Opioid Epidemic and Relevant Therapeutic Strategies

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Objectives

- Review opioid epidemic in the U.S. and AL
- Describe the natural history of opioid use disorder.
- Describe the comparative effectiveness of opioid agonist maintenance vs. taper treatment.
- State the indication and rationale for using buprenorphine/naloxone.
- Safe and effective prescribing of opioid medications in the treatment of addiction.

CASE

Mr. Smith

- 55 y/o male with depression seen for routine follow-up
- HTN, DM, hyperlipidemia
- History of heroin and cocaine addiction in his 20s
- During the session, he c/o uncontrolled depression with current meds and admitted to "borrow" opioid for "good" feelings for a while.
- Red flags; but unremarkable neuro exam; no personal history of malignancy

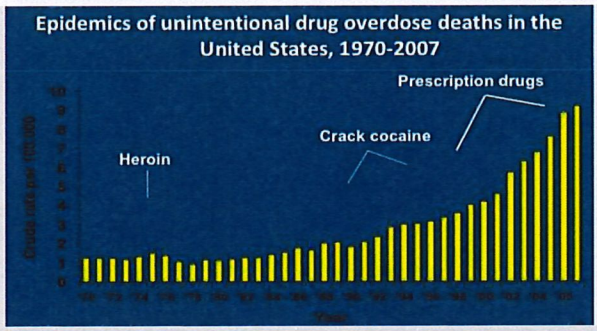
What do you do next? Choose one

a. Adjust his anti-depressants, and arrange follow-up in 1-2 months
b. Inform him that you do not prescribe opioids to patients with a history of addiction, and refer him to an addiction specialist.
c. Tell him you will like to order some test to confirm what he reported. If he meets the criteria for opioid use disorder, you will consider MAT
d. Perform a history and physical exam, consider whether additional workup is needed, and discuss his diverting behavior and discharge him from your clinic

Questions

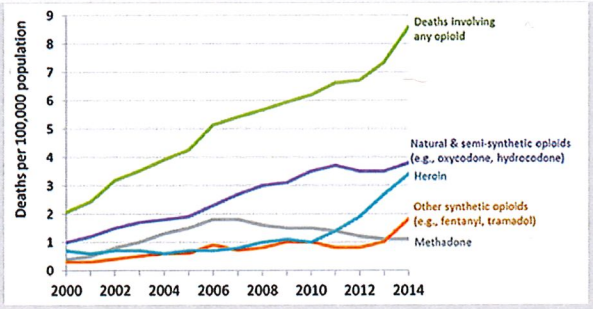
- How often do you meet patients like Mr. Smith in your practice?
- How many are aware of CDC new guidance released in March of 2016 in terms of opioid prescription ?
- How many are using buprenorphine/methadone to treat patients with opioids use disorder ?

Drug Epidemics from 1970-2006



Opioids are the 2nd most commonly abused drug in the U.S

Significant Opioid overdose death increases from 2000 to 2014 in the US

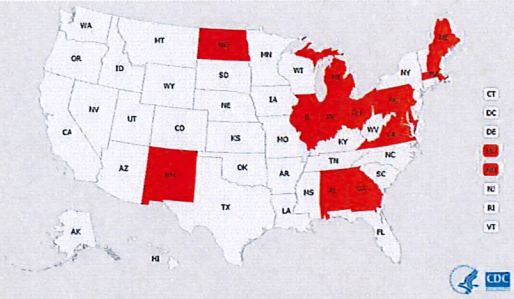


www.cdc.gov/drugoverdose

Thus **more** overdose deaths than heroin

Why are there so many people who overdosed on opioids?

Drug epidemic in Alabama



- The number of opioid prescription-related death in AL is 598 and 723 in 2013 and 2014, respectively.
- Outnumber heroin and cocaine overdoses
- Per the CDC, Alabama ranks third in nation for highest # of painkiller prescription rates per person in 2014.

