Medication Assisted Treatment

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ADVERSE OUTCOMES ASSOCIATED WITH OPIOID DEPENDENCE

Natural Course:

- **Medical risks:**
  - **Abscesses**
  - **Sepsis**
  - **Osteomyelitis**
  - **Thrombophlebitis**
  - **Endocarditis**

Natural Course:

- **Medical risks:**
  - **HCV**
    - **70% IV users**
    - **65% after 1 yr needle use; ~85% at 5 yrs**
  - **HIV**
    - **IV users ~25% of new HIV infections**
    - **HIV ~20%**

Natural Course:

- **Death**
  - **Overdose 1.5%/yr**
  - **24 yr study – 28% sample deceased**
  - **30 yr. study in California: 49% sample deceased**
  - **Annual risk of dying for a heroin addicted person is increased upto 20x compared to someone who does not use**
  - **Not in tx; 63x expected mortality rate**

- **Major causes of death**
  - **Drug overdose, suicide, violence, accidents, infection, chronic diseases**

Natural Course:

- **Low employment:**
  - **36.4% active users employed**
  - **Heroin dosed Q 6 hours**
  - **Need time to recover**
  - **But need money to buy the drug**

- **Crime:**
  - **Most commit crimes**
  - **F/u 10 years ~18% incarcerated**
  - **One study n=573 12 month period:**
    - **>80,000 crimes reported**

- **Costs:**
  - **Medical costs: $1.2 billion per yr**
  - **Total cost estimate: $20 billion per yr**

Natural Course: Summary

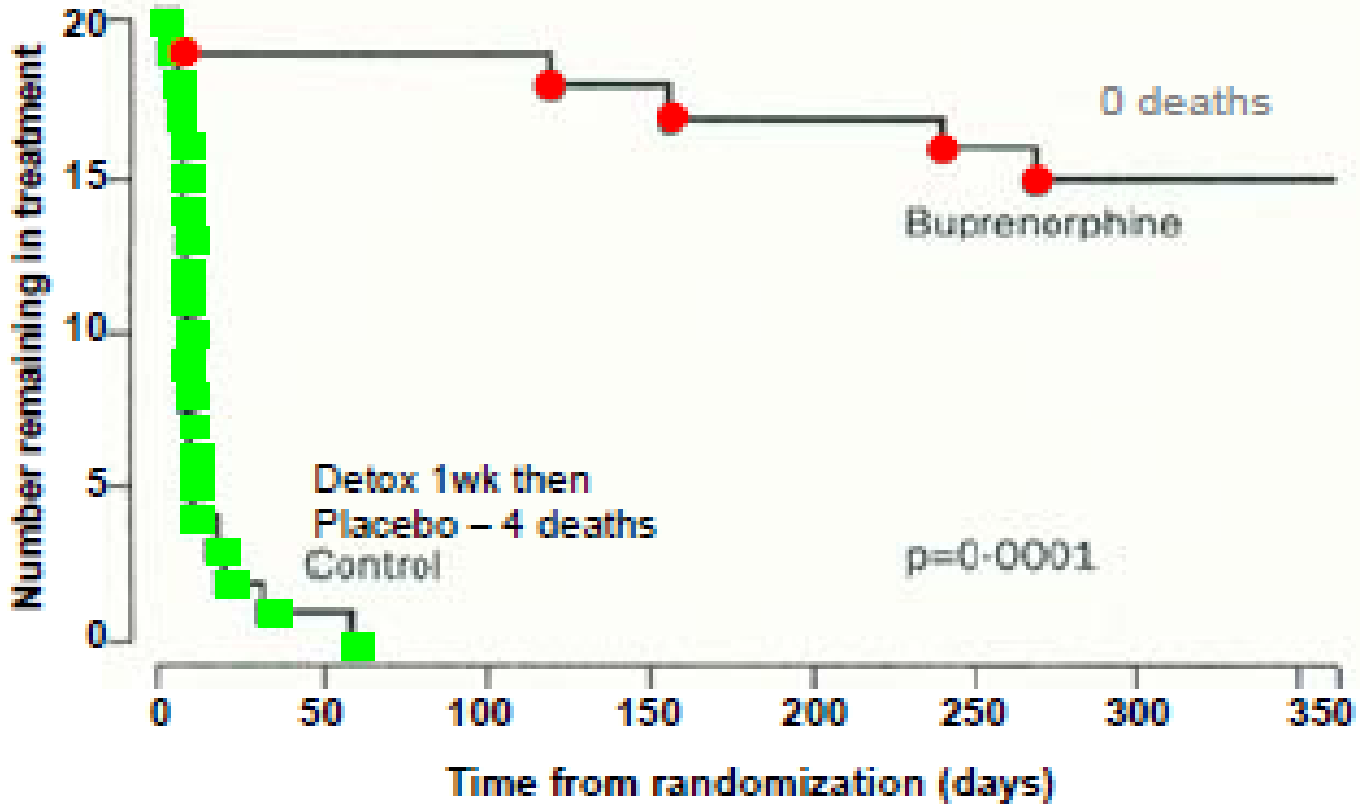
- **Medical risks**
- **High mortality**
- **Low employment**
- **Crime**
- **High cost to society**

DETOX ALONE DOES NOT WORK!

“ Detoxification from heroin is good for many things – but staying off heroin is not one of them”

Walter Ling

Buprenorphine Maintenance vs Detox. RCT of cumulative retention in treatment



Number at risk

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

Kakko, et al, Lancet, 2003

Successful Outcomes at 3 Time Points

		Success
Phase 1	4-week taper + 8 weeks follow-up	**7%**
Phase 2	Week 12 (end of stabilization)	**49%**
	Week 24 (8 weeks post-taper)	**9%**

