
    - Self assess again in 1-3 hours. If still withdrawing, self administer another 2mg dose
  - May repeat until a maximum total dose of 8-12mg during first day

Home Induction Instructions
Day #2

- Day #2: Continue dose established on Day #1
  - Encourage patient to preferably take Day #1 dose on the morning of Day #2
  - Encourage office staff to contact patient on Day #2 to assess dose response
  - After contact with patient there may be reason for additional dose adjustments:
    - If patient feels well, instruct patient to continue Day #1 dosing
    - If patient is experiencing cravings or discomfort consider increasing dose by 2-4 mg

    OR

    - discuss relapse prevention and assure patient that discomfort will stabilize over time
  - Avoid rapid dose adjustments

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

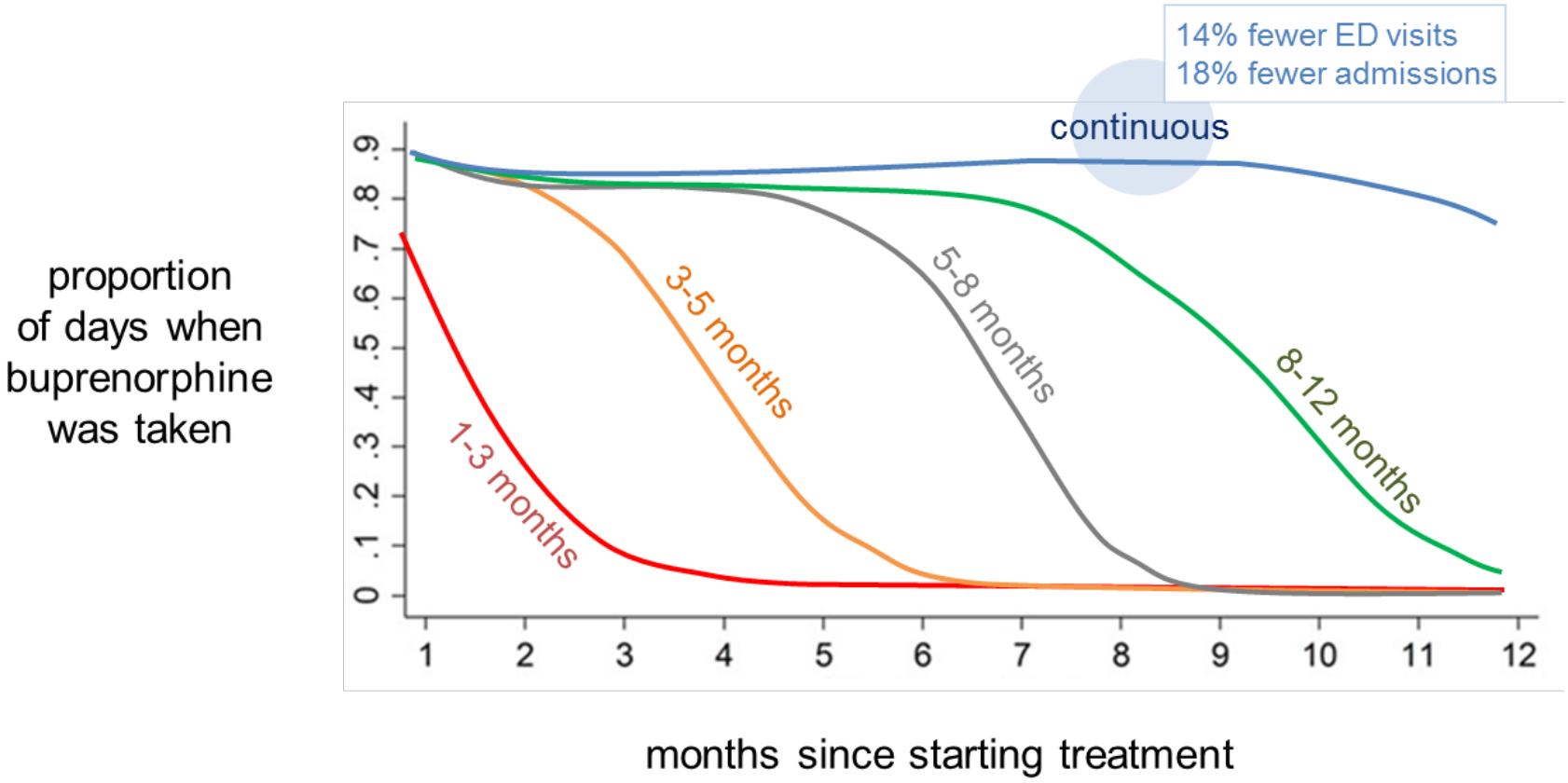
- Adjust daily dose by increments of 2-4 mg as needed:
  - Increase primarily for persistent cravings

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

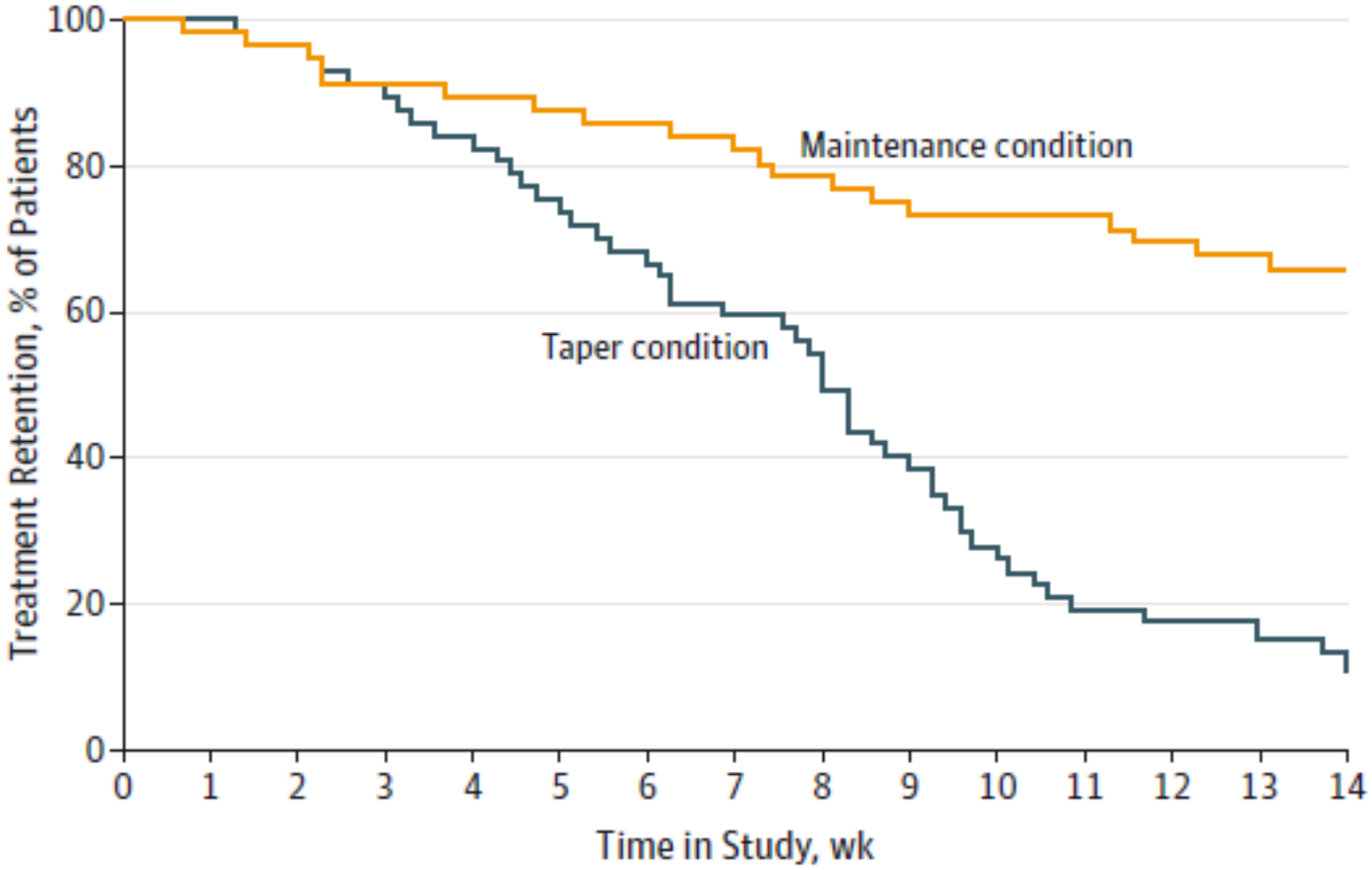
Kakko et al., 2003
Weiss et al., 2011

Optimal Duration of MAT



Lo-Ciganic et al., 2016

Treatment Retention and Buprenorphine Dosage



Fiellin et al., 2014

Medically Supervised Withdrawal
from Full-opioid Agonist Using Buprenorphine

- Buprenorphine suppresses opioid withdrawal symptoms
- When stopping buprenorphine:
  - A more gradual taper decreases the severity of withdrawal symptoms
  - Taper durations ranging from 4 to 30 days are common in clinical practice
- Withdrawal symptoms may not occur until 2-3 days after stopping buprenorphine
- Adjunctive medications (E.g. clonidine) to manage symptoms supportively