What to do when a patient is sitting in front of you

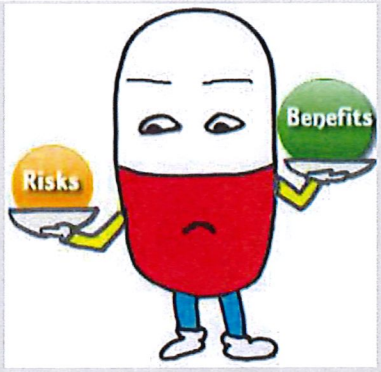


Image courtesy of: www.pilladvised.com

Benefits of Opioid Therapy

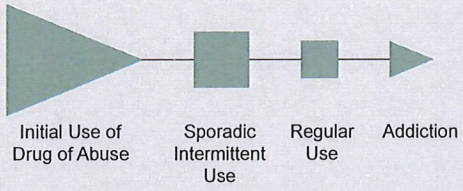
- **Preservation of mobility**
  - In older patients with osteoarthritis and intermittent use
  - In patients with progressive rheumatological or autoimmune disease
- **Palliation of severe intractable chronic pain**
  - Patients who have failed all other multi-modal therapies, including psychiatric therapies
  - Patients who would otherwise not be able to live at home, avoid hospitalization, ED visits

Slide courtesy of Jessica Merlin at UAB

Risks of Opioid Therapy

- ***To patients:***
  - Side effects:
  - **Addiction**: about 10%
  - Induced depression (duration > dose)
  - Overdose, death, ED visits (>700,000 in 2012)
  - Motor vehicle accidents, dose-dependent (OR=1.2-1.5)
- ***To family and friends:***
  - Misuse of opioid (12th graders: 10% 2010 → 6% 2014)
  - Accidental overdose, death (2010, 2x heroin)
  - **Addiction**
- ***To culture***
  - Inability or unwillingness to manage pain in non-medical ways
  - Once a medical pain treatment is available, it ceases to be noble to endure pain

What is Addiction?

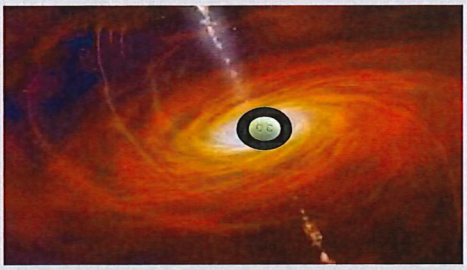


A **primary** chronic neurobiological **disease** characterized by impaired control over drug use, compulsive use, continued use despite harm, craving and other negative consequences (APS, ASAM, 2001)

Opioid Use Disorder: DSM-V

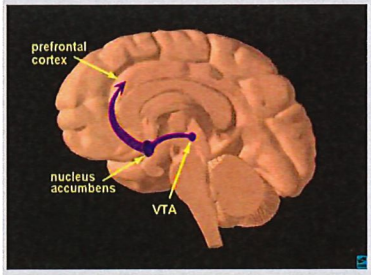
1. Opioids are often taken in longer amounts or over a longer period than was intended.
2. There is a **persistent desire** or **unsuccessful efforts to cut down** or control opioid use.
3. **A great deal of time is spent** in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. **Craving**, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a **failure** to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. **Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.**

What are the factors contributing to develop opioid use disorder?



- **Genetic: 25-60% (*Kreek et al., 2000; 2005)***
- **Neurobiological: drugs-induced "high" feelings, et al.**
- **Environmental**
- **Increased Availability**

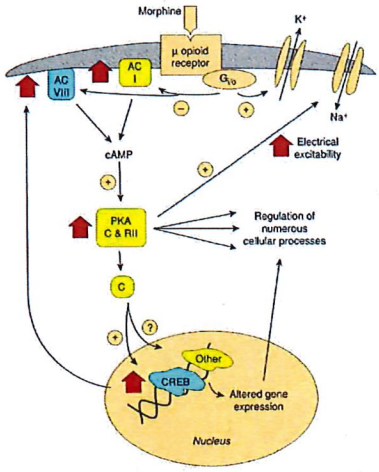
Neural Circuitry of Reward



- Present in all animals
- Produces pleasure for behaviors needed for survival:
  - Eating
  - Drinking
  - Sex
  - Nurturing

Primary sites of actions of drugs of abuse with respect to their reward or reinforcing effects have been identified as specific brain regions, rich in dopamine nerve terminals or cell bodies, the mesolimbic and mesocortical dopamine systems especially the nucleus accumbens, as well as the amygdala, the anterior cingulate and the insula, with related actions in the nigrostriatal dopaminergic regions. Each of these areas also has abundant receptors and peptides of the endogenous opioid system.