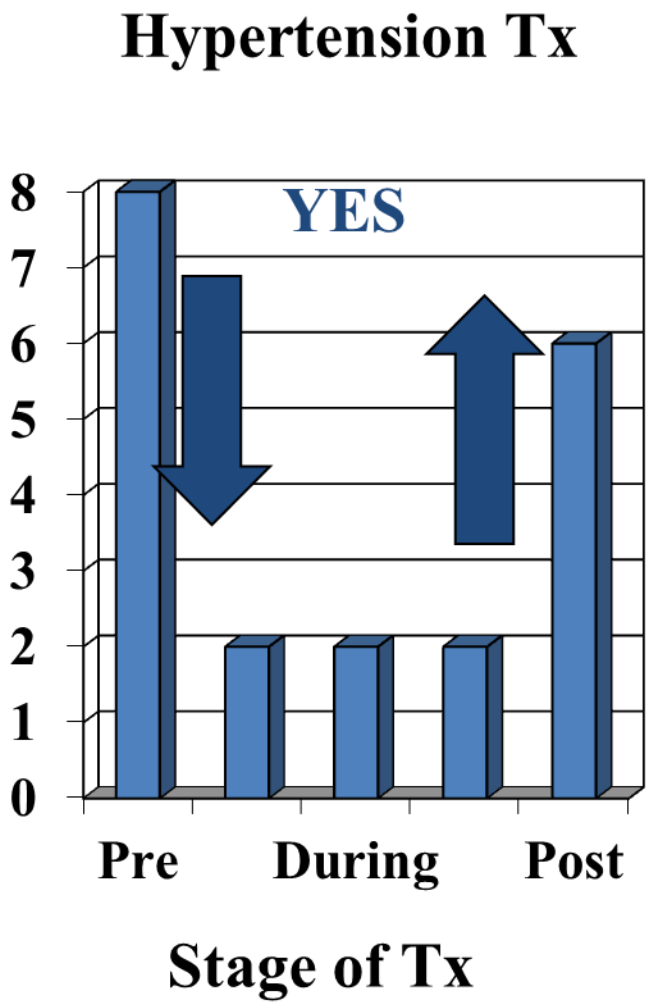
Time Points	*P* Value
Phase 2 week 12 vs phase 2 week 24	**<.001**

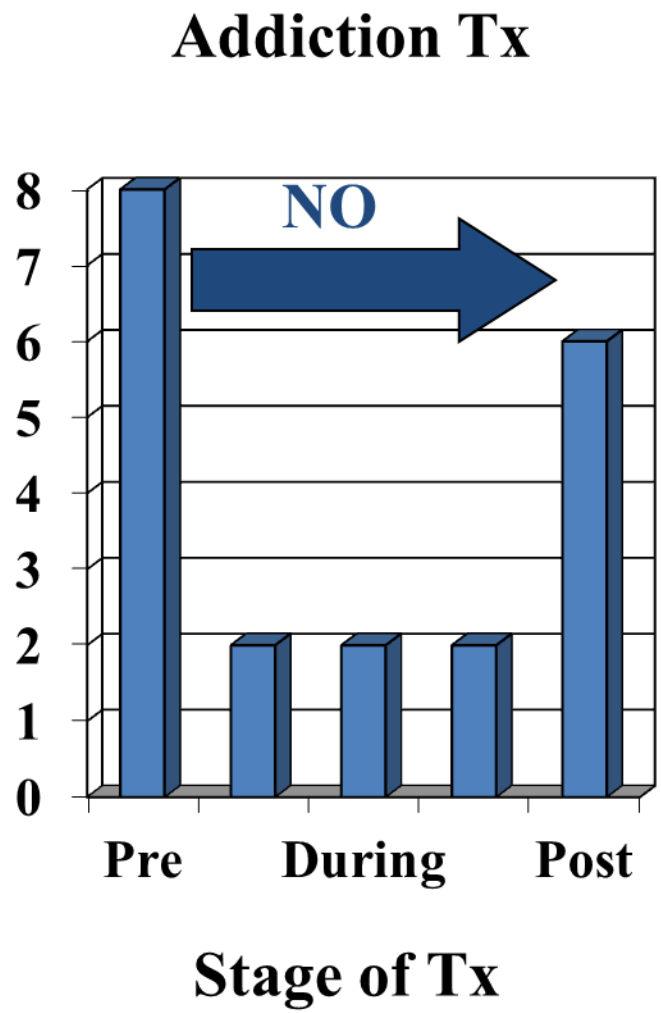
Weiss RD et al. *Arch Gen Psychiatry*. 2011;68(12):1238-1246.

Similarities with Other Chronic Diseases (Type II Diabetes, HTN, Asthma)

- **Genetic impact is similar**
- **The contributions of environment and personal choice are comparable**
- **Medication adherence and relapse rates are similar.**
- **Long term maintenance treatments proven most effective. (McLellan, JAMA 2000)**

There is a right way and a wrong way to Measure the Outcome of Treating Chronic Illnesses like Addiction





Implications

- As in all chronic diseases, treatment should be continuous rather than episodic
- Goal should be improvement, not “cure”
- Available treatment leads to substantial improvement in:
  - Reduction of alcohol and drug use
  - Increases in personal health and social functioning
  - Reduction in threats to public health and safety
  - Reduction in monetary costs
- Therefore, a case must be made to treat addictions like all other chronic illnesses.

Redefining Success

- Appropriate comparisons
  - Treat SUDs as chronic diseases
  - Comparable to other chronic diseases

- Reasonable expectations
  - Complete abstinence is not the only successful outcome

METHADONE- AGONIST THERAPY

Methadone

- Schedule II medication
- Highly regulated
- Narcotic program treatment settings
- Full Mu agonist
- Who is appropriate:
  - At least 1 year of documented opioid dependence
  - Parental consent needed if 16-17 years of age; also need to show at least 3 failed prior detoxification attempts
  - Infectious disease
  - Pregnant women

Methadone outcomes

- ↓ Heroin use by 50%
- ↓ HIV 4 fold
- ↑ Employment 24%
- ↓ 60% criminal activity
- Less incarceration
- More child support payments
- 3x as likely to remain in treatment
- Improved hepc treatment adherence
- Mortality reduced
- Cost effective
- Drug users out of methadone treatment 6x more likely to become HIV positive than those in methadone treatment [Metzger et al., 1993]

More benefits of maintenance treatment

- Decreased IV drug use
- Decreased needle sharing
- Decreased cocaine use
- Decreased unprotected sex
- Decrease in multiple sex partners
- Decrease in commercial sex work

Methadone- initial assessment

- Determine opioid dependence
- History, including previous records
- Signs of dependence [withdrawal, track marks]
- Urine toxicology
- Check ECG to determine if prolonged QTc present.

Methadone dosing

- First dose 30 mg or less [10-15 mg if low tolerance]
- Once daily
- Start low, go slow
- Rapid oral absorption
- Half life 24 hours, so dose increases every 5 days or more
- If in withdrawal at peak, raise dose 5-10 mg
- If intoxicated at peak, reduce dose 5-10 mg
- Peak happens 4 hours post dosing
- Monitor closely; overdoses tend to occurr early in treatment
- Peak and trough levels can help guide treatment

Methadone dosing

- Target levels 60-120 mg
- Individualize dose to target withdrawals, while avoiding sedation or euphoria
- Higher doses generally more effective, so AVOID UNDERTREATING
- Beware accumulation in first 5-10 days, so do not make rapid dose increases
- Even a dose of 40 mg will control most withdrawal symptoms [but NOT cravings], so no need to rush

What is an optimal dose?