Ling et al., 2009
Sigmon et al., 2013

XR-NTX Practical Considerations

- Logistics
  - Adequate insurance or program coverage
    - Out of pocket XR-NTX is ~ $1100/dose
  - Ordered from specialty pharmacy, shipped to physician
  - Keep refrigerated until dosing visit
- Check Opioid free status of patient by self-report and verified by urine drug screen
- Consider administering Naloxone challenge before first dose

  OR
- Preload oral Naltrexone

XR-NTX Considerations

- XR-NTX injection
  - Side Effects
    - Opioid blockade may interfere if acute pain management is needed
    - Headaches, nausea, flu-like: common with 1st injection, but not subsequent injections
    - Injection site pain: common

Naltrexone Initiation

- Naltrexone is an opioid receptor antagonist and can only be started in individuals who are completely free of opioids
- Official prescribing information for injection naltrexone recommends 7-10 days “washout” period between the two phases: last dose of opioid and first dose of NTX
- When naltrexone is given to patients who are physically dependent, or have opioids in their system, naltrexone will displace opioids off the receptor and withdrawal symptoms will rapidly emerge
  - Precipitated withdrawal as opposed to a slow onset of a spontaneous withdrawal can look atypical and can involve delirium

Medically Supervised Withdrawal

Approach	Details
Symptomatic-only treatment	A variety of adjunctive medications are used to decrease specific symptoms of withdrawal
Rapid medically supervised withdrawal using antagonist	Naltrexone is added few (3•4, days after the last dose of opioid starting with very low doses (3-6 mg} Emerging withdrawal symptoms are treated with adjunctive medications to minimize discomfort

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.

Acute Withdrawal Using Buprenorphine

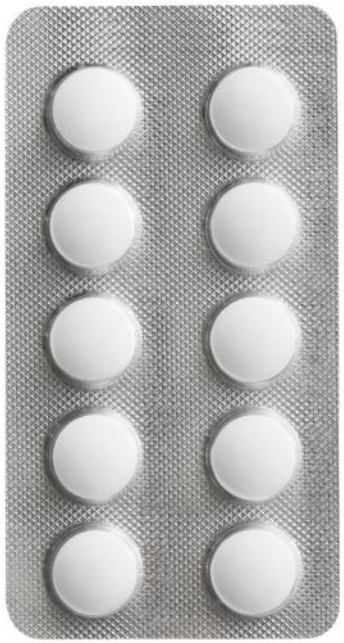
- Withdrawal can be primary treatment or termination of period of maintenance therapy
- Many regimens can be used based on clinical practice and patient needs
- Example: Withdrawal over 3 days:
  - First day: 8/2-12/3 mg s.l.
  - Third (last) day: 6/1.5 mg s.l.
- Can extend taper by 2-3 days if patient has trouble tolerating the procedure; offer reassurance and treat emerging insomnia, anxiety, and/or myalgias
- Withdrawal symptoms may not occur until completely off drug for 2-3 days

Adjunctive Medication Options
During Medically Supervised Withdrawal

Withdrawal Symptoms	Adjunctive Medications
Anxiety/restlessness	▪ a-$_2$ Adrenergic agonists (e.g. clonidine)
Insomnia	▪ Sedating antidepressants (e.g. trazadone)
Musculo-skeletal pain	▪ Acetaminophen, Ibuprofen
GI Distress (nausea, vomiting, diarrhea)	▪ Oral hydration ▪ Antiemetics (e.g. ondansetron) ▪ Anti-diarrheals (e.g. loperamide)

α_2-Adrenergic agonists

- **Clonidine**
  - Administer 0.1 mg as needed for symptoms of withdrawal every 6 hours
  - Assure continuous hydration (juice>water)
  - Medication reduces physical withdrawal but not craving for opiates
  - Side-effects are sleepiness, dizziness, fainting, headache



Protracted Withdrawal:
Naltrexone Flu

- Patients who start naltrexone right after medically supervised withdrawal commonly experience “flu-like” symptoms that are consistent with subacute opioid withdrawal
  - Somatic complaints: insomnia, GI distress, hyperalgesia, anergia
  - Anxiety, irritability, dysphoria, anhedonia
  - Symptom severity correlated with naltrexone dose
  - Severity may be lower if naltrexone initiation is postponed (but relapse risk)
- Partially alleviated with aggressive symptomatic treatment
- Most of these symptoms remit by 2 weeks
  - Unusual for these symptoms to occur after 2nd and subsequent injections

Initiating IM Naltrexone (XR-NTX)
Summary

- Effective suppression of withdrawal symptoms, accomplished with a range of adjunctive medications, is essential to the success
- Effective method will balance the degree of discomfort and the duration of treatment
- Ability of the team to expect and respond to emerging complications, to maintain enthusiasm as confidence in the method can influence outcome
- Anticipatory guidance and motivational techniques should accompany the initiation of treatment with XR-NTX to improve long-term adherence as many patients will experience internal barriers to continuation

Sigmon et al., 2012

Case Study #2: The Teacher

Robert, a 35-year old teacher Considering Treatment Options

The patient is a 35-year-old school teacher. He has been injecting heroin on and off since he was 16. He has never been arrested. He has been through many episodes of heroin detoxification, mostly outpatient methadone detoxification but has also been in three inpatient drug treatment programs. The last inpatient program was a 28-day, drug-free recovery program, and he remained both heroin and alcohol free for about 6 months following treatment. He teaches math at a junior high school and is in some difficulty because of “calling in sick too much.” His wife is in recovery, and insisted that he return to treatment after she discovered he was taking large quantities of codeine pills from several doctors for a back injury following an automobile accident. She is unaware that he is also injecting heroin at least once daily. He has been alcohol abstinent for the past two years. His only current medical problem is that he is hepatitis C positive and he has been so for at least 10 years.

He states “Doc, I know I’m an addict. My wife cleaned up when she was pregnant with our daughter, and she just got her 12-year chip. She moved on with her life, but I’m stuck. My back injury threw me into a tailspin. At first, I really needed the codeine, but now I’m just using them to stave off heroin withdrawal. I really need your help. If my wife finds out I’m back on the needle, she’ll leave me this time.”