μ receptor mediates opioid effects

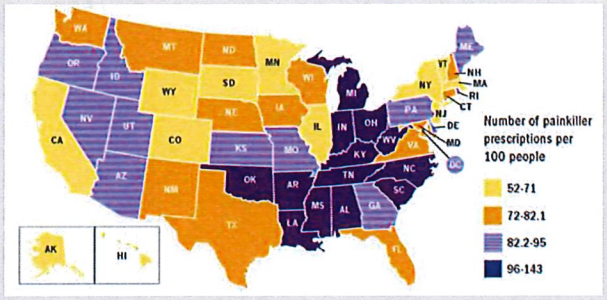


μ1 and μ2 receptors are involved in

- Euphoria
- physical dep
- w/d and tolerance
- inhibitory pain pathways or pain-producing neurotransmitters

Nestler et al. Science, 1997

Painkiller Prescription Rate per 100 people in the U.S



AL is one of the **5** states that have the highest number of prescription painkillers per 100 people: 128-143, in 2012. The other 4 are OK, WV, TN and KY.

National Prescription Audit (NPA™), 2012.

What happened in 2012

46
Each day, 46 people die from an overdose of prescription painkillers in the US.

259 M
Health care providers wrote 259 million prescriptions for painkillers in 2012, enough for every American adult to have a bottle of pills in that year.

10
10 of highest prescribing states for painkillers are in the South.

What do these numbers tell us?

CDC, July, 2014

- Is there on overall change in the amount of pain that Americans report?—**No**
- Southern states had the most prescriptions per person for painkillers, especially ***Alabama***, Tennessee, and West Virginia.
- Health care providers in different parts of the country don't agree on when to use prescription painkillers and how much to prescribe.
- Some of the increased demand for prescription painkillers is from people who use them **non-medically** (using drugs without a prescription or just for the high they cause), sell them, or get them from multiple prescribers at the same time.
- Many states report problems with for-profit, high-volume pain clinics (so-called "**pill mills**") that prescribe large quantities of painkillers to people who don't need them medically.

⇩
↑ Painkiller Prescription
⇩
↑ Availability
⇩
↑ Prescription Overdose

CDC, July, 2014; Chang H, et al. Amer J of Emergency Med 2014; 32(5): 421-31.

Responding to the Opioid Epidemic

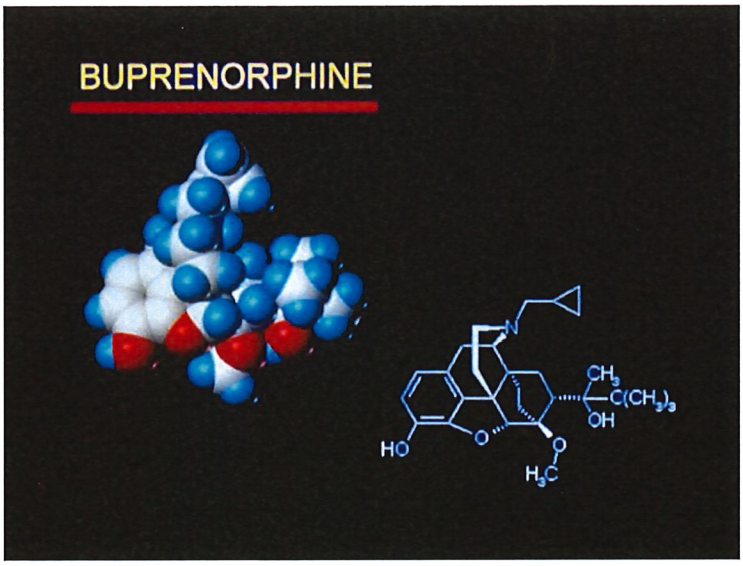
Prevent People from Starting Opioid : reduce prescription opioid painkiller abuse

Reduce Opioid Addiction : Ensure the access to Medication-Assisted Treatment (**MAT**)

Reverse Opioid Overdose : Use naloxone, a life-saving drug that can reverse the effects of an opioid overdose when administered in time.

