



**UW PACC**

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

# PHARMACOLOGIC TREATMENT OF OPIOID USE DISORDER

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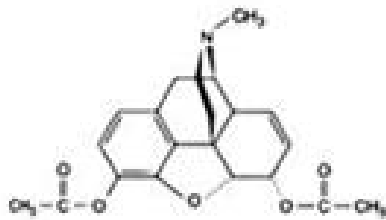
University Of Washington & VA Puget Sound Health Care System



# OBJECTIVES

1. Quick overview of physiology & epidemiology of opioid use
2. Review Rx treatments for opioid use disorder:
  - Opioid receptor antagonists
    - Naloxone
    - Naltrexone
  - Opioid receptor agonists (full/partial)
    - Buprenorphine
    - Methadone

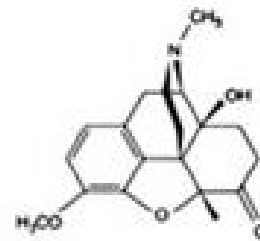
# OPIOIDS: A (VERY) BRIEF REVIEW



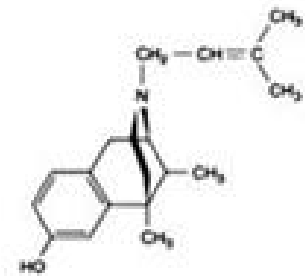
MORPHINE



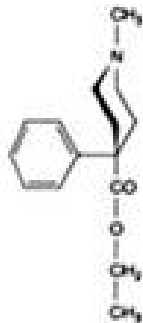
HEROIN



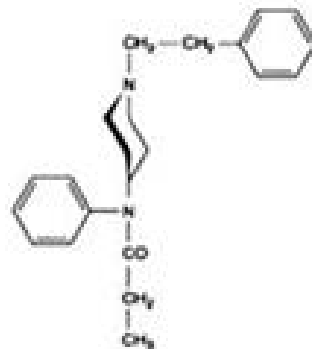
OXYCODONE



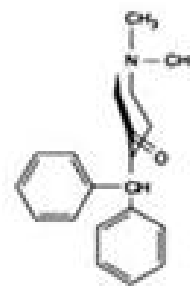
PENTAZOCINE



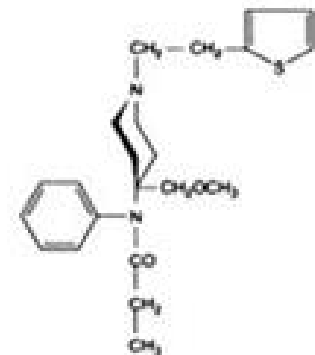
PETHIDINE



FENTANYL



SUFENTANIL



METHADONE

# OPIOIDS: NATURAL & SYNTHETICS

## Natural Alkaloids (“opiates”):

- **Morphine**
- **Codeine**

## Semisynthetics:

- **Heroin**  
**(diacetylmorphine)**
- **Oxy/hydrocodone**
- **Oxy/Hydromorphone**
- Desomorphine (krokodil)
- Etc...

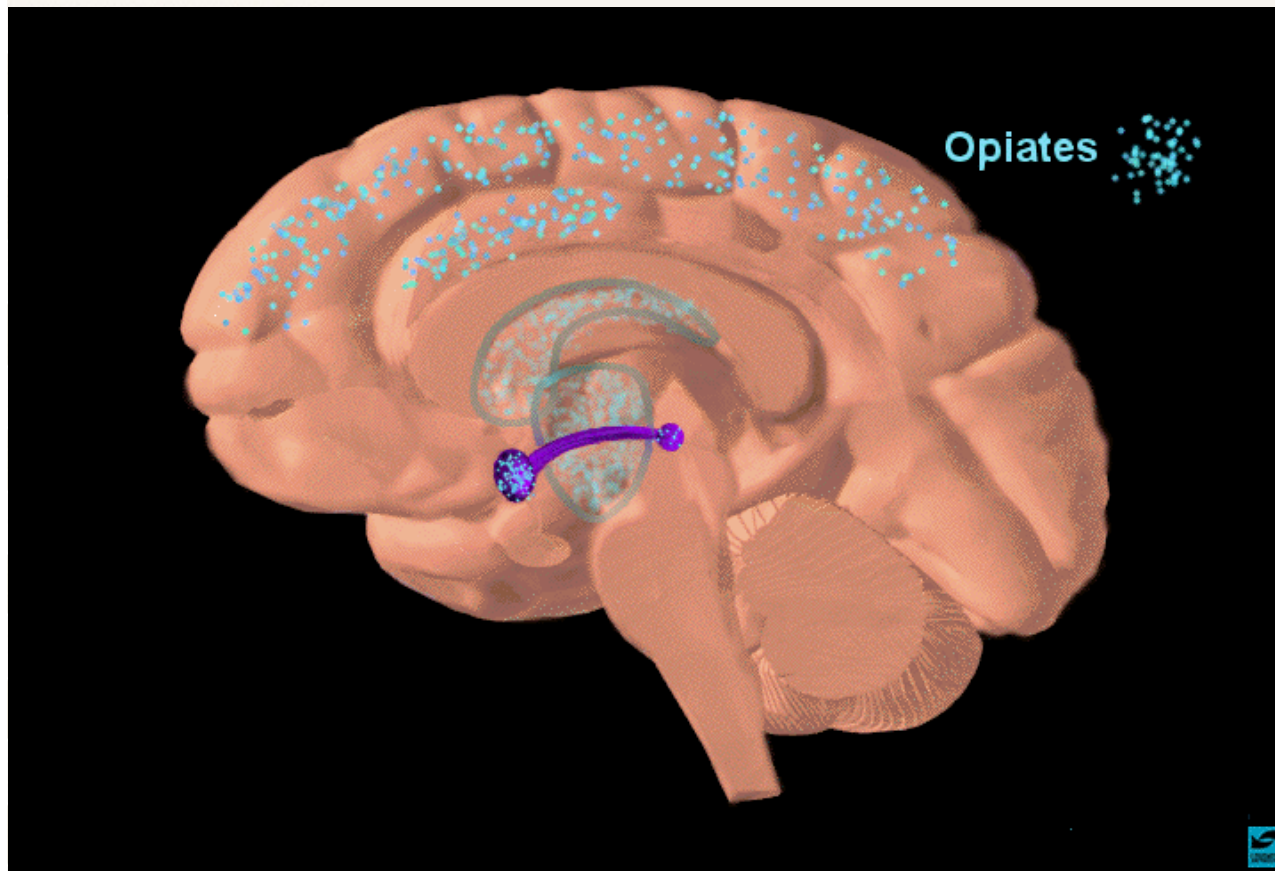
## Synthetics:

- **Methadone**
- **Buprenorphine**
- **Fentanyl**
- Merperidine
- Etc...

