Buprenorphine
A Slice of the Pie

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Disclosures

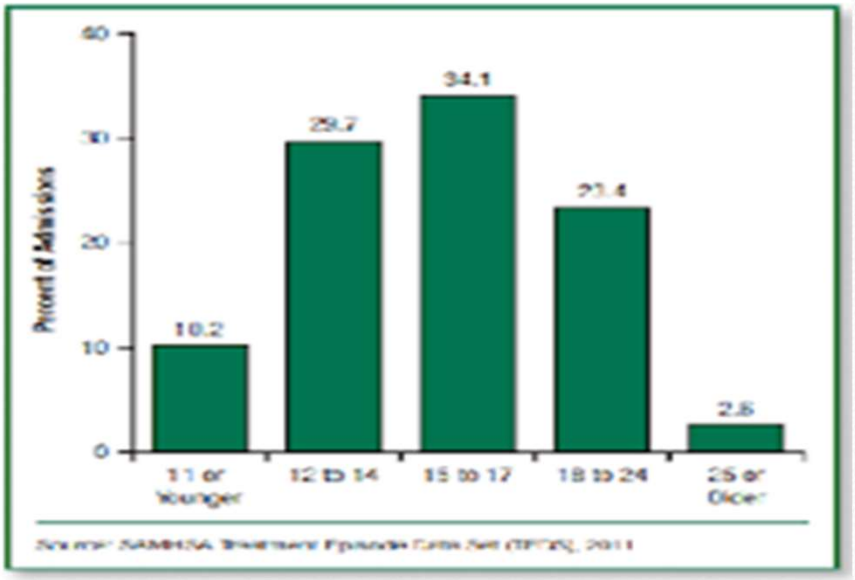
- None

The scope of the problem[1]

- It has been estimated that about 23% of people exposed to opioids develop OUD, a risk of transition to addiction second only to tobacco (32%) and higher than that for cocaine (17%), alcohol (15%), or cannabis (9%).
- Risk factors for OUD include genetic as well as psychosocial factors, including history of sexual and/or physical abuse.

- In a study of more than 1.2 million opioid prescriptions written for 16- to 18-year-olds, individuals with pre-existing psychiatric problems, including anxiety, mood, neurodevelopmental, sleep, and nonopioid substance use disorders, were more likely to be prescribed long-term (e.g., >90 days) opioids (e.g., for pain).

Figure 1. Age of Substance Use Initiation among Treatment Admissions Aged 18 to 30: 2011



Ref 5

- "The nation's growing opioid use disorder epidemic disproportionately impacts rural areas, where physicians who can prescribe buprenorphine are scarcest. Among physicians approved to prescribe buprenorphine, family physicians (FPs) are the most likely to work in rural areas."

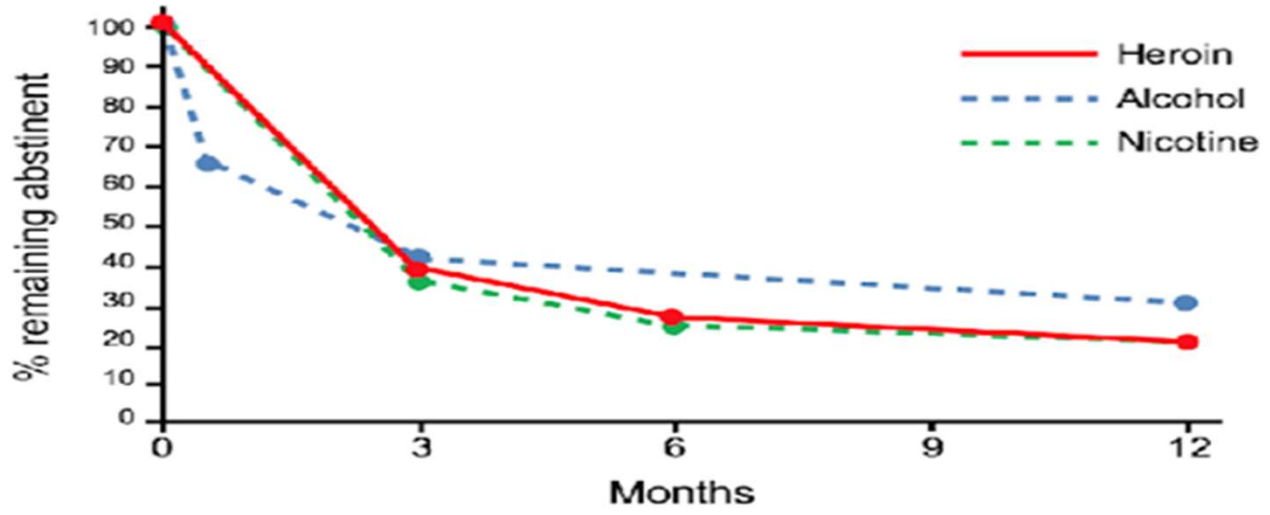
ROBERT GRAHAM CENTER

Policy Studies in Family Medicine and Primary Care

Treatment[1]