Case #2: Robert, a 35-year old teacher

- ***Does this patient meet DSM-5 criteria for opioid dependence?***
- ***What are the treatment options for this patient?***
- ***How would you assess the need for pharmacotherapy for this patient?***
- ***Is this patient a candidate for buprenorphine?***

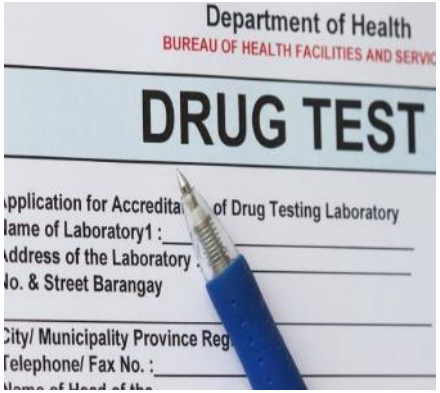
Urine Drug Testing

General Goals of Drug Testing in Office-Based Treatment

- Important and routine component of treatment
- Urine testing can be viewed as a means for helping the provider to help the patient
- Testing is not meant to "catch" the patient, and a positive test result should not simply lead to discharge from treatment, but an opportunity for reviewing the patient's Recovery Management

Drug Testing in Office-Based Treatment Specifics

- Laboratory testing for evidence of substance use has several roles in office-based treatment for opioid use disorder, including:
  - Initial assessment
  - Treatment planning
  - Screening to identify non-prescribed substances/medications
  - Monitoring adherence to pharmacotherapy
  - Evaluating efficacy of treatment and assist in treatment planning



- <u>Ideally</u> laboratory testing should be:
  - Random
  - Observed
  - Convenient for the patient
  - High quality
  - Able to offer timely result

CSAT, 2004
SAMHSA, 2012

PCSS Providers Clinical Support System

Screening and Confirmatory Tests

- A common clinical approach:
  - Test for a panel of commonly-used substances using screening tests
  - Then to perform confirmatory tests for:
    - Positive results whose accuracy is important for treatment planning
    - Periodic general screening assessing commonly used substances that are not evident on POCT
    - Identification of prescribed medications or metabolites
- Confirmatory testing is not necessary at every visit

DuPont et al., 2013
Moeller et al., 2017
SAMHSA, 2012

PCSS Providers Clinical Support System

Common Tests

- Some commonly-used screening tests include:
  - Benzodiazepines
  - Cannabinoids
  - Amphetamines
  - Cocaine metabolite (benzoylecgonine)
  - Opiates (detects morphine, codeine, and metabolites)

- Less commonly-used screening tests include:
  - Alcohol metabolite (ethyl glucuronide or ethyl sulfite)
  - Buprenorphine
  - Fentanyl
  - Oxycodone
  - Methadone

these and other synthetic opioids require specific tests—they are not detected by the test for opiates

Providers Clinical Support System

Moeller et al., 2017

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

References

- DuPont RL, Shea CL, et al. 2013. *Drug testing: a white paper of the American Society of Addiction Medicine (ASAM).* Chevy Chase, MD: American Society of Addiction Medicine.
- Fiellin DA, Schottenfeld RS, Cutter CJ, et al. 2014. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Internal Medicine* 174(12):1947–1954.
- Hull MJ, Bierer MF, Griggs DA, et al. 2008. Urinary buprenorphine concentrations in patients treated with Suboxone as determined by liquid chromatography-mass spectrometry and CEDIA immunoassay. *J Anal Toxicol* 32(7):516–521.
- Kakko J, Svanborg KD, Kreek MJ, Heilig M. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 361(9358):662–668.
- Kampman S, Comer S, Cunningham C, et al. 2015. *National practice guideline for the use of medications in the treatment of addiction involving opioid use.* Chevy Chase, MD: American Society of Addiction Medicine.
- Ling W, Hillhouse M, Domier C, et al. 2009.Buprenorphine tapering schedule and illicit opioid use. *Addiction* 104(2):256–265.
- Lo-Ciganic WH, Gellad WF, Gordon AJ, et al. 2016. Association between trajectories of buprenorphine treatment and emergency department and in-patient utilization. *Addiction* 111(5):892–902.

References

- Lofwall MR and Walsh SL. 2014. A Review of Buprenorphine Diversion and Misuse: The Current Evidence Base and Experiences from Around the World. *J Addict Med* 8(5):315–326.
- Moeller KE, Kissack JC, Atayee RS, and Lee KC. 2017. Clinical interpretation of urine drug tests: what clinicians need to know about urine drug screens. *Mayo Clin Proc* 92(5):774–796.
- Orman JS, Keating GM. 2009. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs* 69(5):577–607.
- Pergolizzi J, Pappagallo M, Stauffer J, et al. 2010. The Integrated Drug Compliance Study Group (IDCSG). The Role of Urine Drug Testing for Patients on Opioid Therapy. *Pain Practice* 10(6):497–507.
- Rosado, J., Walsh, S. L., Bigelow, G. E., & Strain, E. C. (2007). Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100mg of daily methadone. *Drug and Alcohol Dependence, 90*(2–3), 261–269.
- Sethi R, Petrakis I. 2013. Differential diagnosis for a stable patient maintained on buprenorphine who gives a urine toxicology screen negative for buprenorphine. *Am J Addictions* 23:318–319.
- Sigmon SC, Dunn KE, Saulsgiver K et al. 2013. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry* 70(12):1347–1354.
- Sigmon SC, Bisaga A, Nunes EV, et al. 2012. Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice. *Am J Drug Alcohol Abuse* 38(3):187–199.

References

- Substance Abuse and Mental Health Services Administration (SAMHSA). 2012. Clinical drug testing in primary care. *Technical Assistance Publication (TAP) 32*. HHS Publication No. (SMA) 12-4668. Rockville, MD: Substance Abuse and Mental Health Services Administration.
- Substance Abuse and Mental Health Services Administration. Medications To Treat Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 18-5063FULLDOC. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.
- Wald A.2016.Constipation: advances in diagnosis and treatment. *JAMA* 315(2):185–191.
- Weiss RD, Potter JS, Fiellin DA et al. 2011. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Archives of General Psychiatry* 68(12):1238-1246.
- Wesson DR, Ling W. 2003. The clinical opiate withdrawal scale (COWS). *Journal of Psychoactive Drugs* 35:253–259.

Case Study #3: The Student

19-year-old university student
Clinical Management - Part I

A 19-year-old woman university student comes to you asking for treatment of her heroin use. She has been using heroin intranasally for the last 15 months, daily for the last 3 months. She is now using about 1 gram daily. Some of her friends are now switching to intravenous use because it takes less heroin to keep from getting sick. She says she does not want to do that but may be “forced” to because she cannot keep paying the “extra cost” of nasal use. She has used all the money her parents gave her for school expenses to buy heroin, her credit cards are maxed out, and she has borrowed money from her friends. Until last semester, she had an overall B average, but this semester she is in academic difficulty. When she doesn’t use heroin, she has muscle aches, diarrhea, insomnia, and anxiety. She recognizes the symptoms as heroin withdrawal and was surprised because thought she could not develop dependence with nasal use. She has no prior history of drug treatment.

19-year-old university student
Clinical Management - Part I

- ***What is the diagnosis?***
- ***Is this patient a candidate for treatment with buprenorphine?***
- ***What are the treatment goals?***
- ***What is the initial treatment plan?***

19-year-old university student
Clinical Management - Part II

The clinic physician gives her a prescription for 6 day supply of buprenorphine (4 mg/day), and she is told to participate in the clinic's relapse prevention workshop six days a week and to schedule individual counseling at the clinic once a week.

She returns 3 days later having taken 8 mg/day for 3 days. She has not attended the relapse prevention workshop nor scheduled an individual counseling session. The counselor is not available to see her when she comes

- ***What is the treatment plan at this point?***

19-year-old university student
Clinical Management - Part III

Part III

She returns the following day at a time when neither the group nor the counselor is available. She is told she has to attend the relapse prevention workshop in order to get medication. She does not return to the clinic for 4 weeks. When she does, she is smoking more heroin than before, but having no difficulty with finances because she has dropped out of school and is working as a stripper at a local “gentlemen’s club.”

