MEDICATION ASSISTED TREATMENT- SAFE PRESCRIBING

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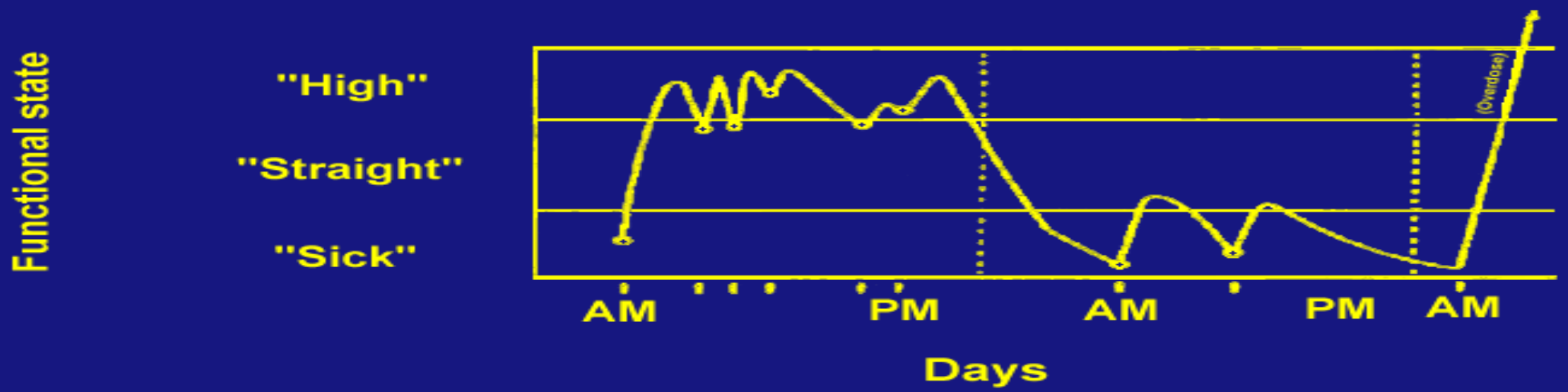
4/21/2018

LEARNING OBJECTIVES

1. Analyze medication options for MAT regimens.
2. Evaluate MAT regimens for individual patients.

WHAT THE OPIOID DEPENDENT PATIENT FEELS…



Diagrammatic summary of functional state of typical "mailine" heroin user. Arrows show the repetitive injection of heroin in uncertain dose, usually 10 to 30 mg but sometimes much more. Note that addict is hardly ever in a state of normal function ("straight").

From "Narcotic Blockade," by V. P. Dole, M. E. Nyswander, and M. J. Kreek, 1966, Archives of Internal Medicine, 118, p. 305.

Dole, Arch Int Med, 1966

THE OPIOID DISEASE PROCESS

- Repeated exposure to short acting opioids leads to neuronal adaptations
  - Meso-limbic dopaminergic system
    - adaptations in G protein-coupled receptors
    - up regulation of cyclic cAMP second messenger pathway
- These changes:
  - Mediate tolerance, withdrawal, craving, administration
  - Basis of specific pharmacotherapies to stabilize neuronal circuits

RATIONALE FOR OPIOID REPLACEMENT THERAPY

- Reduces drug use
  - Total amount used
  - Number of days/month used
  - Number of weeks with any drug use
- Stabilize neuronal circuitry
  - Mu occupation/blockade
  - Cross-tolerant, long-acting, oral
- Prevent withdrawal and craving
- Extinguish compulsive behavior
- Prevent spread of HIV and HCV
- Prevent criminal activity

STABILIZATION BY BLOCKADE TREATMENT

Stabilization of patient in state of normal function by blockade treatment.
A single daily oral dose of methadone prevents him from feeling symptoms of abstinence ("sick") or euphoria ("high"), even if he takes a shot of heroin.
Dotted line indicates course if methadone is omitted.