- One person's optimal dose is not another person's optimal dose
- Usually 80-120, but much variability
- Remember, patients on higher doses exhibit superior outcomes in terms of abstinence, treatment retention, and psychosocial rehabilitation [Payte et al., 2003]
- High dose maintenance=REDUCED risk of fatal heroin overdose during treatment [Caplehorn, 1996]
- Dole: "As with antibiotics, the prudent policy is to give enough medication to ensure success." [1988]

Methadone side effects

- Minimal sedation at right dose
- Constipation
- Increased appetite- weight gain
- Lowered libido
- May decrease gonadal hormone levels
- Extensively studied in other organ systems with no evidence of harm in long term use
- QTc prolongation

Methadone drug interactions

- Decreased methadone concentrations- opioid withdrawals
  - pentazocine
  - Phenytoin
  - Carbamazapine
  - Rifampin
  - Efavirenz
  - Nevirapine
  - Lopinavir
  - Risperidone

- Increased methadone concentrations- sedation, respiratory depression, QTc prolongation
  - Ciprofloxacin
  - Fluvoxamine
  - Fluoxetine
  - Erythro,ezythromycin
  - [Drugs that inhibit CYP3A4, CYP2D6, CYP2B6]

Consensus Recommendations [2009]

Table 2. **Consensus Recommendations**
Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
Recommendation 4 (Risk Stratification): If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

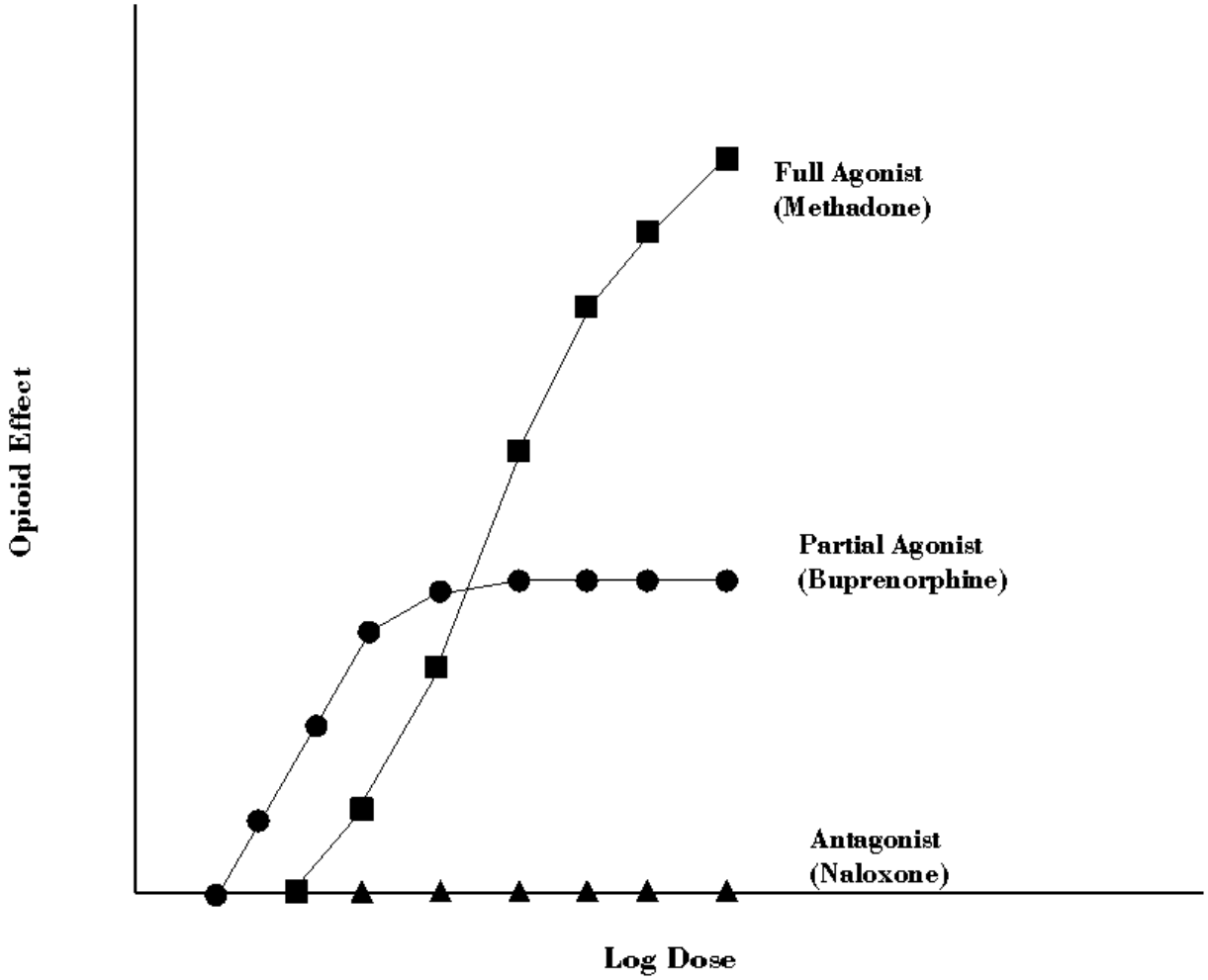
QTc = rate-corrected QT.

Methadone: treatment barriers

- **Out of medical mainstream**
- **Stigma of specialized clinics**
- **Location of clinics**
- **Daily dosing**
- **Federal regulations**