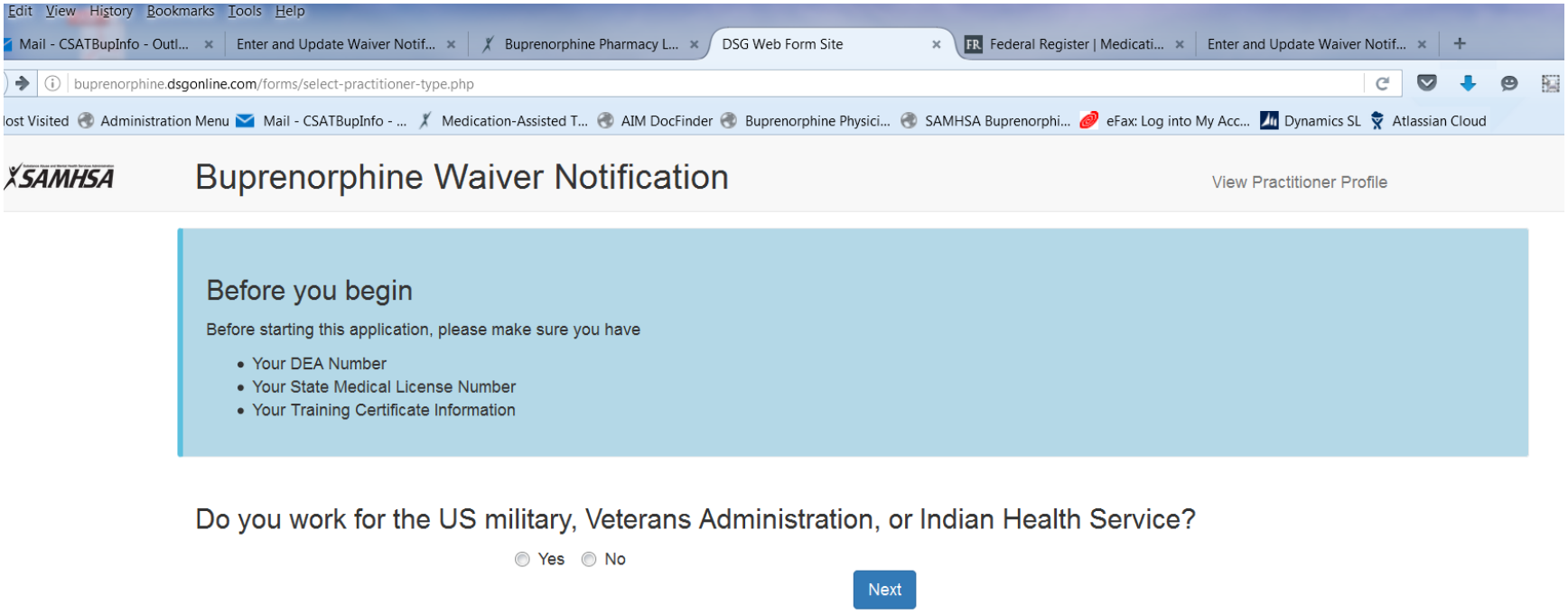
- ***What would you recommend at this point?***

BUPRENORPHINE Waiver Notification Form

Entering a 30 Patient Notification

PCSS Providers Clinical Support System

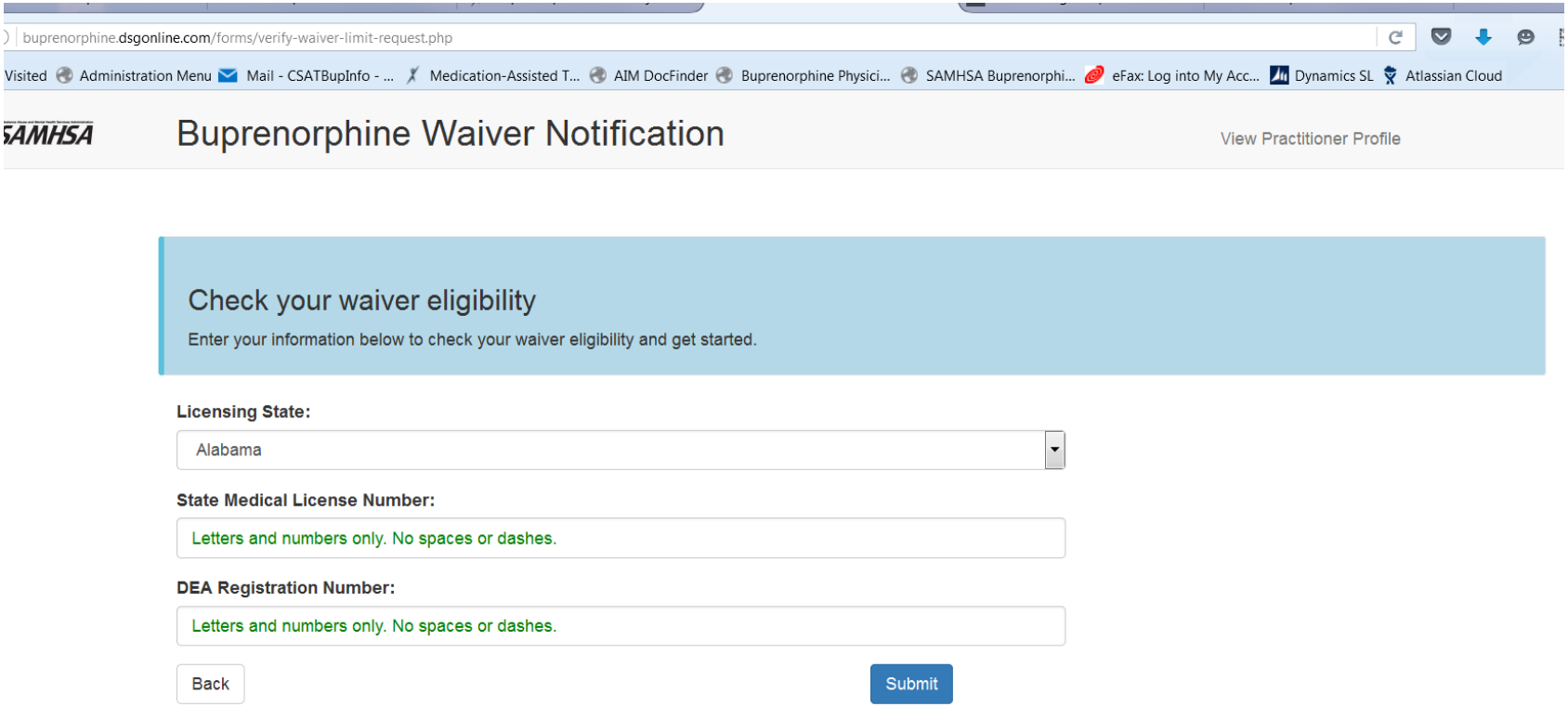
Submitting a 30 Patient Notification Form Online



Answer the question yes or no and click the Next button.

Check your eligibility

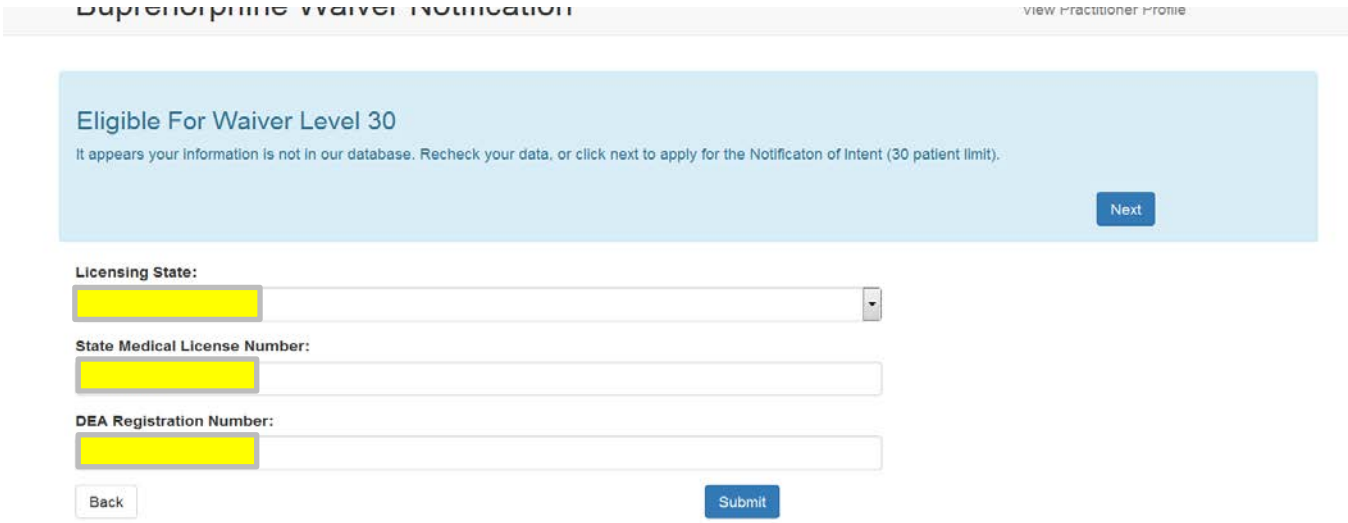
- Use the drop down menu to select your licensing state.
- Enter your medical license number, letter and numbers only. No spaces or dashes.
- Enter your DEA number, letter and numbers only.
- Click the Submit button.