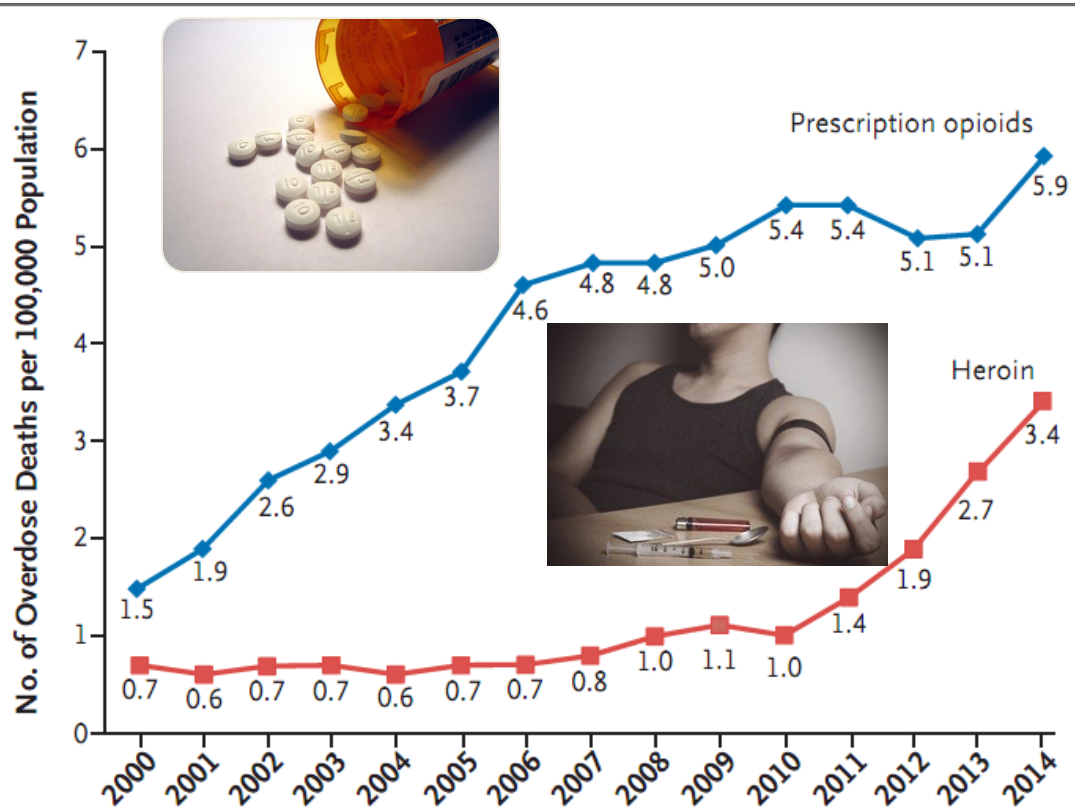
# OPIOID RECEPTORS, REWARD, & ADDICTION

Receptor class	Mu ( $\mu$ )	Delta ( $\delta$ )	Kappa ( $\kappa$ )
Activity	Mu-1: analgesia Mu-2: sedation, vomiting, respiratory depression, pruritis, euphoria, anorexia, urinary retention, physical dependence	Analgesia, spinal analgesia	Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria

Trescot, AM et al. 2008. Pain Physician 11:S5-S62.



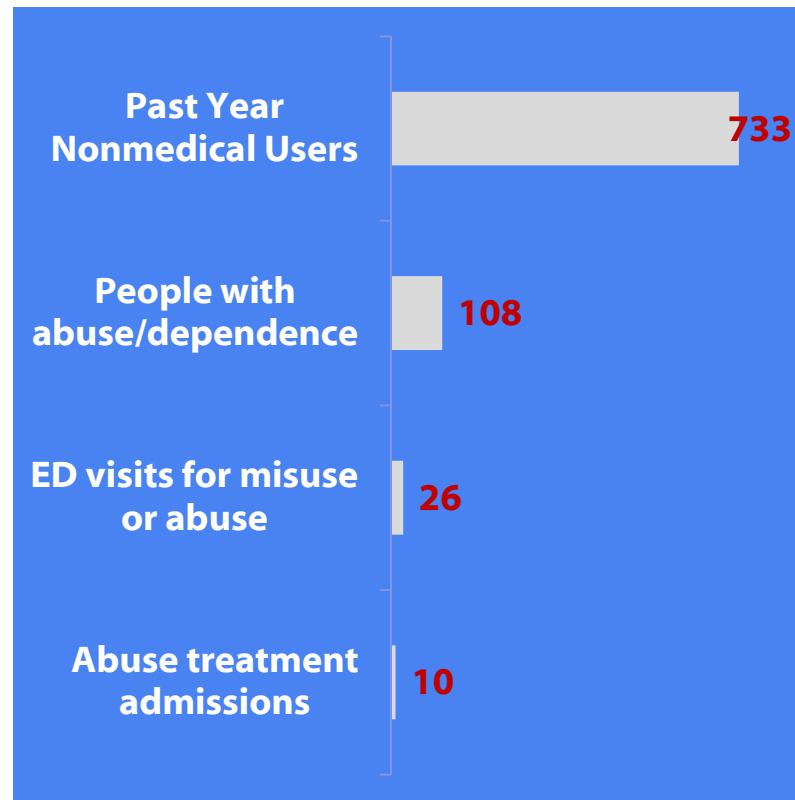
# OPIOID MISUSE AND ITS CONSEQUENCES



**Figure 1.** Age-Adjusted Rates of Death Related to Prescription Opioids and Heroin Drug Poisoning in the United States, 2000–2014.

Data are from the Centers for Disease Control and Prevention.<sup>5</sup>

For every 1 death in 2010, there were:

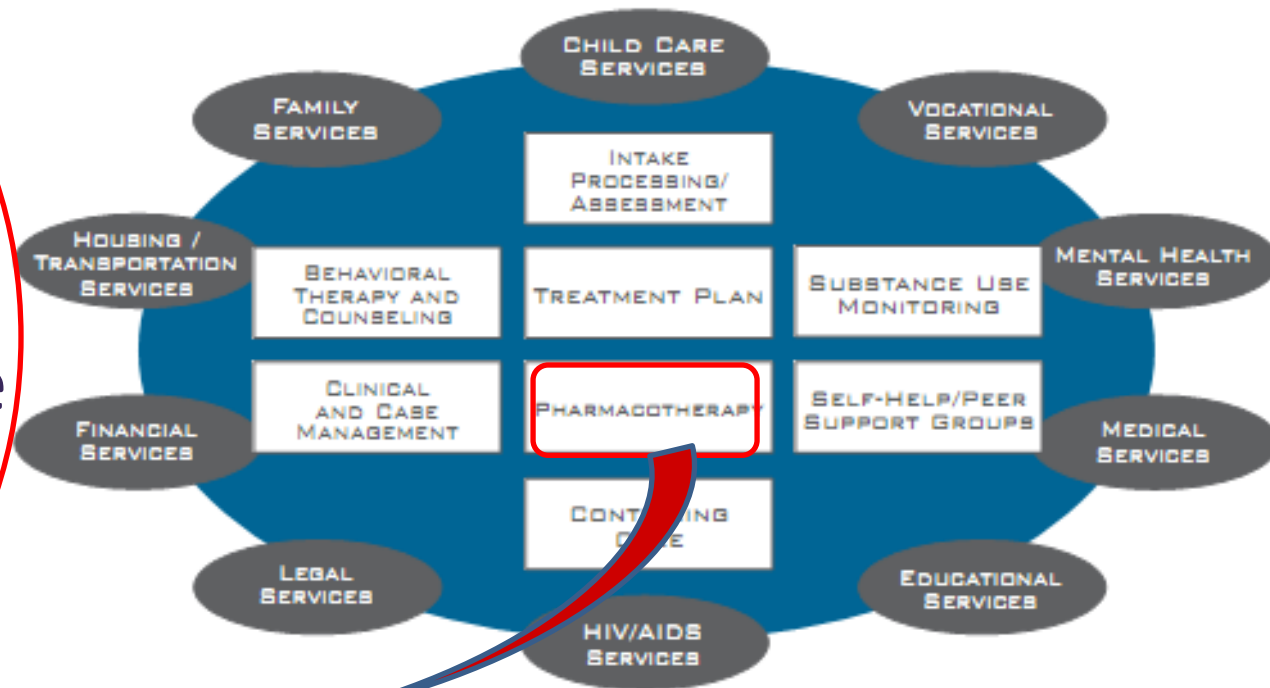


<https://dawninfo.samhsa.gov/default.asp>.

# PHARMACOTHERAPY FOR OPIOID USE DISORDER

- Naloxone
- Naltrexone
- Buprenorphine
- Methadone

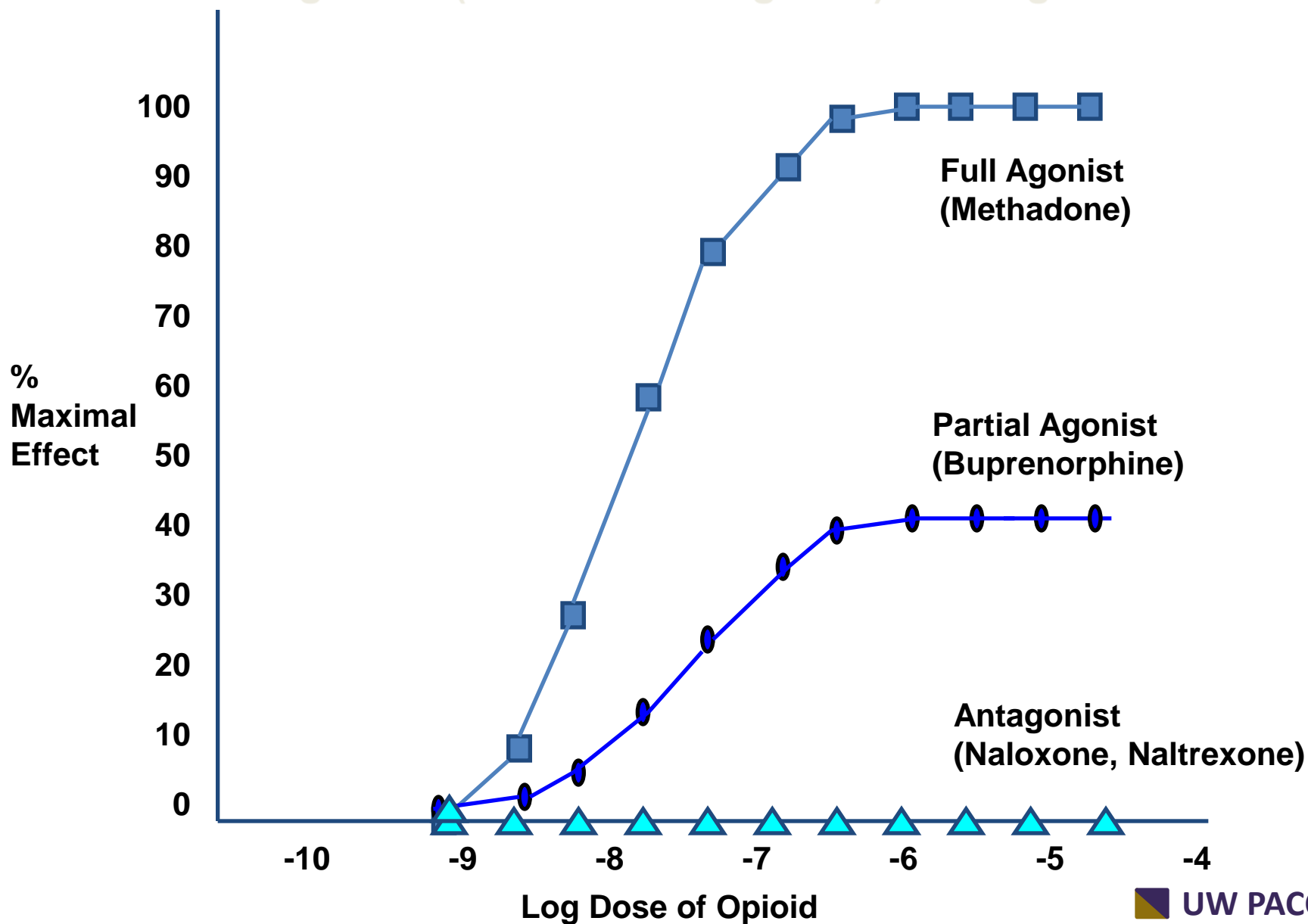
*Components of Comprehensive Drug Abuse Treatment*



*The best treatment programs provide a combination of therapies and other services to meet the needs of the individual patient.*