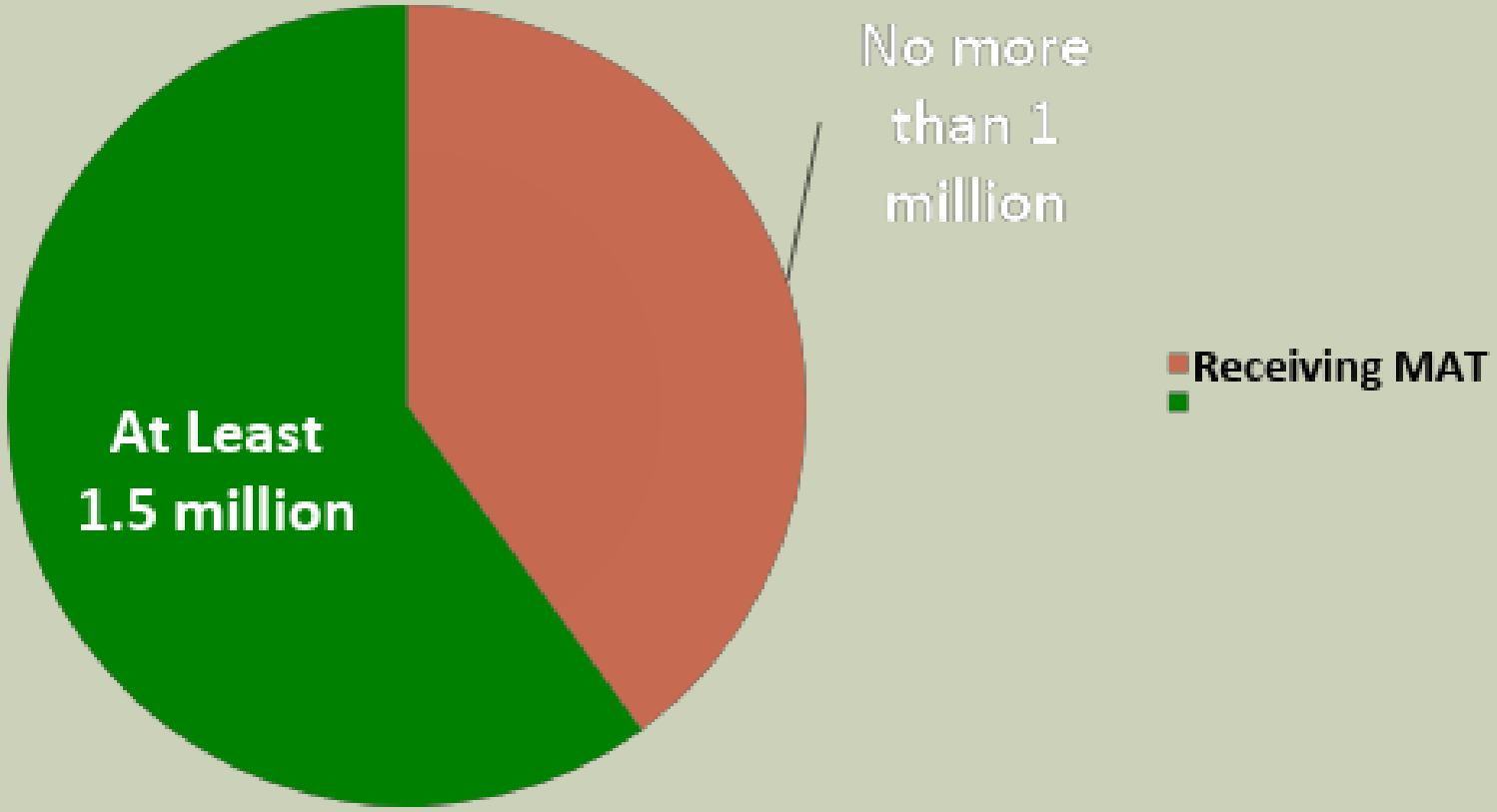
From "Narcotic Blockade," by V. P. Dole, M. E. Nyswander, and M. J. Kreek, 1966, Archives of Internal Medicine, 118, p. 305.