PCSS Providers Clinical Support System

Eligible?

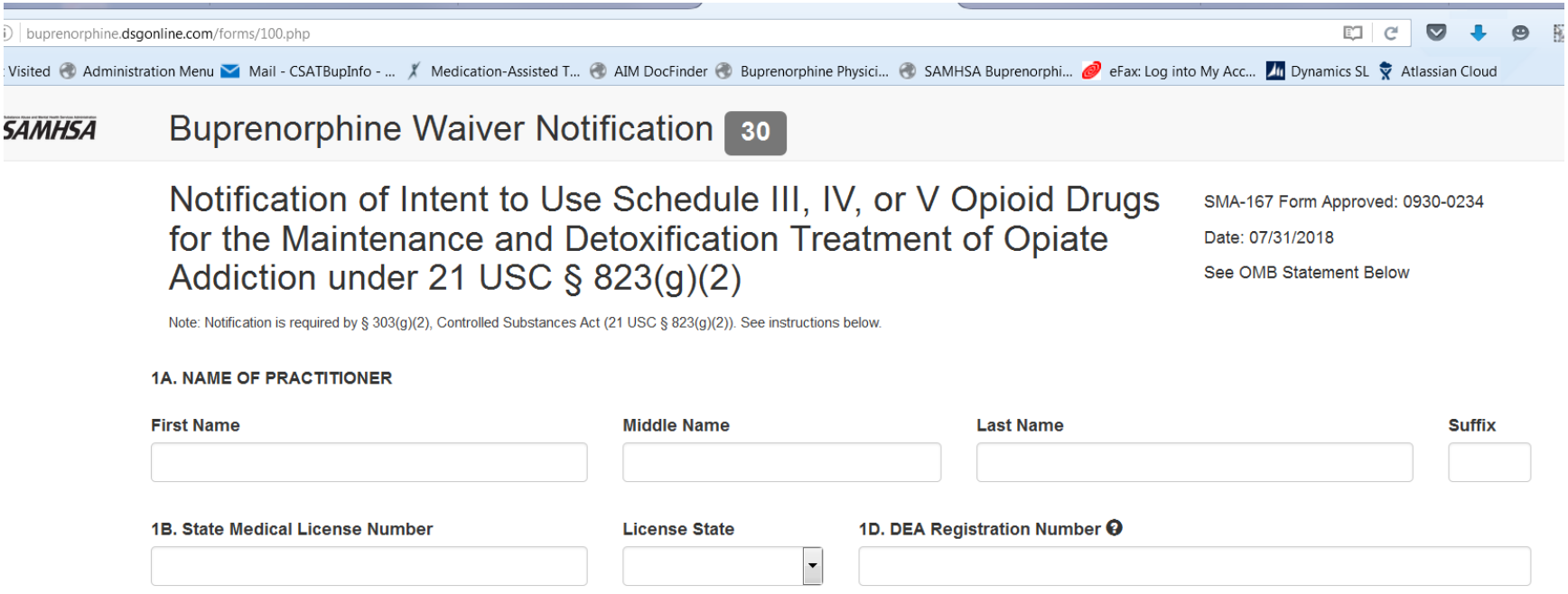
*The system will indicate the number of patients you are eligible to submit a Notification for. Click the Next button.



*The state, medical license and DEA number will be pre-populated.

Complete Notification Form

1A. Enter your name and suffix. (M.D. or D.O.)
1B. Medical license number will be pre-populated
1C. License state will be pre-populated
1D. DEA number will be pre-populated

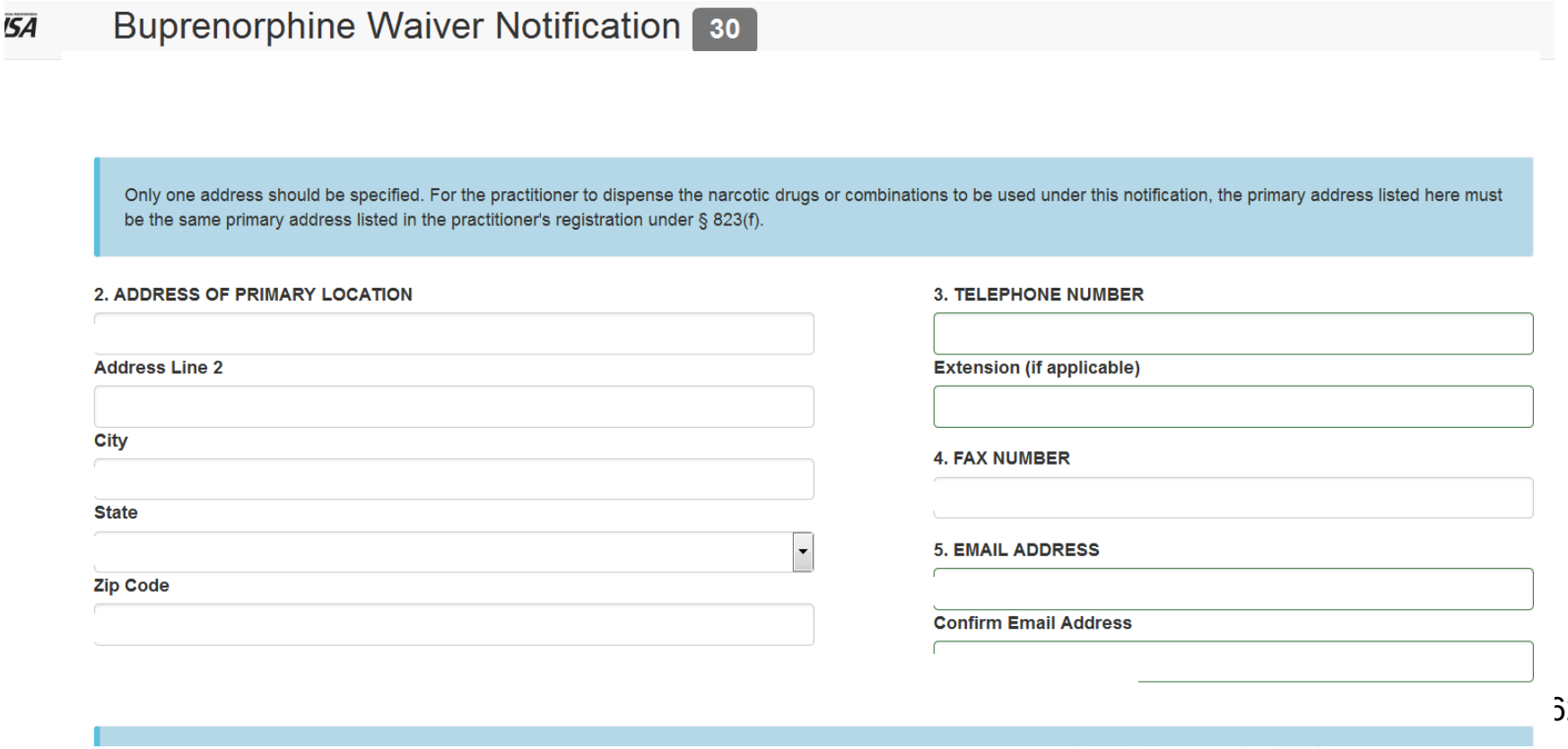


2. Address – if you are planning to store buprenorphine on site you will need to provide the address you are listed under with DEA. Otherwise you may provide an address in your licensing state. Do not enter a P.O. Box as your street address.