BUPRENORPHINE- PARTIAL AGONIST TREATMENT

Figure 2-1. Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists*



Buprenorphine

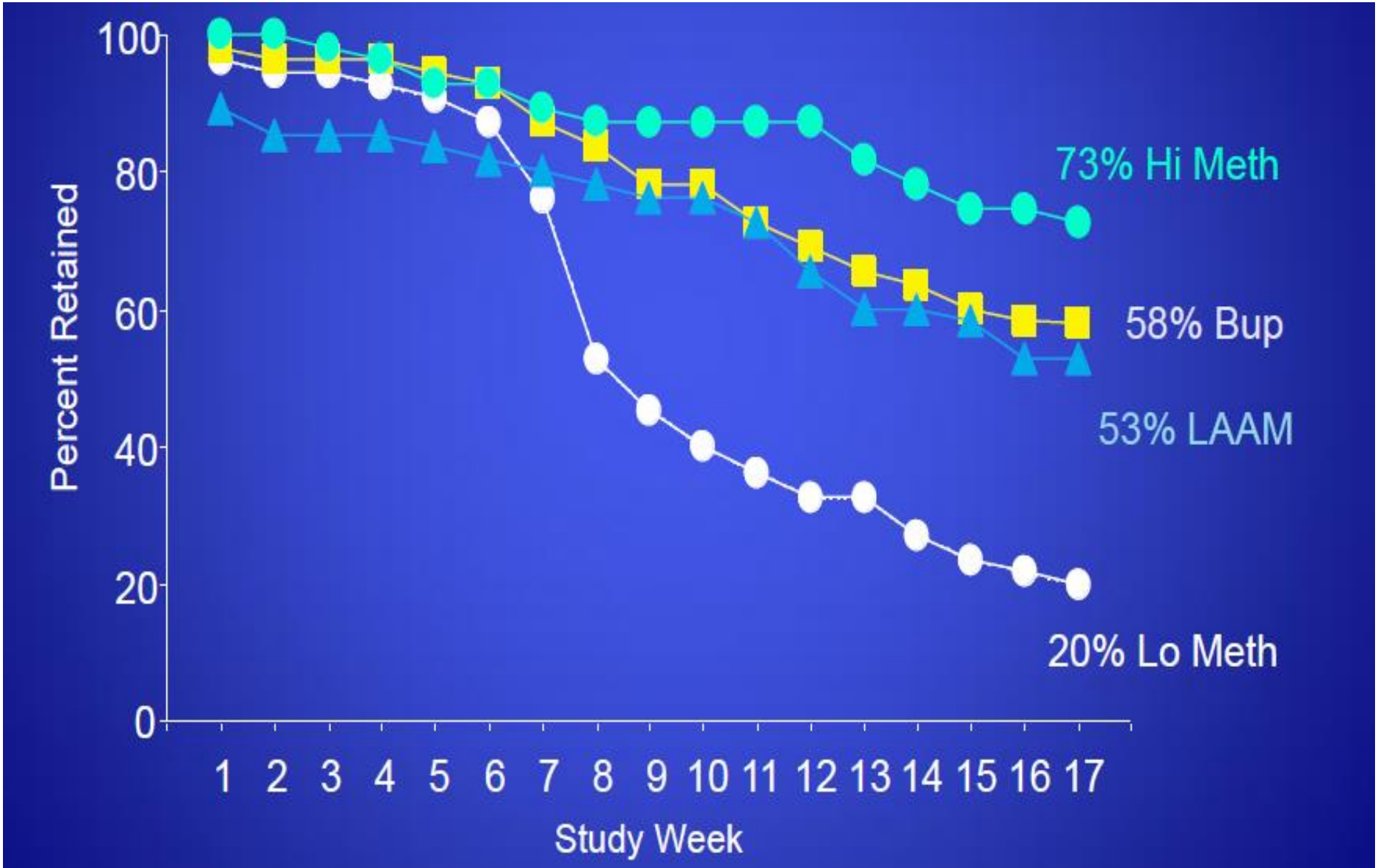
- 2000: Drug Abuse Treatment Act [DATA] made possible office based prescribing of schedule III opioids
- 2002: FDA approves long acting sublingual buprenorphine as schedule III opioid
- Drs required to have 8 hour special training and an X number
- Upto 30 patients 1st year, then may apply to treat upto 100 patients

Buprenorphine

- High affinity partial mu agonist and kappa antagonist
- Available as sl strips and tablets
- Two forms- mono [subutex], and combo [suboxone]: 4/1 ratio of bup:naloxone to reduce IV use
- Reduced opioid agonist effects, ceiling at 24-32 mg; less respiratory suppression
- Half life 37 hrs
- Dosing 8-32mg/d
- Can precipitate withdrawal
- Absorption (poor oral)
- Metabolized by CYP 3A4 system

Benefits of Office-Based Treatment

- Private, confidential, and safe treatment provided in a doctor's office
- Allows for continuity of care with primary physician
- Does not require daily visits to a clinic or out-of-town, costly residential treatment
- May allow more patient time for work, family and other activities
- Improved access



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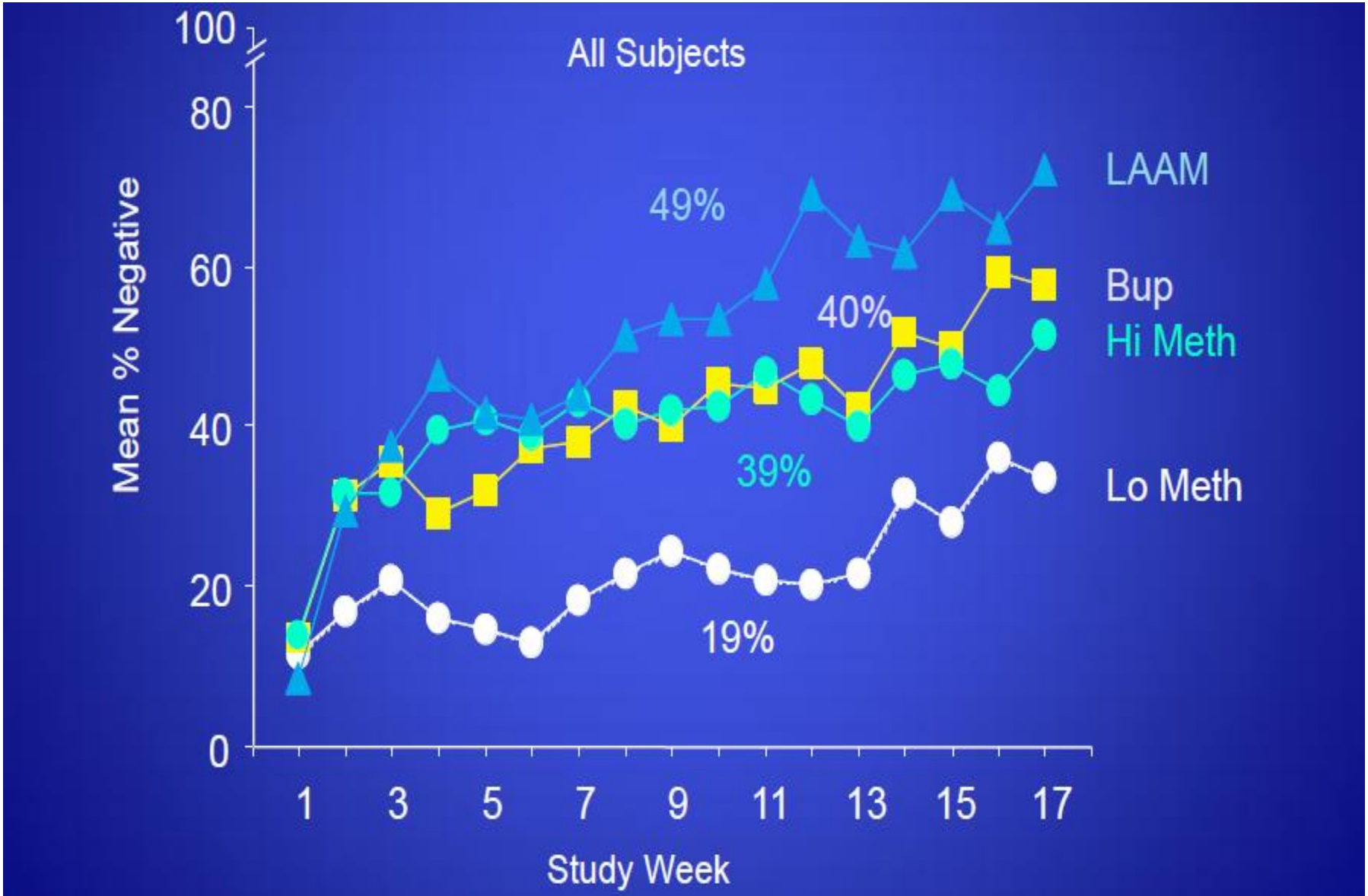