TREATMENT OPTIONS FOR OPIOID USE DISORDERS

- Self-help groups
- Detoxification +/- Medication Assisted Treatment (MAT)
- Outpatient treatment +/- MAT
- Residential treatment +/- MAT

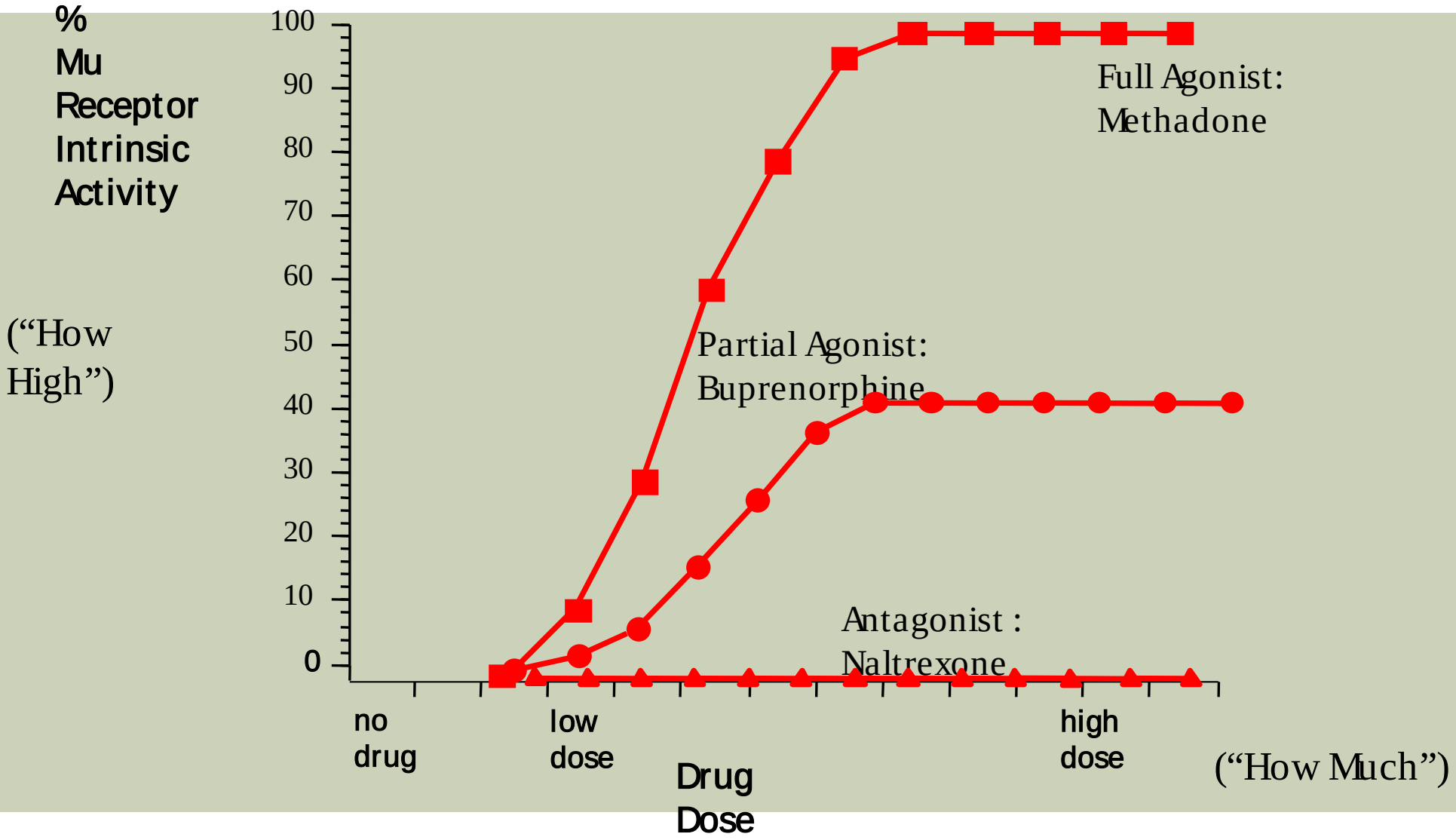
- MAT = Methadone, Buprenorphine, or Naltrexone