Medication Assisted Treatment (MAT) for Opioid Use Disorder

- *Opioid agonist treatment*
  Methadone
  Buprenorphine
- *Opioid antagonist treatment*
  Naltrexone



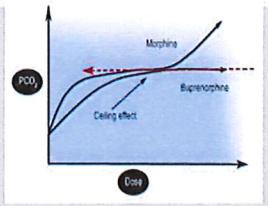
History of Buprenorphine as MAT

- Created 1980's in small doses for analgesia
- In the 2000's higher doses were used for treating opiate addiction
  Drug Addiction Treatment Act of 2000 (DATA 2000)
- In 2002, was approved for clinical use by the FDA
- Expands treatment options to include both the general health care system and opioid treatment programs.
  - Expands number of available treatment slots
  - Allows opioid treatment in office settings
  - Sets physician qualifications for prescribing the medication

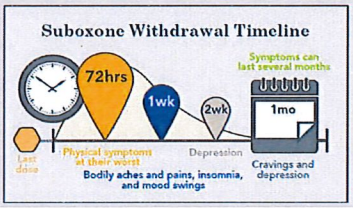
Buprenorphine Properties

- Partial-μ receptor agonist: very high affinity to the receptors
  - Less reinforcing than a full agonist → not enough to cause intense euphoria less abuse potential and physical dependence
  - When other opioids are on board, could precipitate withdrawal
  - but can be used for opiate detoxication as well due to less severe/shorter duration of withdrawal symptoms
- Half-life 24-48 hrs, so long duration of action (24-72hr) and dissociate from receptors at a slow rate → so enable daily or 3/wk dosing
- Side effects: respiratory suppression (can not be reversed by naloxone), nausea, dizziness, dysphoria
- Strong safety profile
  - Little respiratory depression
  - Little overdose potential

➢ **Ceiling** effect: typical dose 12-16mg, daily



➢ **Withdrawal**



Buprenorphine Formulations and Routes

The FDA has approved the following buprenorphine products:

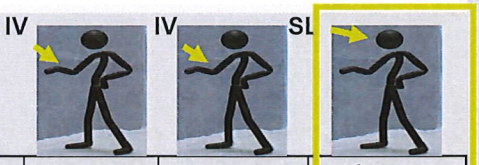
➢ **Bunavail** (buprenorphine and naloxone) buccal film

➢ **Suboxone** (buprenorphine and naloxone) film

➢ **Zubslov** (buprenorphine and naloxone) sublingual tablets

➢ **Subutex** (buprenorphine) film-really one indication--**Pregnancy**

Suboxone (buprenorphine + naloxone) vs. Subutex (buprenorphine only)



	Incorrect	Incorrect	Correct
Route	IV (diversion)	IV (diversion)	Sublingual
Buprenorphine Absorbed?	YES	YES	YES
Naloxone Absorbed?	no	YES!!!	NO !
Outcome	Euphoria (High)	☹ (withdrawal)	☺!
	↑ Subutex	↑ Suboxone	

Gordon, 2006

Pharmacokinetics for Buprenorphine

- Taking orally would undergo extensive first-pass metabolism in the small intestine and liver, so used sublingually
- The absorption of buprenorphine is followed by a rapid distribution phase
- Peak plasma concentration is achieved 90 mins after SL administration
- CYP3A4 is responsible for the metabolism of buprenorphine
- Elimination o buprenorphine is 70% in the feces and the rest excreted in the urine.

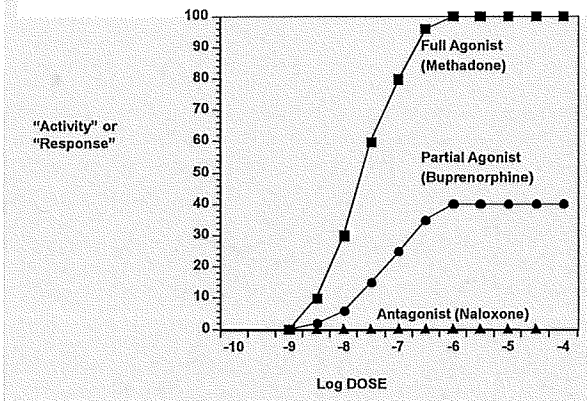
Drug-drug Interaction with Buprenorphine

CYP3A4		Potential Results
Inhibitor	▪ Azole antifungal agents ▪ Macrolide Abx ▪ HIV protease inhibitors	May require dose-reduction of one of both agents
Inducer	▪ Phenobarbital ▪ Carbamazepine ▪ Phenytoin ▪ Rifampicin	Not studied, however, it is recommended that patients with buprenorphine be monitored for signs of w/d if co-administered

Comments: Drug-drug interactions are not supposed to decrease or increase plasma levels of buprenorphine significantly.