3. Enter phone number

4. Enter fax number

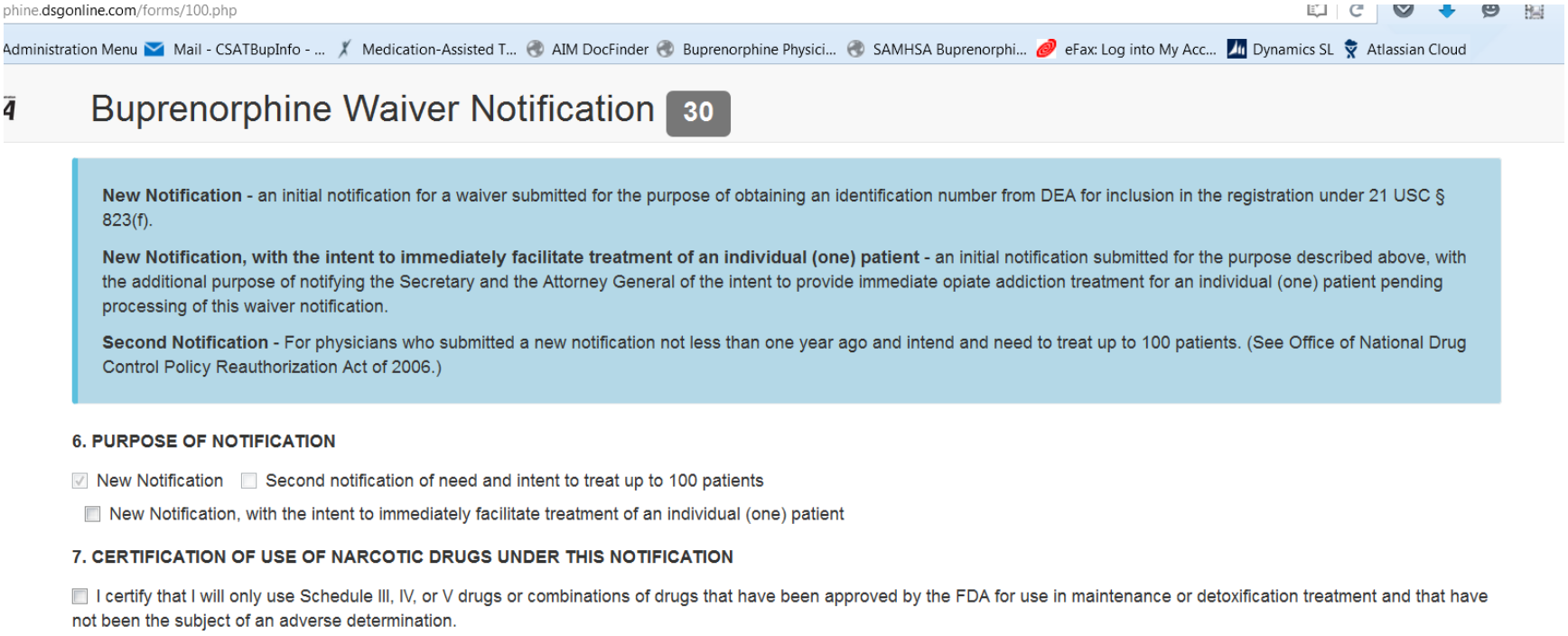
5. Enter email address, twice. Please provide an email address the regularly access. All correspondence form SAMHSA will be via email.



6. Purpose of Notification

the New box will be pre-checked

7. Check box, that you will only use approved Schedule III, IV, & V medications



8. Certification of Qualifying Criteria

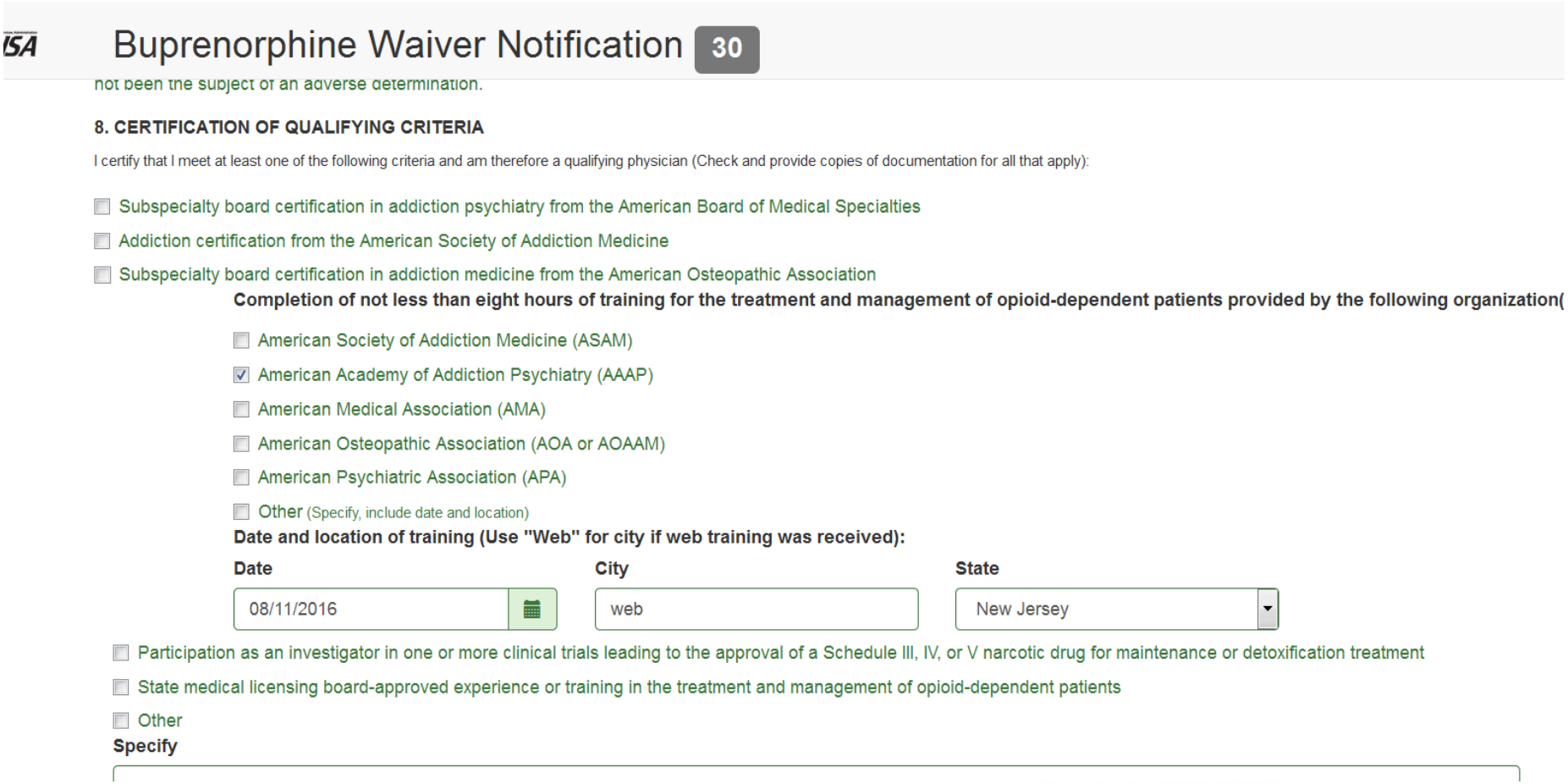
Check the appropriate box if you have a sub-specialty in Addiction medicine or psychiatry.

Check the appropriate box for the 8 hour training course you completed.