MOST PEOPLE WITH ADDICTION ARE NOT RECEIVING MEDICATION-ASSISTED TREATMENT



Volkow et al. NEJM 2016;370:2063-2066.

OPIOID ACTIVITY LEVELS



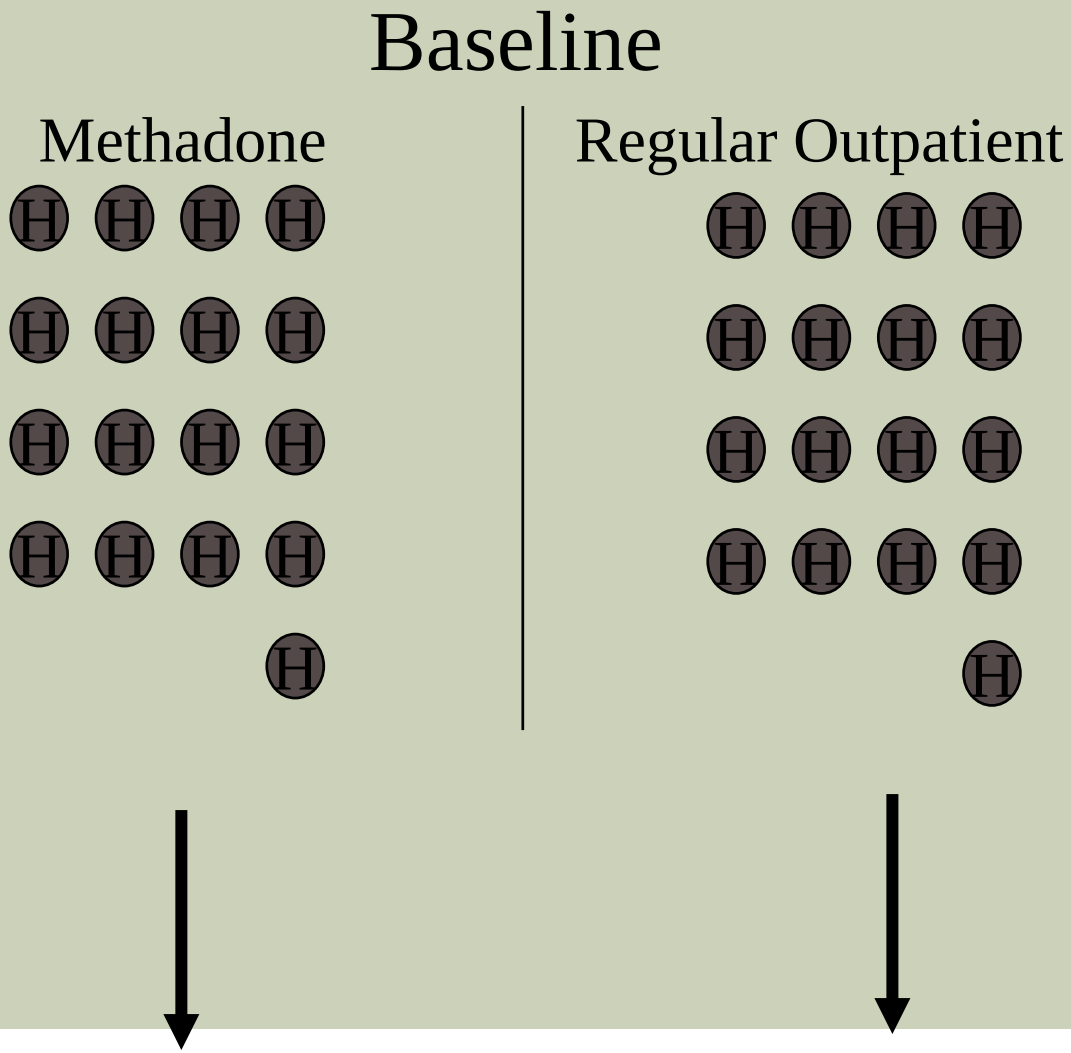
METHADONE MAINTENANCE THERAPY

- Full agonist with long elimination half-life
- Once daily dispensing
- Reduces euphoria of subsequent opioid use