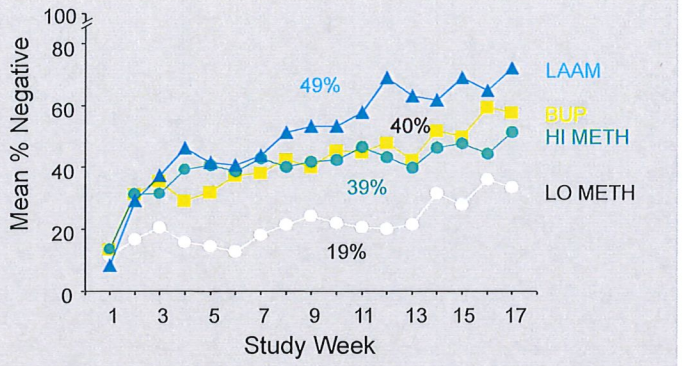
Buprenorphine vs. Methadone

Location	Methadone clinic	Office-based treatment
Criteria	Withdrawal/12 months	DSM-V, no time criteria
Efficacy	equal	equal
Side effects	Similar, but more sedative	similar
Drug-drug interaction	more	less
Agonist	Full	Partial
Ceiling effect	No	Yes
Convenience	less	more
Cost	less	more
Age	>18 yo	>16 yo
Take home amount	Very limited	30 days
Services	requested	available



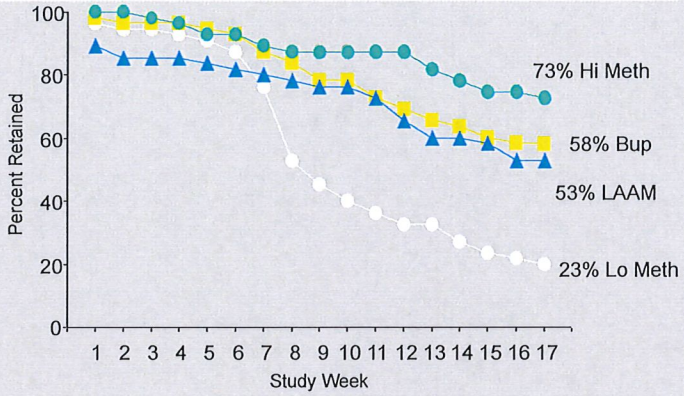
Gordon, 2006

Buprenorphine: "Clean" Urine



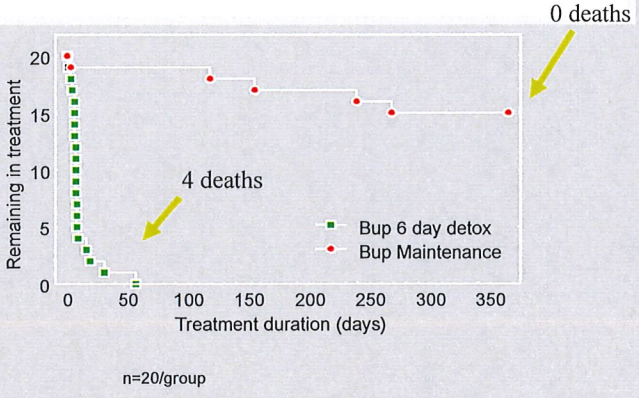
Johnson R, NEJM 2000

Treatment Retention



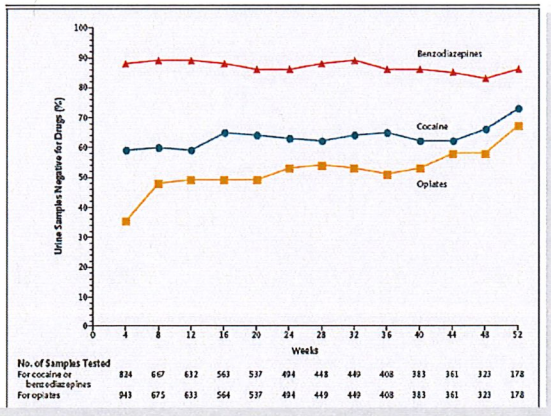
Johnson et al. (2000)