# PHARMACOLOGIC TREATMENTS:

## Agonists (Full & Partial Agonist) & Antagonist

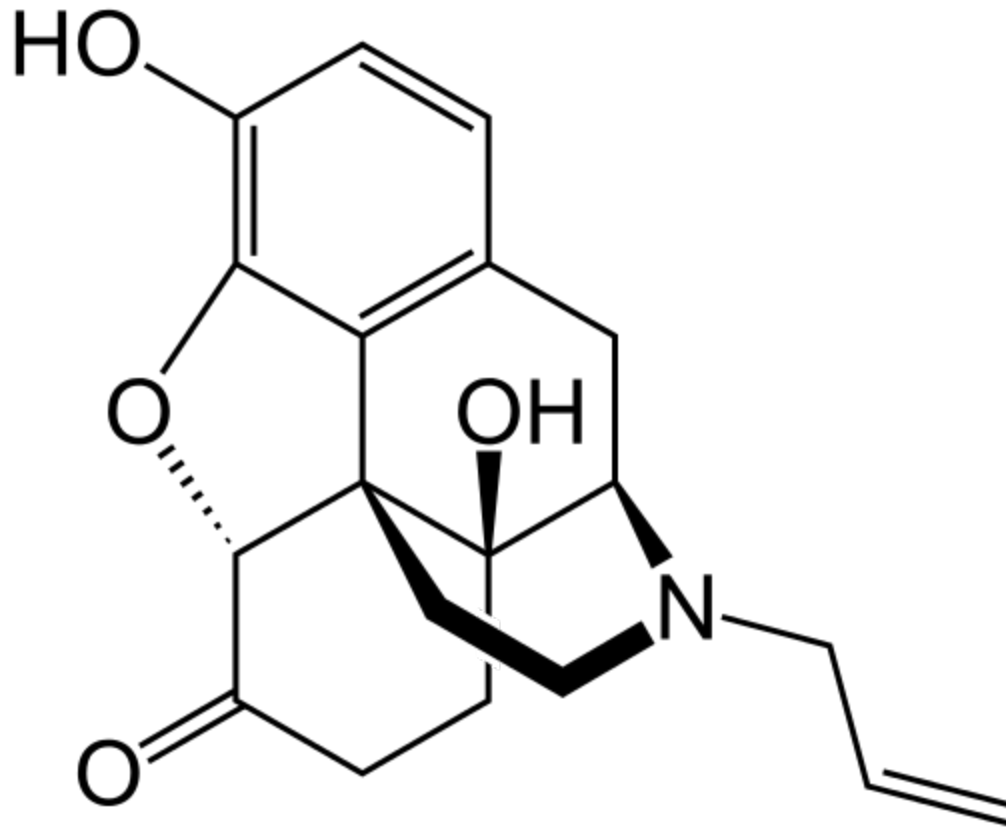




# OPIOID ANTAGONISTS

- Naloxone (rescue)
- Naltrexone (abstinence maintenance)

# NALOXONE (FOR ACUTE OVERDOSE RX)



# NALOXONE, CONT.

Use: **opioid reversal** (e.g., rescue from opioid OD)

MOA: opioid receptor **antagonist**

Route: **IM & intranasal** (common in-field), nebulized  
(rare), IV (preferred if available)

## Pharmacodynamics/kinetics:

- **Onset:**
  - **IM, SubQ: 2-5min (Peak ~15min)**
  - **Intranasal: ~8-13min (Peak ~20-30min)**
- **Duration & Half-life: ~30-120min** depending on ROA.
- **Metabolism: Primarily hepatic** via glucuronidation;  
metabolites excreted in urine

# Naloxone Product Comparison for Community Programs

	Intramuscular injection naloxone		Intranasal spray naloxone	
<b>Product</b>		 Brand name: Evzio®	 (FDA approved as injectable but used off label as intranasal.)	 Brand name: Narcan®
<b>Packaging</b>	2 single use 1 mL vials. Requires 2 intramuscular syringes (23G, 3cc, 1-1.5), sold separately.	Two-pack of autoinjector devices.	2 Luer-Jet™ Luer-Lock 2mL needleless syringes. Requires assembly with 2 mucosal atomizer devices (MAD-300) sold separately.	Two-pack of autospray devices in individual foil packs.
<b>Administration</b>	 Inject 1 mL in shoulder or thigh.	 Follow English voice prompt. Press black side firmly on outer thigh for 5 seconds.	 Spray 1ml (1/2 of vial) into each nostril.	 Spray unit into one nostril.
	<i>For all products, repeat administration if no or minimal response after 2-3 minutes.</i>			
<b>Strength</b>	0.4mg/mL	0.4mg/0.4mL	1mg/mL	4mg/0.1mL
<b>Storage</b>	68-77°F away from light Fragile: Glass	59-77°F away from light	59-86°F away from light Fragile: Glass	59-77°F away from light
<b>Cost</b>	\$	\$\$\$*	\$\$	\$\$*
	* Special pricing or donation programs available. See manufacturer website.			

<http://stopoverdose.org/docs/NaloxoneProductGuide.pdf>



# NALOXONE, CONT.

## Rescue Dosing and Administration:

- ‘Evzio’ IM/subQ (thigh) auto-injector (0.4 mg)
- ‘Narcan’ intranasal spray (4 mg)
- May repeat Q2-3min (but only 1 dose/device)

*\*\*\* NOTE: repeat dosing may be required; EMS need to be involved \*\*\**

## Significant Adverse Rx:

- precipitated w/d & analgesia reversal

# NALOXONE, CONT.

Prescribe to anyone at risk of (1) OD or (2) witnessing OD

- Opioid Use DO (or even other hx of substance use DOs)
- Chronic high-dose pain management (>120mg Mes/day)
- Concurrent Benzodiazapine, EtOH (or other sedative) use
- Comorbid conditions that ↑ OD/medical risk (e.g. impaired respiratory function, OSA, smoker, fall risk, altered drug metabolism ~ age/renal/hepatic/cardiac/med interactions)
- Hx of OD (accidental or intentional)
- Significant psychiatric, neurocognitive DO
- At-risk/vulnerable pops (e.g., children or others at risk in home)

Educate pt, family, friends as available & appropriate

- ID possible OD, call 911, admin naloxone, rescue breathing

Resources: <http://stopoverdose.org>

# MEDICATION ASSISTED TREATMENT (MAT):

## Indications & Conditions for Rx:

- Opioid use DO
- Pt willing/able to consent to & engage in Rx

## Other Screening & Assessment:

- Gen. Med:
  - Active conditions, med hx, rxs
  - Evidence of intox/withdrawal
  - SU-assoc. conditions (abscesses, HIV, HepB/C, TB)
  - Cardio-pulmonary, hepatic, renal dysfunction
  - Labs: HCG, tox screen, BMP, LFTs, CBC, UA, Lipid, ID screens (HepB/C, HIV, TB, syphilis)
- Psych:
  - SU hx (substances, timecourse, severity, sequelae, prior tx/rx exp., check PDMP!)
    - Opioids: which, duration, frequ, recency, risk of relapse
    - Active sed/hypnotic, EtOH use DOs?
  - Other psych comorbidities, hx of self-harm & current risk
  - Social context: safety, stability, rx-barriers, etc



## MAT Options:

- Opioid Substitution:
  - Buprenorphine
  - Methadone
- Abstinence Maint.
  - Naltrexone