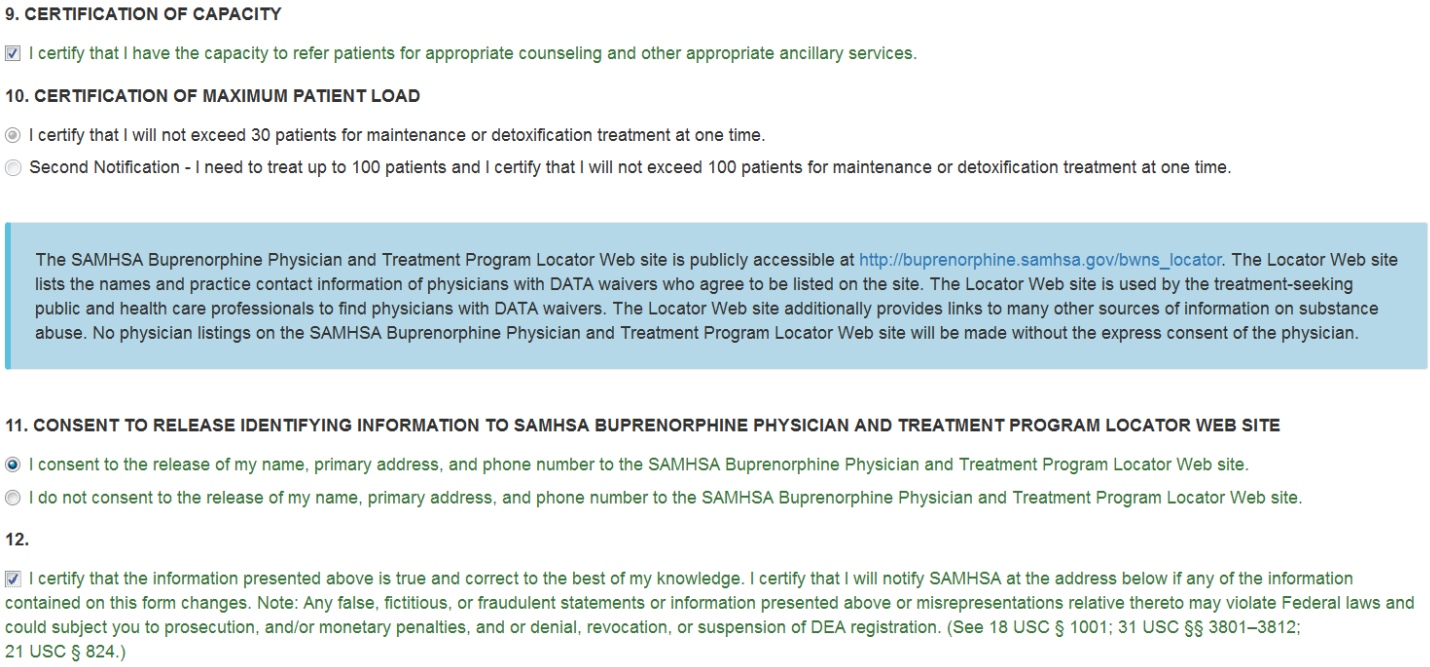
Enter the date the training was completed.

Enter the city where the training was completed. If you have complete an on-line course type “web” for your city

The state will be pre-populated but you may change it if it does not correspond with where you complete on site training.



9. Certification of Capacity Check box –must certify that you will refer patients for counseling.
10. Certification of Maximum Patient Load –button is pre-populated
11. Consent to Release Contact Information –click the “consent” or “do not consent” button
12. Check the box which states that you have not knowingly given false information.



9. CERTIFICATION OF CAPACITY

☑ I certify that I have the capacity to refer patients for appropriate counseling and other appropriate ancillary services.

10. CERTIFICATION OF MAXIMUM PATIENT LOAD

◉ I certify that I will not exceed 30 patients for maintenance or detoxification treatment at one time.

○ Second Notification - I need to treat up to 100 patients and I certify that I will not exceed 100 patients for maintenance or detoxification treatment at one time.

The SAMHSA Buprenorphine Physician and Treatment Program Locator Web site is publicly accessible at http://buprenorphine.samhsa.gov/bwns_locator. The Locator Web site lists the names and practice contact information of physicians with DATA waivers who agree to be listed on the site. The Locator Web site is used by the treatment-seeking public and health care professionals to find physicians with DATA waivers. The Locator Web site additionally provides links to many other sources of information on substance abuse. No physician listings on the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site will be made without the express consent of the physician.

11. CONSENT TO RELEASE IDENTIFYING INFORMATION TO SAMHSA BUPRENORPHINE PHYSICIAN AND TREATMENT PROGRAM LOCATOR WEB SITE

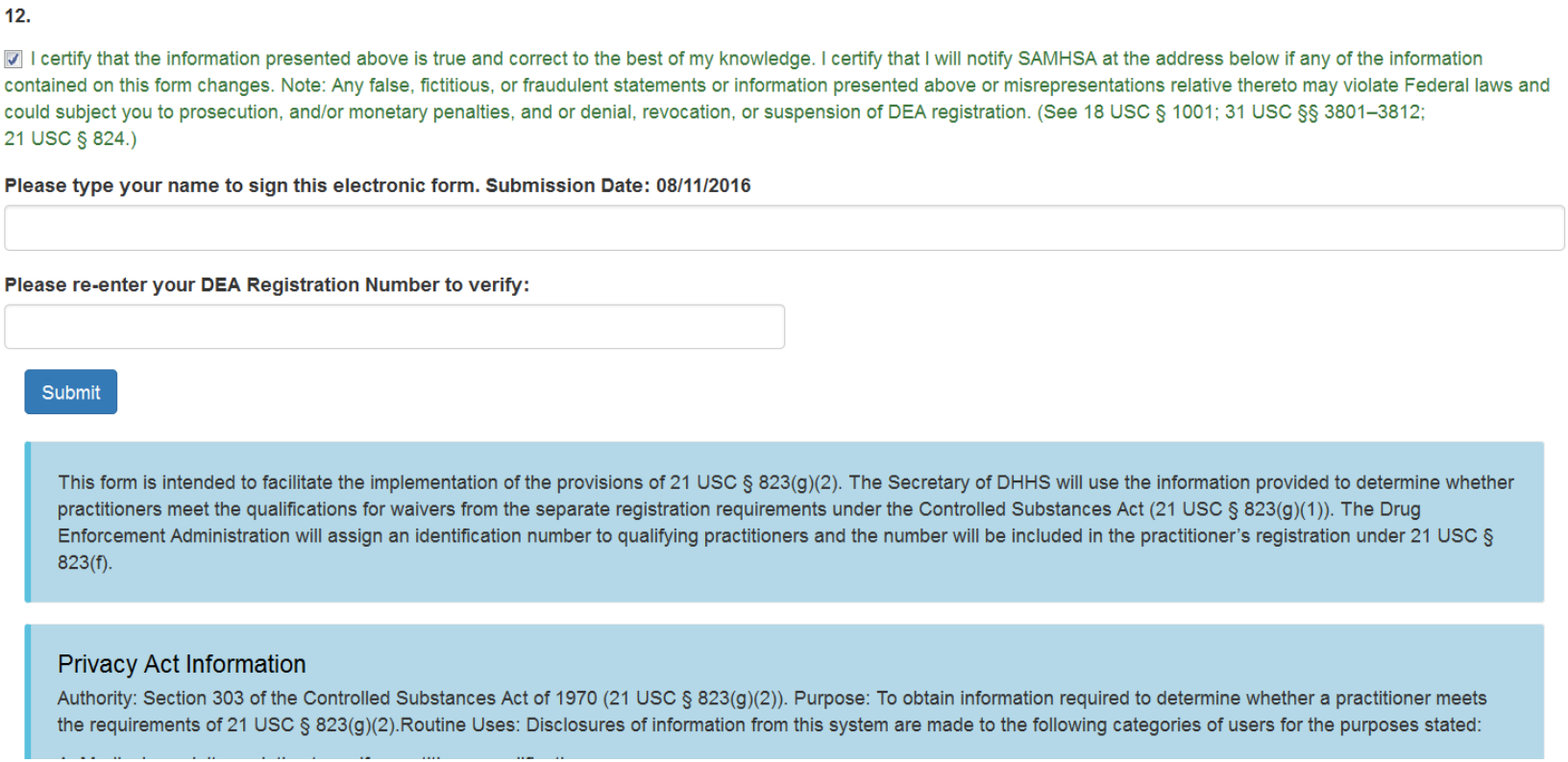
◉ I consent to the release of my name, primary address, and phone number to the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site.

○ I do not consent to the release of my name, primary address, and phone number to the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site.