- Typical effective dose range 60-90mg/day*
- Contingency management – Take home doses (NTE 28 days)
- Integrated individual and group counseling

*higher for pregnant patients

METHADONE EFFECTIVENESS

GUNNE & GRONBLADH, 1984



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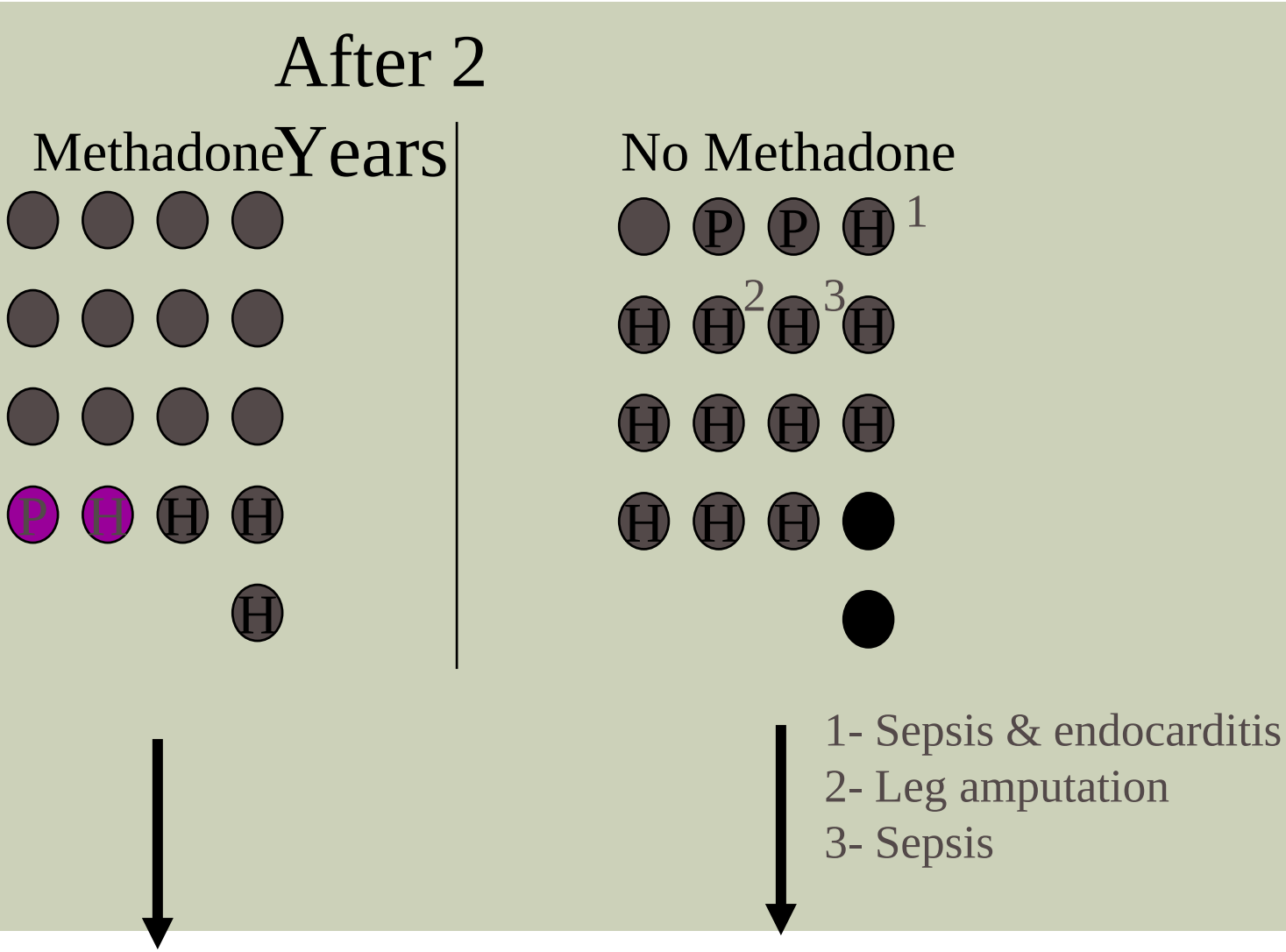
GUNNE & GRONBLADH, 1984