- Available treatments for OUD consist of pharmacotherapy and behavioral therapies.
- The gold standard is medication assisted treatment (MAT), wherein pharmacotherapy is combined with some form of counseling or behavioral therapy.

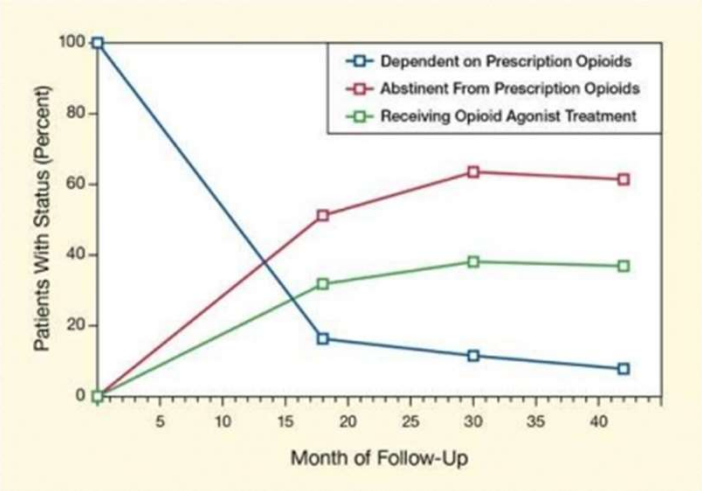
Abstinence Without MAT



Hunt et al., 1971

PCSS Providers Clinical Support System

Ref 2



NIDANotes

"…whereas 49.2 percent of POATS participants who received 12 weeks of Bp/Nx were abstinent at the end of this treatment period, the abstinence rate rapidly collapsed, to 8.6 percent, within 2 months after patients were tapered off the medication. The 18-month follow-up found many patients currently or recently re-engaged in opioid agonist therapy, and the abstinence rate rebounded to 51.2 percent."

Prescription Opioid Addiction Treatment Study (POATS)[7]

Good for Patients[3, 4]

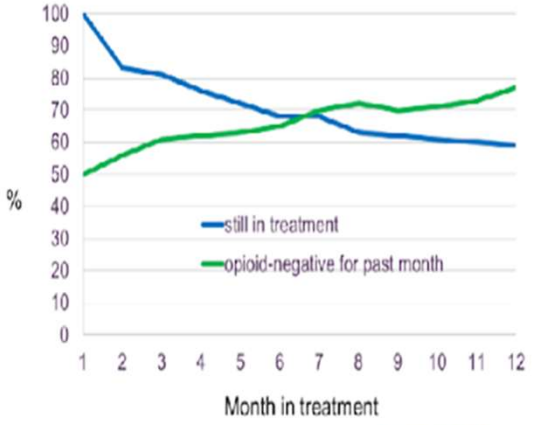
- An opportunity for abstinence from illicit opiates and other substances.
- Harm reduction in relationships, employment, and legal consequences.
- Decreased health needs (as noted in decreased utilization of ERs and inpatient needs)*
- Better sense of quality of life
- More treatment flexibility and safety than some other MATs.

*MAT in the Emergency Department

- https://www.acep.org/patient-care/bupe/
  - Amazing website with loads of direction and instruction from the American College of Emergency Physicians
- **An X-waiver to your DEA registration is NOT required to order/administer a dose of buprenorphine in the hospital, or in the ED.**
- **A patient may come to the ED 3 days consecutively to be treated with buprenorphine in the ED, for opioid withdrawal or for the initiation of MAT ("the 3 day rule"** = Title 21, Code of Federal Regulations, Part 1306.07(b)**).**
- **An X-waiver IS, however, required in order to WRITE A PRESCRIPTON (to be filled at a pharmacy) for buprenorphine for addiction treatment, withdrawal, or to "detox."**
- **Most hospitals are probably NOT licensed to dispense buprenorphine (patients should NOT be sent home with take home doses of buprenorphine, unless the ED provider has an X-waiver, and approved by the hospital).**
- **Any practitioner with a DEA registration can prescribe buprenorphine** (butrans) **for pain management.**