## Treatment context:

- Office-based
- Clinic-based
- Residential

# M.A.T. FOR OPIOID USE DISORDER

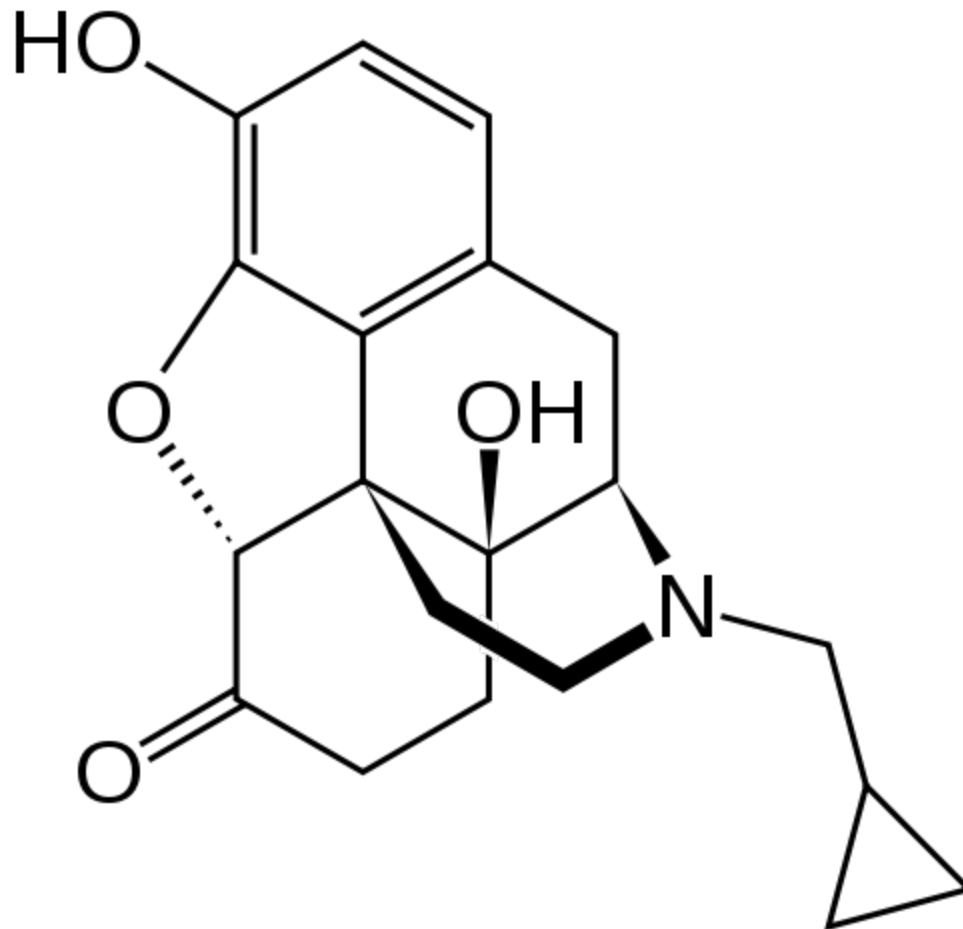
## ► Clinical Uses/Ideal Candidates

Extended Release Injectable Naltrexone	Methadone	Buprenorphine
<p>Prevention of relapse to opioid use disorder following opioid detoxification; studies suggest benefits for patients who are experiencing increased stress or other relapse risks (e.g., visiting places of previous drug use, loss of spouse, loss of job).</p> <p>Appropriate for patients who have been detoxified from opioids and who are being treated for a co-occurring alcohol use disorder.</p> <p>Extended-release naltrexone should be part of a comprehensive management program that includes psychosocial support.</p> <p>Other good candidates include persons with a short or less severe addiction history or who must demonstrate to professional licensing boards or criminal justice officials that their risk of opioid use is low.</p>	<p>Detoxification and maintenance treatment of opioid addiction.</p> <p>Patients who are motivated to adhere to the treatment plan and who have no contraindications to methadone therapy.</p> <p>Methadone should be part of a comprehensive management program that includes psychosocial support.</p>	<p>Treatment of opioid dependence.</p> <p>Patients who are motivated to adhere to the treatment plan and who have no contraindications to buprenorphine therapy.</p> <p>Buprenorphine should be part of a comprehensive management program that includes psychosocial support.</p>



# OPIOID ABSTINENCE MAINTENANCE:

## NALTREXONE



# NALTREXONE, CONT.

Use: opioid-use relapse prevention (for non-OST candidates)

MOA: opioid receptor antagonist (high Mu affinity)

Route: IM (Note: IM >>> PO in opioid use DO)

## Pharmaco-dynamics/kinetics:

- Peak: biphasic w/ ~2hrs and then 2-3days
- Duration & Half-life: 4wks; 5-10 days.
- Metabolism: Primarily hepatic via non-cytochrome-mediated dehydrogenase (to 6- $\beta$ -naltrexol); IM naltrexone  $\downarrow$  1<sup>st</sup> pass metab. Excreted in urine

# NALTREXONE (VIVITROL): DOSING & ADMIN.

“Vivitrol” 380mg IM (gluteal, superior-lateral quadrant) Q4wks

## *Cautions:*

- Pt should be opioid-free for 7-10days before rx; consider naloxone challenge
- For active users, med-managed detox (outpt possible, depending on pt & context)

# NALTREXONE: SPECIAL POPS

- Infant: Excreted in breast milk (avoid if possible)
- Geriatric: same as adult
- Hepatic & renal impairment:
  - no adjustment for mild impairment
  - caution w/mod-severe impairment (not studied)
- Pregnancy: not well studied (some development abnl in animal studies)

# NALTREXONE: CAUTIONS & MONITORING

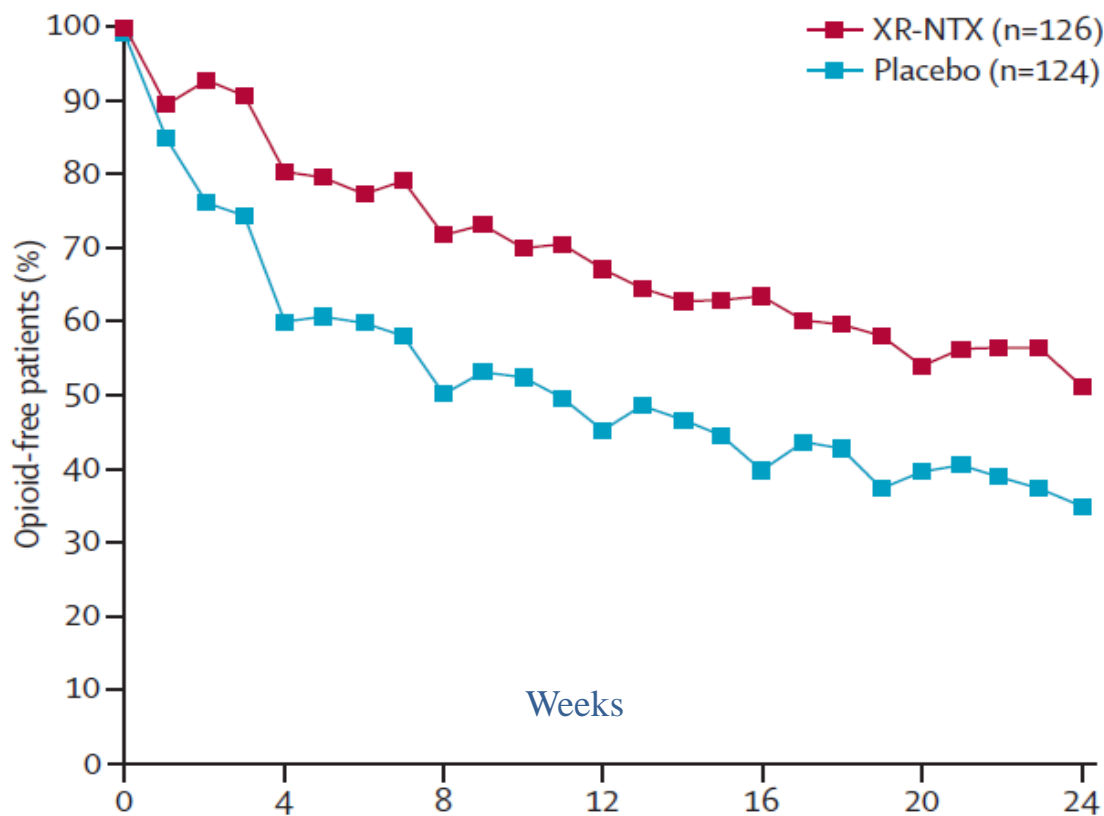
## Potential SEs/Issues:

- Precipitated w/d
- Analgesia reversal/blockade
  - Provide med alert bracelet
- Hepatocellular injury (rare, dose-dependent)
- Risk of OD: if pt stops (loss of tolerance) or attempts to overcome blockade
- Acute/emergency pain management
- Injection site rxs (vivitrol)—rarely clinically signif.