Johnson RE, et al. A Comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. NEJM 343:1290-7, 2000

Cochrane Review

- Meta analysis of 8 studies through 2006
- N = 1068
- Methadone more likely than bup to retain patients [RR 0.85; 95% CI 0.73-0.98]
- No significant differences in opioid use by UA
- [Mattick et al., 2008]

Induction: home vs office based!

- Tip 40 allowed for office based induction only
- However, recent studies have shown potential safety of home based inductions
- No difference in completion of induction [Alford et al., 2007]
- Cunningham et al., JSAT 2011, 40: 349-356
  - 84% chose home based induction
  - NO significant difference in opioid use
  - GREATER reductions in any drug use

In office induction- day 1

- Instruct patients to abstain for 12-24 hours [48-72 hours if switching from methadone]
- Arrange transport home
- COWS of greater than or equal to 12 [withdrawal]
- 1st dose 4 mg bup/ntx
- Reassess 1 hour
- Ok to give another dose if still in withdrawal
- General max dose 1st day: 8-12 mg

In-office induction day 2-3

- Phone contact ok
- Assess how patient did
- OK to increase dose by 4 mg if previous day’s dose inadequate

Home induction

- Lee et al., Gen Int Med 24: 226-232 [2008]
  - Up to 12 mg on day 1
  - 73% completed week 1
  - 5% had mild-moderate precipitated withdrawal
  - 8% had unrelieved prolonged withdrawal [21% who were switching from methadone]
  - Pts with withdrawal just as likely to follow up at week 1

Home Induction

- Teach proper administration
- Teach what symptoms of withdrawals are
- Prescribe only 1 week supply at 16 mg max dose
- Pt monitors for withdrawal
- When in withdrawal, self-administers 4 mg
- May repeat q 1 hrs until total max dose of 12 mg on day 1
- On day 2, phone contact, and may go upto 16 mg

Induction Trouble shooting

- If pt not in withdrawal, generally safest to provide adjunctive meds and re-assess next day

- Precipitated withdrawal:
  - Stop and give comfort meds
  - Continue on with induction- additional dose is not likely to worsen withdrawals, plus it may protect patient in case they use illicit opiates through greater mu receptor blockade, bup will take over after about 3 hours

Maintenance

- ONCE daily dose in most cases when using for addictions
- Doses greater than 16 mg rarely indicated
- 16 mg bup decreased mu opioid availability by 85-92%, and 32 mg decreased it by 94-98% [Greenwald et al., Neuropsychopharm 28: 2000-2009; 2003]

Other tips

- No more than 2 tabs/strips at once under the tongue
- Pregnancy test monthly
- If pregnant, switch to buprenorphine mono-product
- UDS initially weekly, but at least monthly
- PMP monitoring
- Counseling!! [MI, network therapy, drug counseling, CBT, 12 step]
- Collaboration of care
- Treatment of co-occurring illnesses

In case of positive drug screens

- Do not D/c treatment in case of 1, or even several positive urine drug screens
- Increase intensity/frequency of counseling
- Reduction in take home doses
- Raising the dose if ongoing opioid use
- Consider switching to higher structure- OTP, methadone

Strategies to minimize diversion

- Is the person appropriate for office based treatment?
- Open discussion of diversion concerns
- Treatment agreement
- UDS randomly
- PMP monitoring
- Counseling weekly
- Initial weekly scripts-increase to monthly as patient does well
- Use a therapeutic dose
- Random pill counts
- Enlist aid of pharmacists!!
- Consider lock boxes
- Contingency management principles

Training Resources

- PCSS B: http://www.pcssb.org/_training and mentoring program focused on increasing access to treatment for opioid dependent patients.

- PCSS O: http://www.pcss-o.org/_mentoring, webinars

- PCSS-B has patient/family information, screening forms, tx agreements, 42 CFR compliant consent forms, COWS

NALTREXONE

Naltrexone: Potential Benefits

1. Orally Effective
2. Rapid onset of action
3. Long duration of action
4. Safe
5. Few side effects
6. Completely blocks effects of heroin
7. Non-addicting
8. No tolerance
9. No dependence
10. No withdrawal

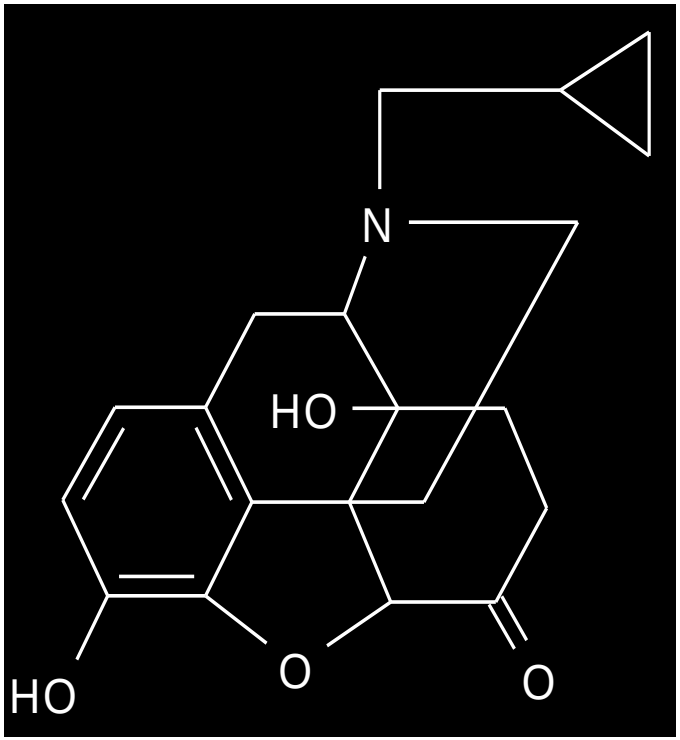


Figure 2-1. Conceptual Representation of Opioid Effect Versus Log Dose for Opiod Full Agonists, Partial Agonists and Antagonist*