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

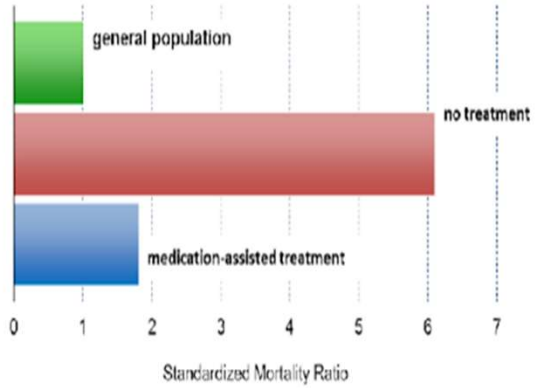


Kakko et al, 2003
Soyka et al, 2009

PCSS

Benefits of MAT: Decreased Mortality

Death rates:



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

PCSS

Ref 2

Good for Providers

- Short term and long term sense of satisfaction.
- Patients get better
- Less feeling of being manipulated or helpless in the context of addiction
- Ability to focus on a large issue that has negative impact on patient's global existence and enable improved outcomes for that individual and your community
- Patients say "Thank you"

Good for Community (Reduced Crime)[6]

HIGHLIGHTS

- During 2007-09, an estimated 58% of state prisoners and 63% of sentenced jail inmates met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for drug dependence or abuse.
- Among prisoners and jail inmates, prevalence estimates for those who met the criteria for dependence were two to three times higher than for abuse.
- The percentage of inmates who met the DSM-IV criteria was higher for those held for property offenses than those held for violent or other public order offenses.
- Lifetime drug use among the incarcerated populations was unchanged from 2002 to 2009.
- During 2007-09, prisoners (77%) and jail inmates (78%) reported having ever used marijuana/hashish, more than any other drug.
- During 2007-09, more females in prison (17%) or jail (60%) used drugs in the month before the current offense than males in prison (38%) or jail (54%).
- More non-Hispanic white than non-Hispanic black prisoners regularly used cocaine/crack, heroin/opiates, or meth/amphetamines.
- Among those who met the criteria for drug dependence or abuse, 29% of prisoners and 22% of jail inmates participated in a drug treatment program since admission.

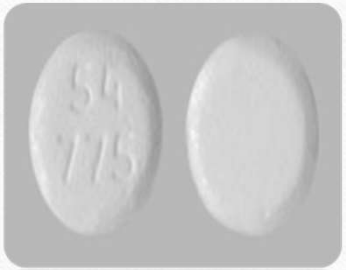
Bureau of Justice Statistics

BJS

FORMULATIONS

Bup+Nal
Suboxone
Zubsolv
Bunavail

Bup
Subutex



Bup+Nal

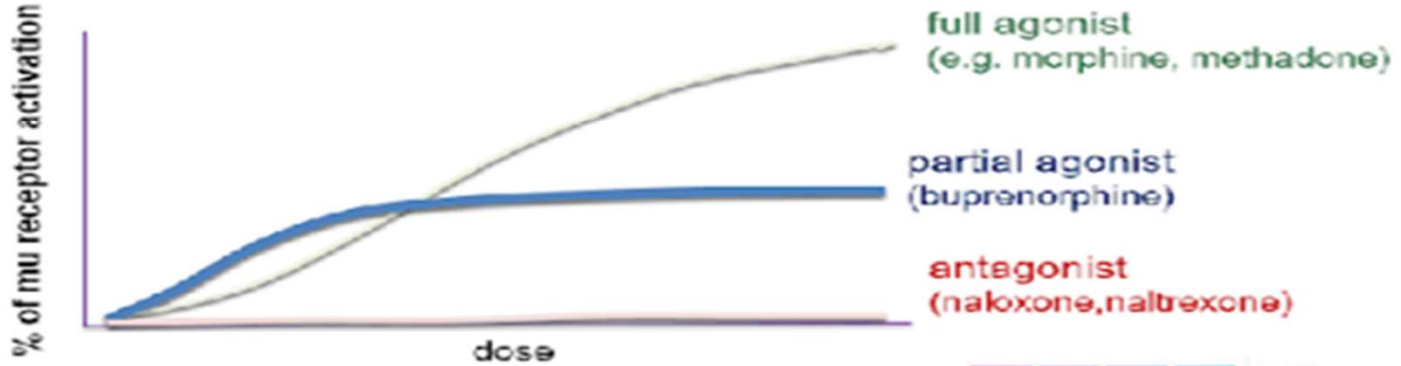
Depot Bup
Sublocade
Brixadi

Mechanisms of action[1]