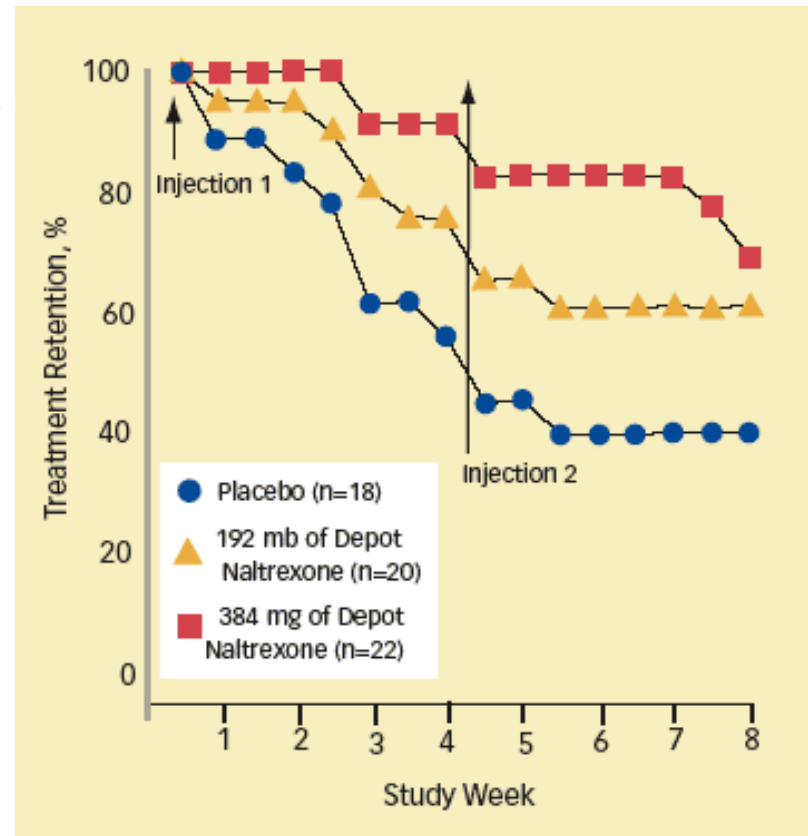
## Monitoring:

- LFTs at initiation, at 1 mo, then annually

# Injectable Extended Release Naltrexone for Opioid Dependence



Krupitsky, et al., 2011. Lancet 30, 377: 1506-13



NIDA Notes Vol.21, No.3 - Research Findings

# OPIOID SUBSTITUTION: BENEFITS

## Studies have found:

- Reduced drug use
- Improved retention in treatment
- Improved health & functionality
- Public health gains (HIV, Hepatitis, etc.)
- Overall health care cost savings
- Reduced criminality (mixed results)
- Reduced mortality (mixed results)

Gunne & Gronbladh, 1981

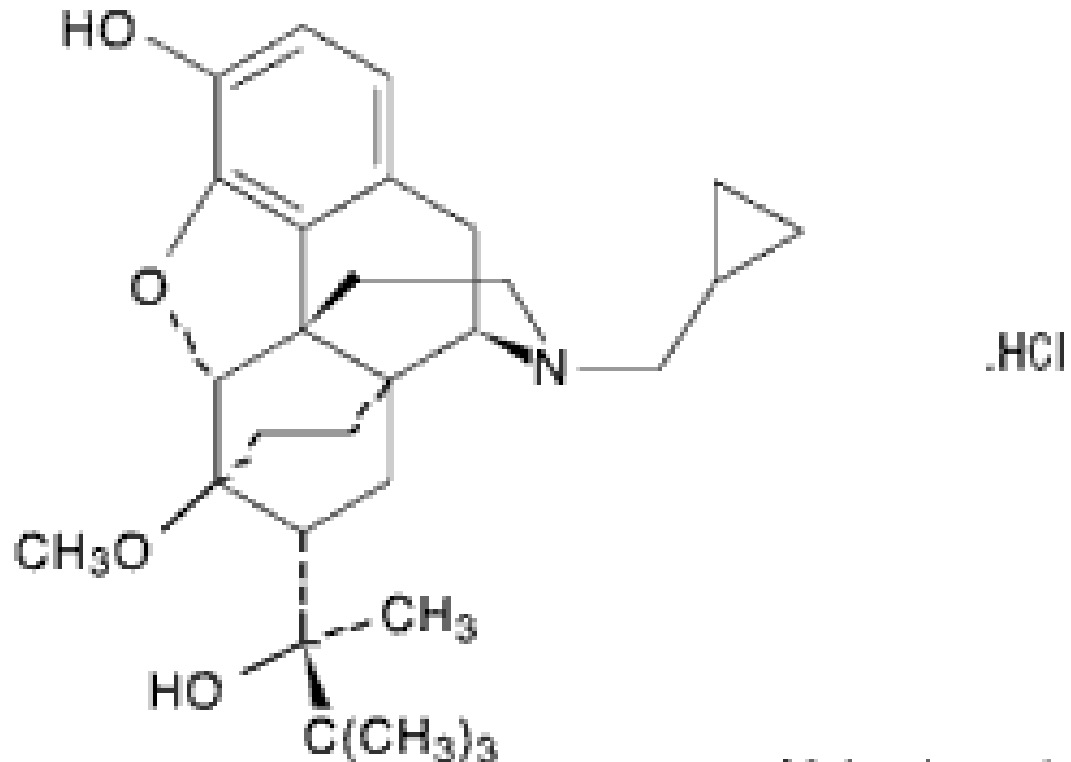
Mattick, RP et al, 2009

Mattick, RP et al., 2014

Kimber, J et al, 2015

# BUPRENORPHINE

(A PARTIAL  $\mu$ -OPIOID AGONIST)



Molecular weight: 504.09



# Buprenorphine

Use: Opioid maintenance, medically supervised w/d

MAO: opioid receptor *partial* agonist (Mu), weak antagonist (Kappa)

## Formulations:

- Bup. & bup/naloxone: SL tablets & films
- Buccal films
- Subdermal implant (Probuphine)