Buprenorphine: Retention and Mortality



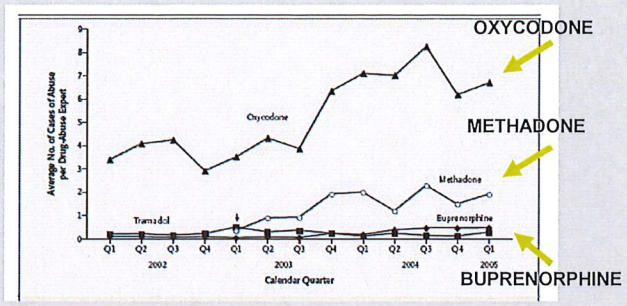
Kakko J, Lancet 2003

Buprenorphine: Reduce other drug use



Fudala, NEJM 2003

Buprenorphine is not diverted



Cicero, NEJM 2005

Summary: Beneficial Effects of Buprenorphine

- Significant enhancement in treatment retention and in the quality of participation
- Greater safety
- Lower diversion risk
- Partial agonist effects make it mildly reinforcing, encouraging medication compliance
- Available evidence in patients maintained on buprenorphine indicates no clinically significant disruption in cognitive and psychomotor performance
- Mainstreaming of opioid dependence treatment with office-based practice

Dagtekin O, et al. Anesth Analg 2007;105:1442-8

Who are ideal candidates for buprenorphine treatment?

- Have been objectively diagnosed with an opioid use disorder using DSM-V
- Are willing to follow safety precautions for the treatment
- Have been cleared of any health conflicts with using buprenorphine, including ??
- Have reviewed other treatment options before agreeing to buprenorphine treatment
- Agree to combine with counseling and behavioral therapies

So, how about Mr. Smith?

What can health care providers do?

- **Identify** ideal candidates for buprenorphine treatment: chart review, clinical assessment, collateral information
- Interdisciplinary **communication**
- **Screen** for other substance use and mental health problems
- **Discuss** with patients the risks and benefits of treatment
- **Make** patient aware of expectations and risks associated with treatment as well as treatment is contingent upon follow-up, compliance, participation in group therapy
- **Avoid** combinations of prescription painkillers and sedatives
- Compliance **monitoring**:
  - Patient safety agreement
  - Frequent follow-up like bi-weekly or monthly
  - Random UDS
  - Medication counts
  - Periodic review of PDMP
- Be alert to **concerning** behaviors that can arise

Patient Treatment Agreements

- NOT contracts
- Informed consent; you and your patient's responsibilities
  - One prescriber, one pharmacy
  - Take as prescribed, no changes on one's own
  - Urine drug testing
  - How medicines are refilled, replacement rxs
  - Conditions for stopping opioids

Urine Drug Testing

- Always ask your patients' current medicaine list including OTC
- Useful for checking for adherence to rx'd drugs and for presence of substances not rx'd
- "A tool not an oracle": lots of pitfalls
- Send screening immunoassay; discuss unexpected results; if still unclear, send confirmatory test (GCMS/LCMS)
- Know your toxicologist
- Be mindful of cost

Starrels JL, Ann Int Med, 2010.