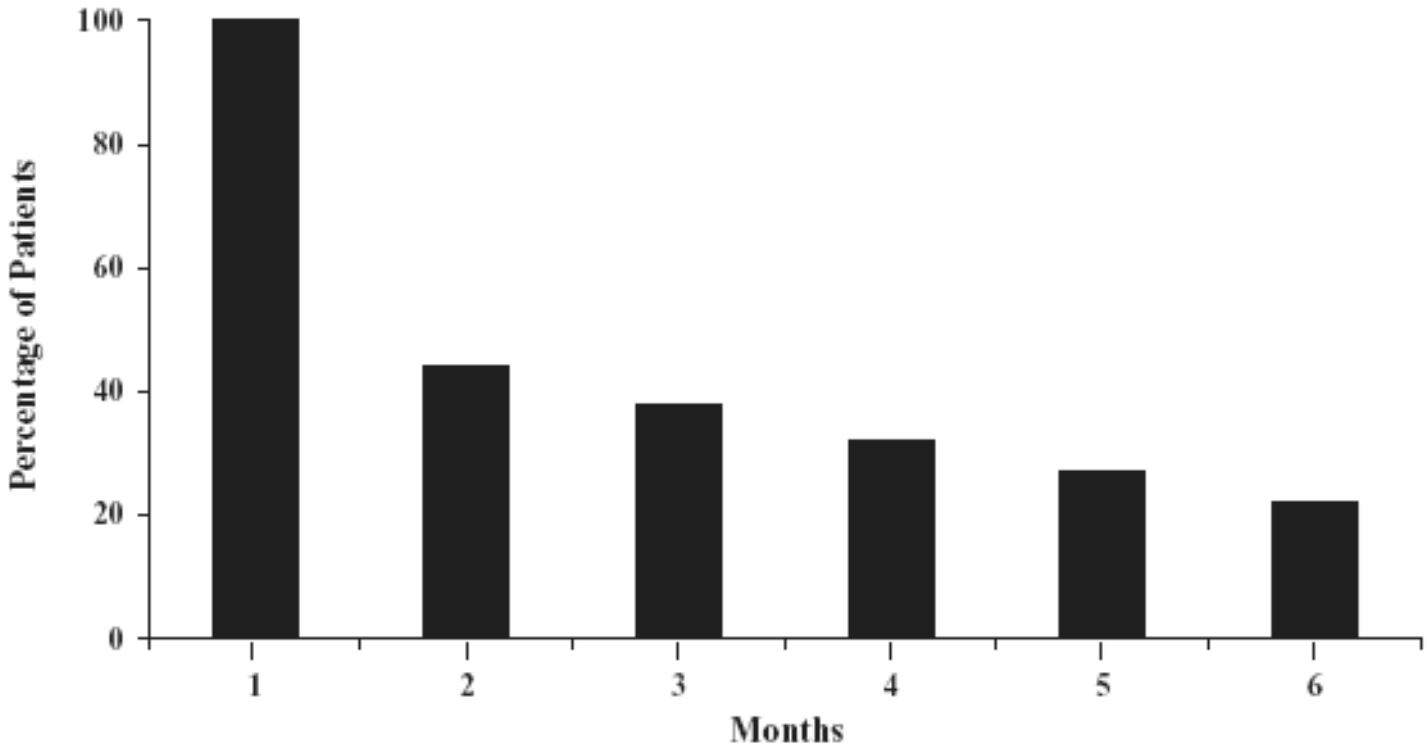
FDA Approval

- 1984: FDA approves Naltrexone as a treatment for heroin addiction

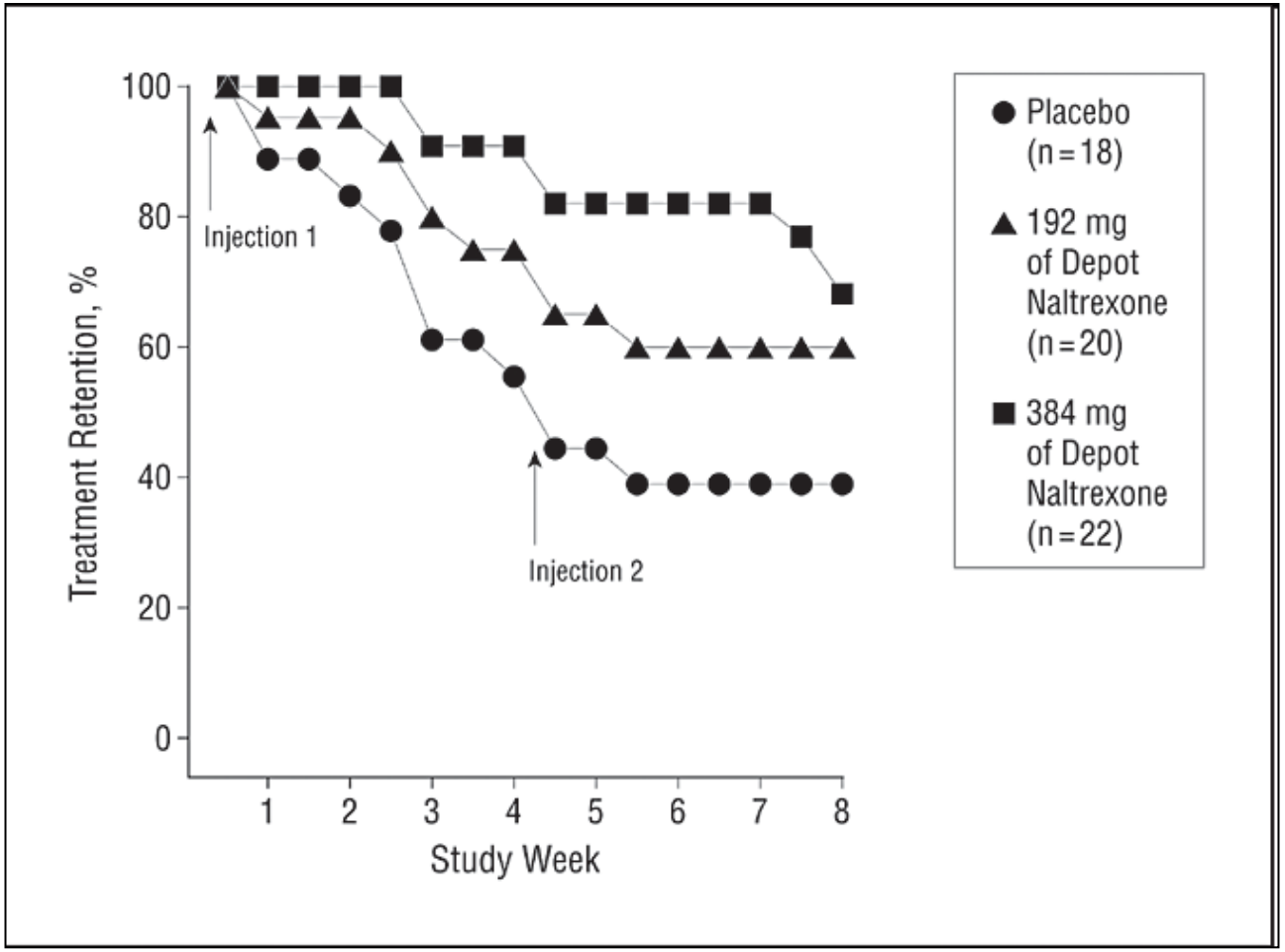
- Marketing issues become problematic
  - Difficult to convince patients to use medication
  - Resistance on part of methadone clinics - cost
  - fails to impact treatment community in a significant way