Clinical context (OST, C-III): office-based, clinic-based

## Pharmaco-dynamics/kinetics:

- High receptor affinity, low intrinsic activity, slow dissociation
- Peak: ~30-60min
- Half-life (adults): ~16-38hrs
- Metabolism: Extensive 1<sup>st</sup> pass (poor PO.) Primarily hepatic N-dealkylation (CYP3A4) to norbuprenorphine (active)
- Excretion: feces (~70%) & urine (~30%)

# BUPRENORPHINE: BENEFITS

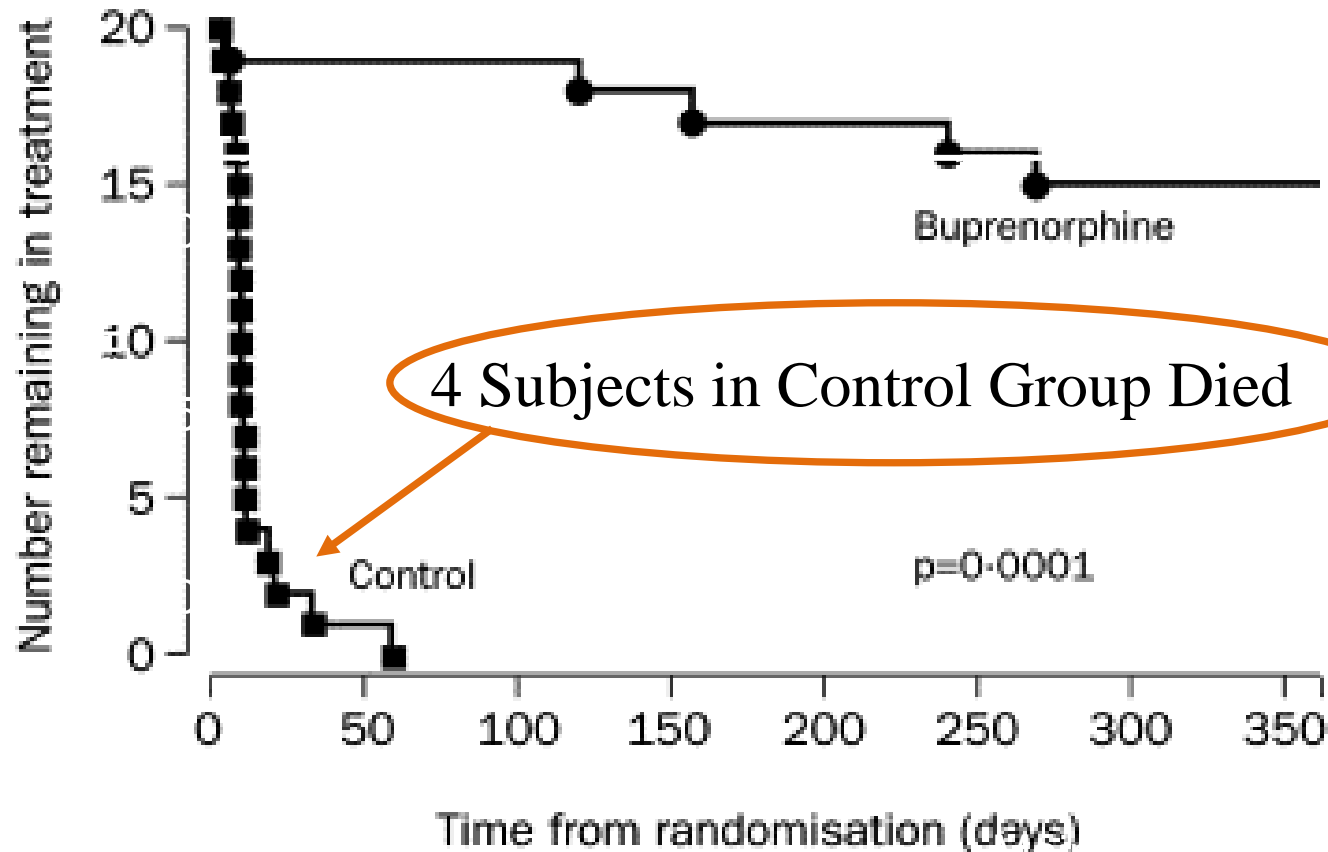
## Safety:

- Partial agonist:
  - Ceiling effect limits respiratory depression; less dangerous in OD or when combined w/benzos
  - Less: re-enforcing, physical dependence, w/d symptoms
- High affinity for Mu-receptor:
  - Limits OD-potential w/concurrent illicit use
- Combination w/naloxone (“Suboxone”) limits abuse/diversion

## Access:

- Option of office-based treatment!

# BUPRENORPHINE VS. PLACEBO FOR HEROIN DEPENDENCE



Number at risk

20	19	18	17	17	16	15	15
20	1	0	0	0	0	0	0

# BUPRENORPHINE: PRE-INDUCTION

## Assess hx of use:

- Duration & pattern of inappropriate opioid use (freq, quantity, time-course, last-use)

## Discuss i/r/b/a to treatment

- Pay attention to pt's hx, current risk-factors, goals/values, etc

## Arrive at shared treatment goals

- Long-term maintenance vs. taper
- Buprenorphine vs. Methadone >>> Naltrexone
- Clinic vs. Office-based?
- Prescribe naloxone rescue kit

# BUPRENORPHINE: DOSING (INDUCTION)

## Induction (Week 1):

– Current opioid users:

- Await COWS  $\geq 13$  (to avoid precip. w/d)
- If on MMT, taper to  $<30\text{mg/day}$  and hold dose  $\geq 2\text{days}$

– Day#1 (in-office or home-based):

- Begin w/2-4mg X 1 (2mg w/o ongoing opioid use)
- If tolerated but w/cont w/d or urges/cravings, then repeat X1 at 60min
- Can titrate by 2mg Q4hrs up to max 8-12mg over first 24hrs

– Day #2-5: titrate to max 16mg/day, PRN cravings -- monitoring SEs, SU

# BUPRENORPHINE: DOSING (POST-INDUCTION)

## Stabilization (1-2mo):

- C/w adjustment (+/- 2mg/day) for urges/cravings, SEs

## Maintenance (thereafter):

- Avg dose range = 8-16mg Qday; range 4-32mg Qday  
(can split dose for OST + pain)

## Taper:

- When: switch to MMT, SEs, non-compliance
- Approach: Very gradual
- Monitor: w/d, cravings/urges, relapse

**\*\* Note: High risk of relapse in pts w/opioid use DO**

**taken off OST – consider Vivitrol post-taper \*\***

# BUPRENORPHINE: POTENTIAL SEs, CONCERNS

- **CNS & respiratory depression** (esp in children & w/benzos/other sedatives)
- **Precipitated w/d**
- QTc prolongation (in theory)
- Hypotension
- Hepatitis
- Hypogonadism (in theory – check T-level only w/clinical s/s)
- May lower sz threshold
- Multiple **med-med interactions** (anti-virals, AEs)
- **Acute pain management** (e.g., surgery)
  - Elective Surg.: dose-reduction vs. dc Bup 24-36 hrs before surgery. SA full agonist. opioids may be given during/after procedure.
  - Unplanned surg.: full agonists added to Bup (usually at higher doses.)