- Buprenorphine is a partial MOR agonist and a weak kappa-opioid receptor (KOR) antagonist.
- In clinically used doses, buprenorphine acts like a typical MOR agonist, such as morphine or methadone.
- At higher doses, however, buprenorphine's MOR agonist effects reach a plateau.
- Also at higher doses, its KOR antagonist effects begin to emerge.
- This ceiling effect of buprenorphine reduces its abuse potential and risk of overdose even at high intravenous doses.
- Its slow dissociation from opioid receptors allows flexible dosing that can range from several times a day to three times per week.

Opioid Partial Agonist Therapy

- The partial agonist **buprenorphine** prevents withdrawal and maintains a steady level of opioid activity like methadone, but like naltrexone also blocks the effects of other opioids
  - Unlike full agonists, buprenorphine is **schedule III** and therefore eligible under DATA 2000 to be prescribed in office-based treatment.
- Because of its partial agonism it is *unlikely* to lead to fatal respiratory suppression even at at high doses



SAMHSA, 2018
Orman & Keating, 2009

PCSS Providers Clinical Support System

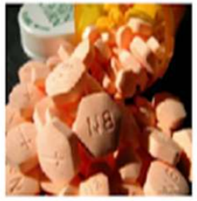
Ref 2

Pharm and Dosing[1]

- Following sublingual administration, peak levels of buprenorphine are reached within 30–60 minutes.
- The plasma elimination half-life of buprenorphine is 37 hours
- Because of its partial agonist actions at MOR, buprenorphine may precipitate withdrawal if initiation of treatment is not managed appropriately.
- The recommended starting dose is 2–4 mg of buprenorphine, which may be followed in 3–4 hours with an additional dose of up to 4 mg.
- On the second day, the dose of buprenorphine may be increased to 12–16 mg, and the stabilization dose, ranging from 8 to 24 mg/day, may be reached within the first week.

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

Ref 2

How Does Buprenorphine Work?

- High affinity for, and slow dissociation from the mu receptor which leads to:
  - Prevention of withdrawal symptoms
  - Decreased cravings
  - Decreased effects of other opioids
- 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

A little more pharm[1]

- Side effects include: dry mouth, nausea, vomiting, constipation, dizziness, sedation, headache, and excessive sweating.
- Buprenorphine is not associated with prolonged QT interval and has lower overdose risk than methadone.

Content	Route	Products	Available Doses	Equivalent Dose to 8mg Buprenorphine
With Naloxone	Sub lingual	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	
	Sub lingual	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 / 2.8mg 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	Sub lingual	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

Ref 2

Advantages of Buprenorphine in the Treatment of Opioid Use Disorder

1. Patient can participate fully in treatment activities and other activities of daily living easing their transition into the treatment environment
2. Limited potential for overdose
3. Minimal subjective effects (e.g., sedation) following a dose
4. Enhances retention in treatment

Advantages of Buprenorphine/Naloxone in the Treatment of Opioid Use Disorder

5. Reduces relapse rates
6. Prevents withdrawal
7. Blocks euphoric effects of opioids
8. Available for use in an office setting
9. Discourages IV use
10. Allows for take-home dosing

Disadvantages of Buprenorphine in the Treatment of Opioid Use Disorder

1. Greater medication cost
2. Patient remains physically dependent
3. Detectable on in specific urine toxicology screenings
4. Potential for diversion


Parenting Classes
Substance Use Counseling
Buprenorphine
Family Counseling
Counseling for Co-Occurring Diagnoses
Job Training/Skills Development

References

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2. PCSS MAT Waiver Training 8 Hour Course slide deck
3. **One year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial.** Kakko, Johan et al. The Lancet , Volume 361 , Issue 9358 , 662 – 668.
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1 Pharmacological and Behavioral Treatment of Opioid Use Disorder

Mehmet Sofuoglu, M.D., Ph.D., Elise E. DeVito, Ph.D., Kathleen M. Carroll, Ph.D.
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