Oral Naltrexone Retention Rates

Kranzler et al., Addiction 2008[4]

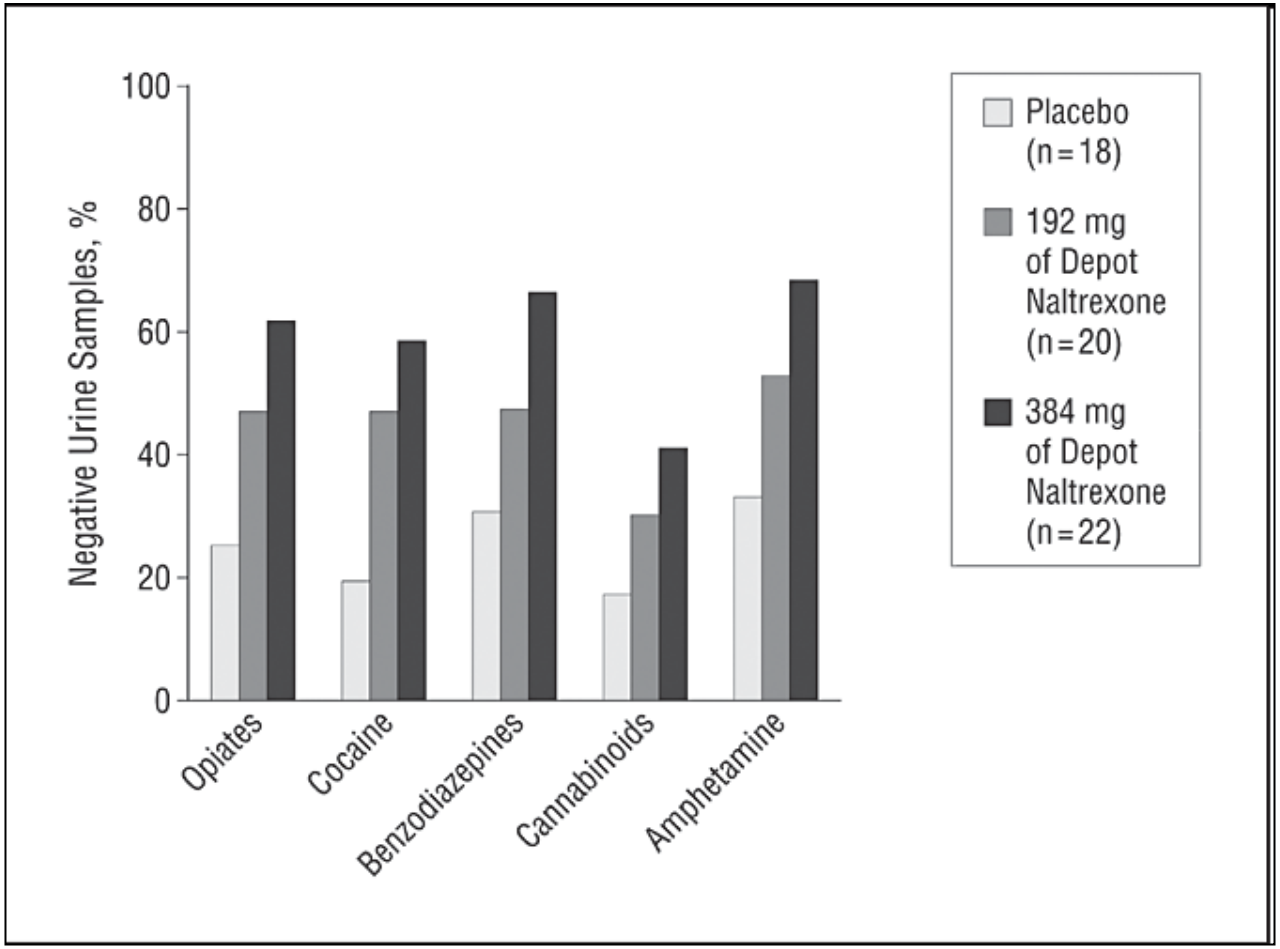


XR-NTX Opioid Treatment, Comer 2006: better retention, less relapse to sustained opioid use



XR-NTX Opioid Treatment, Comer 2006: Less opioid and other drug use

Urine Toxicology Results

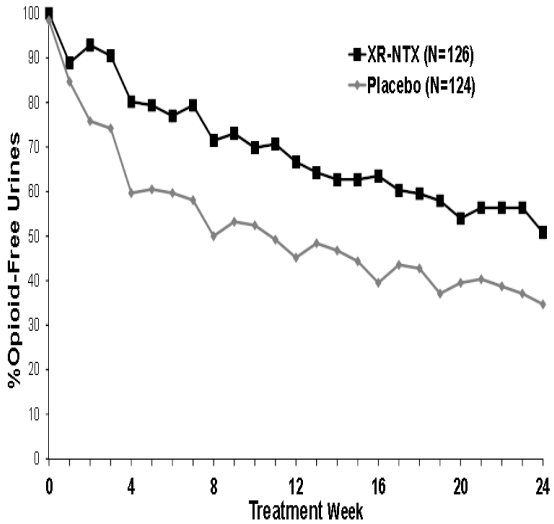


XR-NTX Opioid Treatment Pivotal Trial: Krupitsky 2010 (APA 2010, FDA 2010)