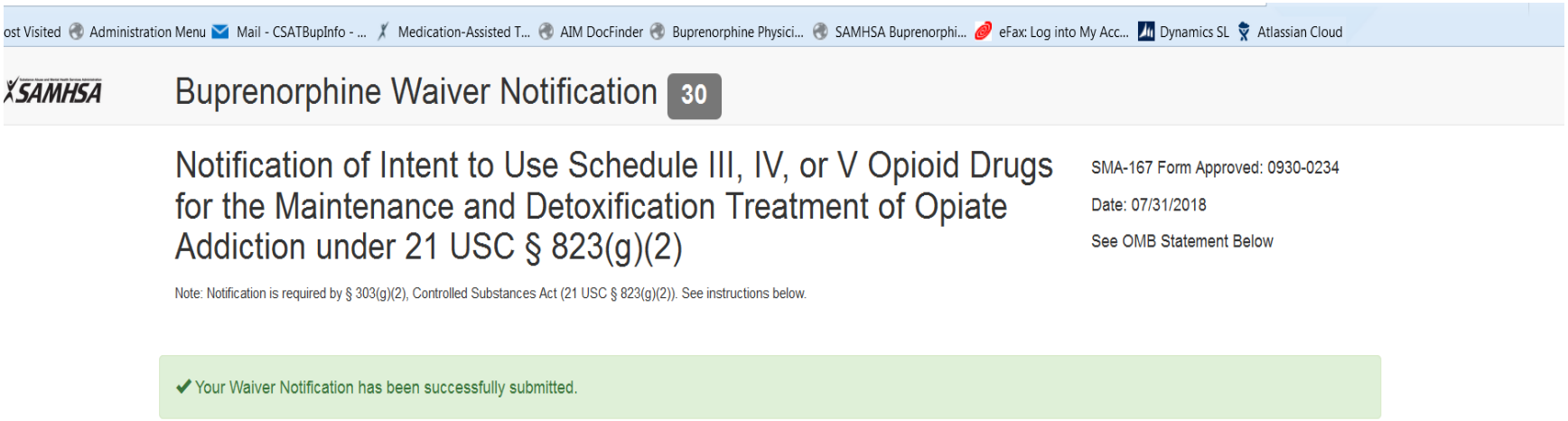
12.

☑ I certify that the information presented above is true and correct to the best of my knowledge. I certify that I will notify SAMHSA at the address below if any of the information contained on this form changes. Note: Any false, fictitious, or fraudulent statements or information presented above or misrepresentations relative thereto may violate Federal laws and could subject you to prosecution, and/or monetary penalties, and or denial, revocation, or suspension of DEA registration. (See 18 USC § 1001; 31 USC §§ 3801–3812; 21 USC § 824.)

Type your name in the box as your signature.
Type in your DEA number matching the one you entered initially.
Click the Submit button.



When the Notification is submitted successfully you will receive a confirmation.
If it has not, an error message will indicate what needs to be correct .



Overview of Clinical Tools

www.pcssnow.org

- For More Information and FREE training and educational resources on Medication Assisted Treatment (MAT) visit www.pcssnow.org.

- PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with the: Addiction Technology Transfer Center (ATTC); American Academy of Family Physicians (AAFP); American Academy of Neurology (AAN); American Academy of Pain Medicine (AAPM); American Academy of Pediatrics (AAP); American College of Emergency Physicians (ACEP); American College of Physicians (ACP); American Dental Association (ADA); American Medical Association (AMA); American Osteopathic Academy of Addiction Medicine (AOAAM); American Psychiatric Association (APA); American Psychiatric Nurses Association (APNA); American Society of Addiction Medicine (ASAM); American Society for Pain Management Nursing (ASPMN); Association for Medical Education and Research in Substance Abuse (AMERSA); International Nurses Society on Addictions (IntNSA); National Association of Community Health Centers (NACHC); National Association of Drug Court Professionals (NADCP), and the Southeast Consortium for Substance Abuse Training (SECSAT).

- PCSS-MAT's mission is to provide free, evidence-based resources to train clinicians and the public about the effectiveness of medications used for treating opioid addiction, including buprenorphine, naltrexone and methadone, in order to more effectively address this public health crisis.

PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction
- PCSS Mentors are a national network of providers with expertise in **addictions, pain, evidence-based treatment including medication-assisted treatment**
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee
- No cost

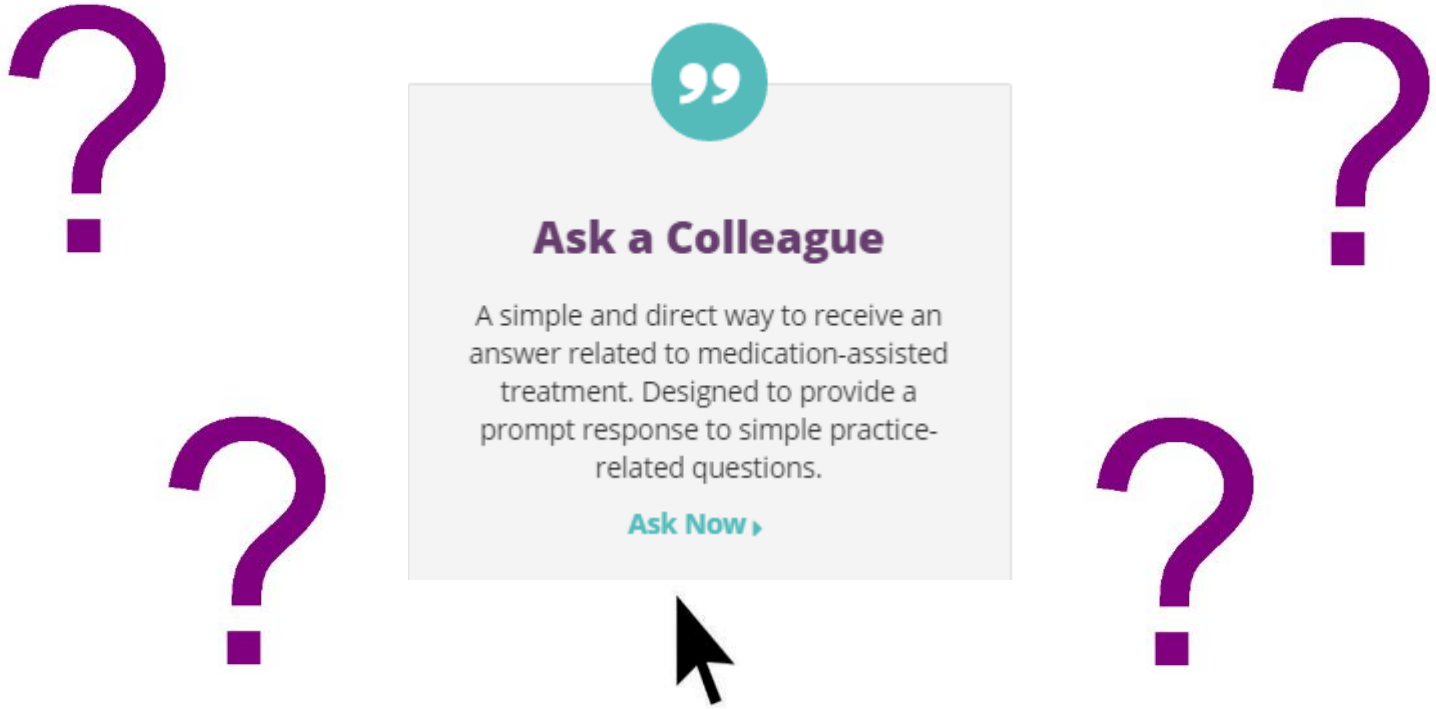
For more information visit:

pcssNOW.org/clinical-coaching

PCSS Providers Clinical Support System

PCSS Discussion Forum

Have a clinical question?



http://pcss.invisionzone.com/register

PCSS Providers Clinical Support System

Providers Clinical Support System

PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

American Academy of Family Physicians	American Psychiatric Association
American Academy of Neurology	American Society of Addiction Medicine
Addiction Technology Transfer Center	American Society of Pain Management Nursing
American Academy of Pain Medicine	Association for Medical Education and Research in Substance Abuse
American Academy of Pediatrics	International Nurses Society on Addictions
American College of Emergency Physicians	American Psychiatric Nurses Association
American College of Physicians	National Association of Community Health Centers
American Dental Association	National Association of Drug Court Professionals
American Medical Association	Southeastern Consortium for Substance Abuse Training
American Osteopathic Academy of Addiction Medicine	