PDMP

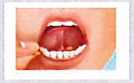
- State-by-state, lots of variability
- Tells you three things that predict OD:
  - Dose
  - multiple rx's
  - opioid and benzo co-rx

Prescription Drug Monitoring Program
PDMP
ALABAMA DEPARTMENT OF PUBLIC HEALTH

How to Start and Taper off Buprenorphine

Start

SL: Dissolve under tongue
Take about 5 min to dissolve
Won't be active if swallowed



Taper off

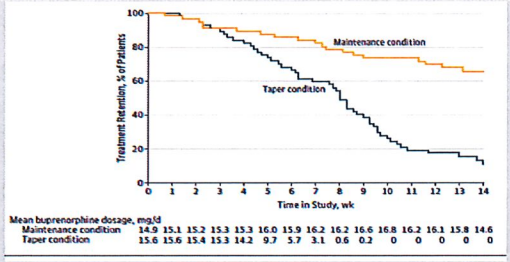
- Reduce by 2mg every other weeks with final reductions being around 400µg/d
- Patients report being able to reduce doses more quickly than methadone

Recovery is a multi-disciplinary work

- Demonstrate improvement in analgesia, physical function, and quality of life
- Absence of significant adverse effects and maladaptive behaviors
- Address the physical, emotional and cognitive management of chronic pain, in conjunction with medical management
- Address the relationship between chronic pain and depression, anger and other emotional states
- Manage and educate on addictive behaviors and addictive thinking, as well as relapse prevention

"Doc, I feel normal"

How long should they be treated?



- Few studies provide sustained follow up after completing buprenorphine taper in terms of long-term abstinence.
- Only 34% of studies reported urinalysis-testing outcomes from follow-up assessments, and the median opioid abstinence rate was 23%.
- Indefinite?? My understanding is that Tx could be continued only after confirming clinically significant improvement in opioid/other drugs abuse and function w/o significant risks/harm.

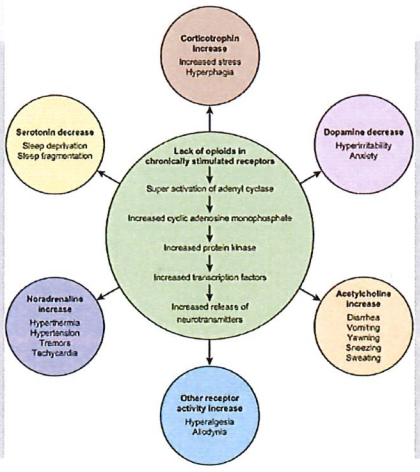
Weiss RD, Arch Gen Psyc, 2011.

MAT in Pregnancy

Parameter	Methadone	Buprenorphine
Patient selection	Treatment of choice for patients with long-standing polysubstance abuse	Not as effective for patients with long-standing addition or multidrug use. May be ideal for prescription opioid abusers or new heroin users
Treatment retention	Higher treatment retention in available randomized controlled trials	Higher rate of dropouts from treatment
Risk of overdose mortality	Higher	Lower (but not absent)
Risk of drug interaction	Higher risk of adverse event or death from drug interactions	Lower (but not absent) risk of adverse event or death from drug interaction
Starting dose	15–30 mg	2 mg
Target dose	90 mg	8–16 mg
Interval at which dose may be increased	3 d	Daily
Risk of NAS	Equal	Equal
Duration of NAS	Longer	Shorter
Breastfeeding considerations	Safe	Safe
Neurodevelopmental outcome in exposed children	Favorable	Less long-term information than with methadone; generally favorable

Mozurkewich EL, Obe Gyn Clin North Am, 2014

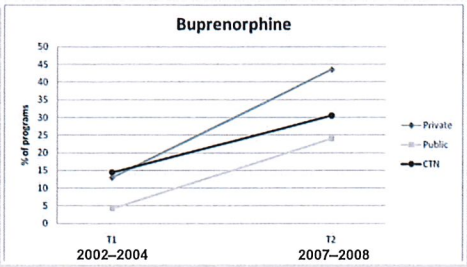
MAT in Neonatal Abstinence Syndrome (NAS)



- Both methadone and buprenorphine improve neonatal syndrome.
- Outcome:
- Shorter hospital stay
- Shorter NAS treatment duration
- But morphine dose lower in those exposed to Buprenorphine
- Buprenorphine-exposed neonates have higher mean gestational age and greater weight, length, and head circumference at birth.
- However, further evidence is needed to guide treatment choices.

Brogly SB, Am J Epidemiol, 2014

Barriers for MAT??



- Programs that place a greater emphasis on the 12-step model were less likely to adopt MAT. Counselors are less likely to rate MAT medications as effective and acceptable for use in treatment.
- Lack of access to a prescribing physician is also a major barrier to adoption of SUD medications
- Cost
- Patients education
- ??