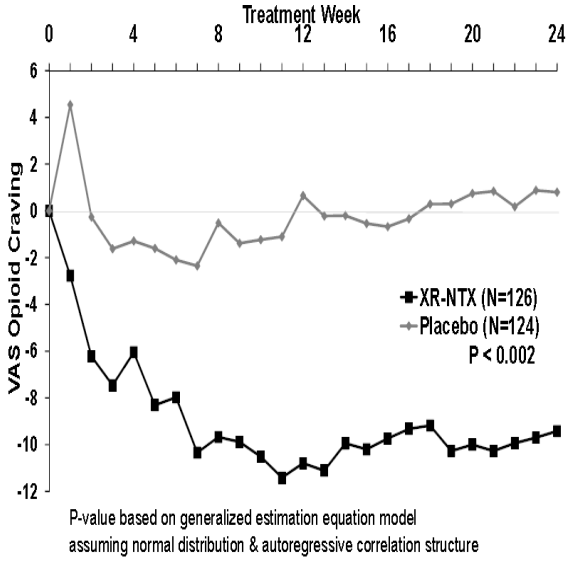
- 24 week double-blind, placebo-controlled, randomized trial following inpatient detox, N=250
- Russia, no agonist TAU alternative
- Clear superiority vs. placebo at preventing lapses and sustained relapse/dependence
- No ODs or deaths
- FDA approval of XR-NTX for opioid dependence Oct 2010

XR-NTX : The Russian study
Key Efficacy Outcomes

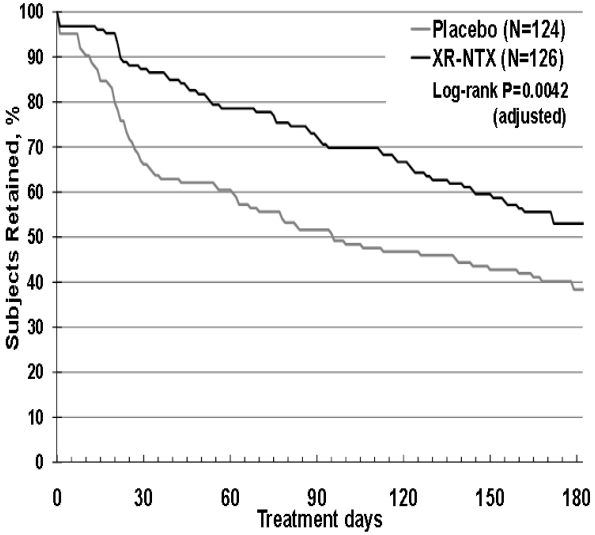
3A. % Opioid-Free Urines by Week (Kaplan-Meier)



3B. Mean Change From Baseline in Craving



3C. Time-to-Discontinuation



Key findings

- **The median proportion of weeks of confirmed abstinence was 90·0% (95% CI 69·9–92·4) in the XR-NTX group compared with 35·0% (11·4–63·8) in the placebo group (p=0·0002).**

- **Patients in the XR-NTX group self reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004).**

- **Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0·0042).**

Safety points

- **XR-NTX** is contraindicated in patients receiving opioid analgesics or with current physiologic opioid dependence, patients in acute opiate withdrawal, any individual who has failed the naloxone challenge test or has a positive urine screen for opioids
- **XR-NTX** patients must be opioid free for a minimum of 7-10 days before treatment. [Per industry]
- Attempts to overcome opioid blockade due to **XR-NTX** may result in a fatal overdose.
- In prior opioid users, use of opioids after discontinuing **XR-NTX** may result in a fatal overdose because patients may be more sensitive to lower doses of opioids

Hepatic Concerns

- a black box warning for hepatotoxicity (causes liver damage).
- does not appear to be a hepatotoxin at the recommended doses.
- In the **XR-NTX** Phase III clinical trial, mean AST and ALT levels did not change significantly over the course of treatment or with medication.
- AST elevation [reversible] in 1.5% vs 0.9% placebo

Emergency pain management

- Patients should be advised to carry a patient alert card that informs medical personnel they are taking **XR-NTX**

- A suggested plan for pain management is:
  - Regional analgesia
  - Use of non-opioid analgesics

- In an emergency situation requiring opioid analgesia, the amount of opioid required may be greater than usual and the resulting respiratory depression may be deeper and more prolonged
  - Such patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure
  - The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation

- A rapidly acting opioid analgesic that minimizes the duration of respiratory depression is preferred

- Patients should be closely monitored by trained personnel in a setting equipped for cardiopulmonary resuscitation.

Do I really need to wait 7-10 days?

- In reality, probably not
- Protocol at Columbia University
  - Day 0: Give bupreorphine 8 mg
  - Day 1: nothing
  - Day 2: oral naltrexone 1-3 mg
  - Day 3: Oral naltrexone 12.5 mg
  - Day 4: Oral naltrexone 25 mg
  - Day 5: Vivitrol injection

Psychosocial Interventions

- Combining psychosocial treatment with medication alone results in:
  - Better treatment retention
  - Less opiate + urines
  - Higher likelihood of abstinence at follow-up
  - Better clinic attendance

Prevention: syringe exchange programs

- HIV testing/counseling, public funding, and expansion of needle exchange programs in NY city led to significant reductions in risk behaviors and HIV incidence among IVDU who participated [Des Jarlais et al., 2000]
- Syringe programs also provide other services- links to tx, counseling and health services
- Education about high risk behaviors is an essential component of these programs [NIDA, 2002]
- NOT associated with increase in initiation, duration, or frequency of IVDU

ADDITIONAL TREATMENT COMPONENTS

Psychosocial Interventions

- Combining psychosocial treatment with medication alone results in:
  - Better treatment retention
  - Less opiate + urines
  - Higher likelihood of abstinence at follow-up
  - Better clinic attendance
  - *Little data to support the use of psychosocial interventions alone in opioid dependence*

Psychosocial interventions

- Twelve step
- Individual and group therapy
- Family therapies
- Network therapy with naltrexone
- CBT
- Motivational interviewing
- Contingency management VERY useful [eg: take home doses]
- Random urine toxicology screening

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Possible role of integrated clinics

- Daily contact with patients in a methadone clinic
- On-site medical care at methadone clinics is associated with better rates of treatment seeking in:
  - Primary care [92% vs 35%]
  - Tuberculosis directly observed treatment completion
  - HIV treatment
  - 81% of IVDU patients voluntarily used on-sire primary care services, with care being used more by HIV positive patients

Conclusions:

- **Opioid dependence is destructive**
- **Treatment helps!**
- **Addiction is a chronic illness, and requires chronic treatment**
- **Treat the whole person!**