# BUPRENORPHINE: SPECIAL POPS

Pregnancy: Increasingly a 1st line option for OST

Neonates: En utero exposure → risk of opioid w/d

Infant: Excreted in breast milk (<0.5% of maternal serum level)

Geriatric: same as adult dosing; use caution

Hepatic: no adjustment for mild impairment; caution w/mod-impairment, dose-reduction w/severe impairment (not well-studied)

Renal impairment: no adjustment

Respiratory conditions (OSA, resp ds): use w/caution

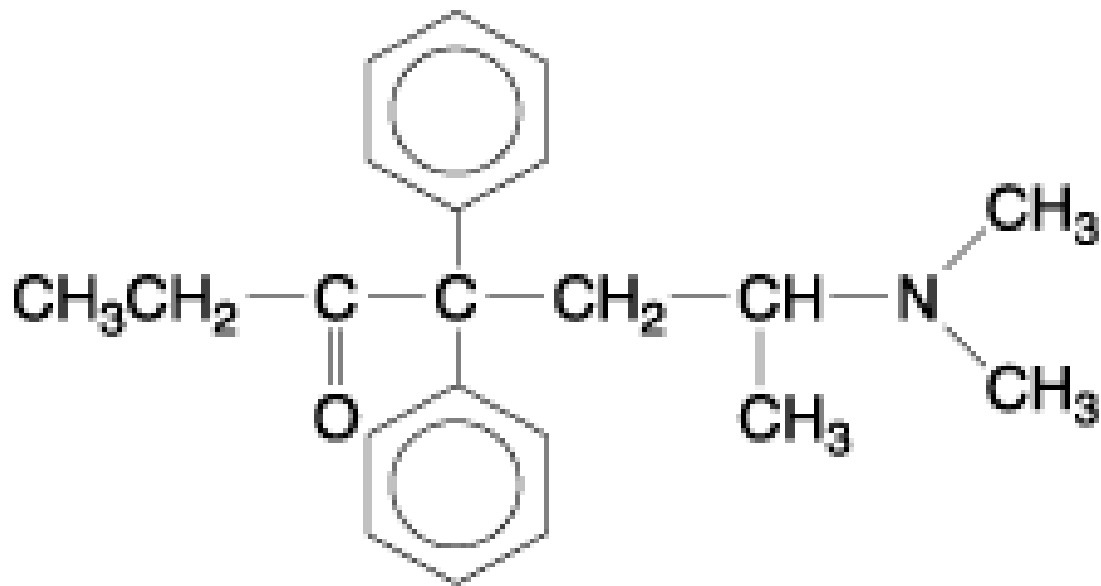
QTc prolongation (in theory): caution w/QTc > 450msec; if >500msec, ↓ other causes vs. ↓ Bup; weigh r:b & consider other tx options



# BUPRENORPHINE: MONITORING

- Consider EKG in select pts (baseline and will titration; consider annual)
- LFTs (baseline & once in maintenance phase)
- Sedative effects
- Non-compliance, concurrent SU/med-med interactions

# METHADONE



METHADONE

# METHADONE: SOME BASICS

Use: **opioid substitution**; pain management

Ideal Pts: Opioid use DO, severe & chronic pain, tolerates/benefits from clinic structure, hx of successful rx w/MMT

MOA: opioid receptor (**full**) **agonist**; weak NMDA antagonist

Route: PO (tabs, syrup); inj

Context (for OST, C-II): **licensed clinic; inpatient, emergency bridging (3-days)**

## Pharmaco-dynamics/kinetics:

- Onset: ~30-60min
- Peak: ~1-7.5hrs w/indiv dosing → **3-5days w/stacking**)
- Half-life (adults): **~10-90hrs**
- Metabolism: Primarily **hepatic** N-demethylation (multiple CYPs, esp p4503A4) → inactive metabolites; 2D6 polymorphism can Δ metab.; parent (10%) & metabolites excreted in urine
  - **Lipophilic**; may persist w/slow-release from liver, etc

# METHADONE: INDUCTION & TITRATION

## Induction & Titration:

- **Conservative** initiation & titration (**w/stacking**)
- **Non-linear dose-potency** when considering morphine equiv (ranging 5-30% ME)

## Maintenance:

- Usual range = **60-120mg/day** (some require high doses)
- **Daily clinic-based dosing** (w/potential for earning carries over long-term)

## Taper: **\*\* High risk of relapse off OST \*\***

- When: switch to suboxone, SEs, non-compliance,
- Approach: Very gradual
- Monitor: w/d, cravings/urges, relapse

# METHADONE: POTENTIAL SEs/ISSUES

- CNS & respiratory depression (w/risk of death, esp w/benzos & other sedatives)
- QTc prolongation (risk of Torsades)—in predisposed pts, dose-dependent
- Hypotension
- Hypogonadism (monitor & tx w/long-term Rx)
- Constipation
- Peripheral edema
- Hyperalgesia
- May lower sz threshold
- Multiple med-med interactions

# METHADONE: SPECIAL POPULATIONS

Pregnancy: a 1<sup>st</sup> line Rx; **clearance ↑ in 2<sup>nd</sup>/3<sup>rd</sup> Trimester**

Neonates: En utero exposure → **risk of severe w/d**

Infant: Excreted in **breast milk (2-3% of maternal serum level)**

Geriatric: consider slower titration

Hepatic: no adjustment for mild-mod impairment; caution with severe (though not studied)

Renal impairment: for CrCl < 10 use 50-75% nl dose

Respiratory conditions (OSA, resp ds): use w/caution

QTc prolongation: caution in QTc > 450**if >500msec, ↓ other causes vs. ↓MMT; weigh r:b & consider other tx options**msec;

# METHADONE: MONITORING

- EKG (baseline and with titration; consider annual f/u EKG)
- Sedative effects
- Non-compliance, concurrent SU/med-med interactions

# OTHER POTENTIAL THERAPIES...

## PHARMACOTHERAPIES

- Long acting Buprenorphine
  - “Probuphine”: Subcutaneous 74.2 mg buprenorphine implants (4 per Kit)
  - In-office under local anesthetic
  - Requires REMS training (<http://probuphinerems.com/>)
- Memantine (equivocal)
- Clonidine (equivocal)

## PSYCHOTHERAPIES



- **Cognitive Behavioral Therapy** seeks to help patients recognize, avoid, and cope with the situations in which they are most likely to abuse drugs.
- **Contingency Management** uses positive reinforcement such as providing rewards or privileges for remaining drug free, for attending and participating in counseling sessions, or for taking treatment medications as prescribed.
- **Motivational Enhancement Therapy** uses strategies to evoke rapid and internally motivated behavior change to stop drug use and facilitate treatment entry.
- **Family Therapy (especially for youth)** approaches a person's drug problems in the context of family interactions and dynamics that may contribute to drug use and other risky behaviors.



# QUESTIONS?

## MANY THANKS!

-Andy Saxon, MD

-Mark Duncan, MD