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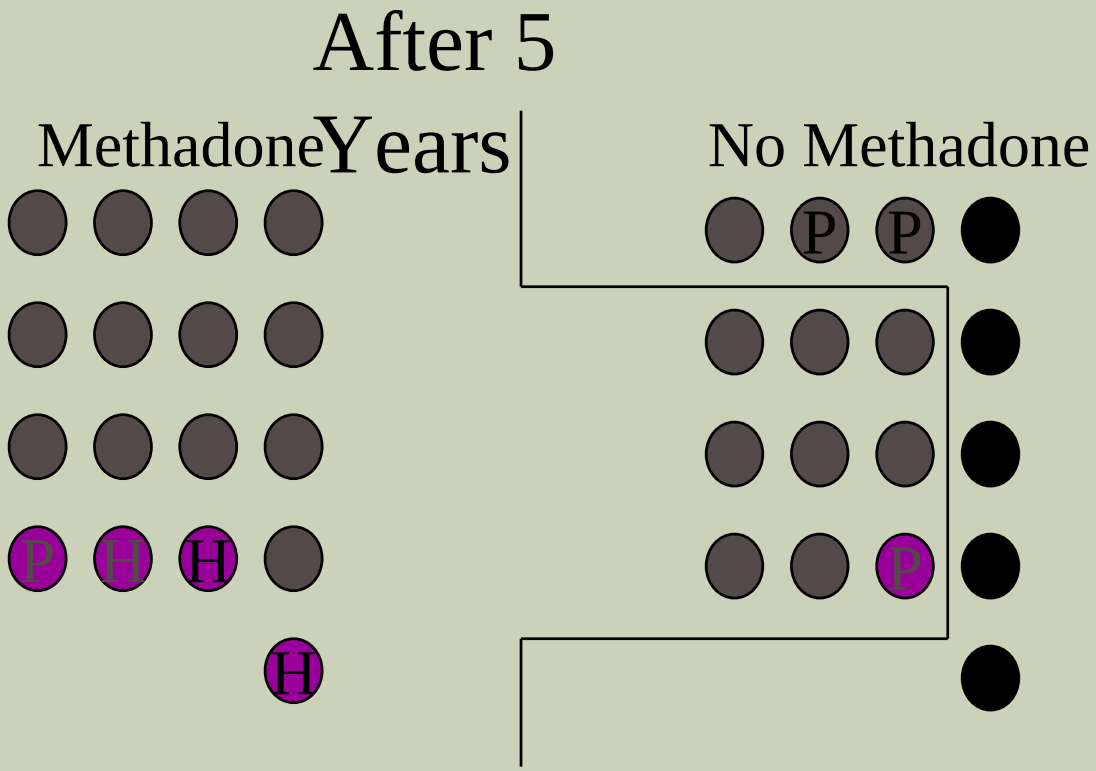
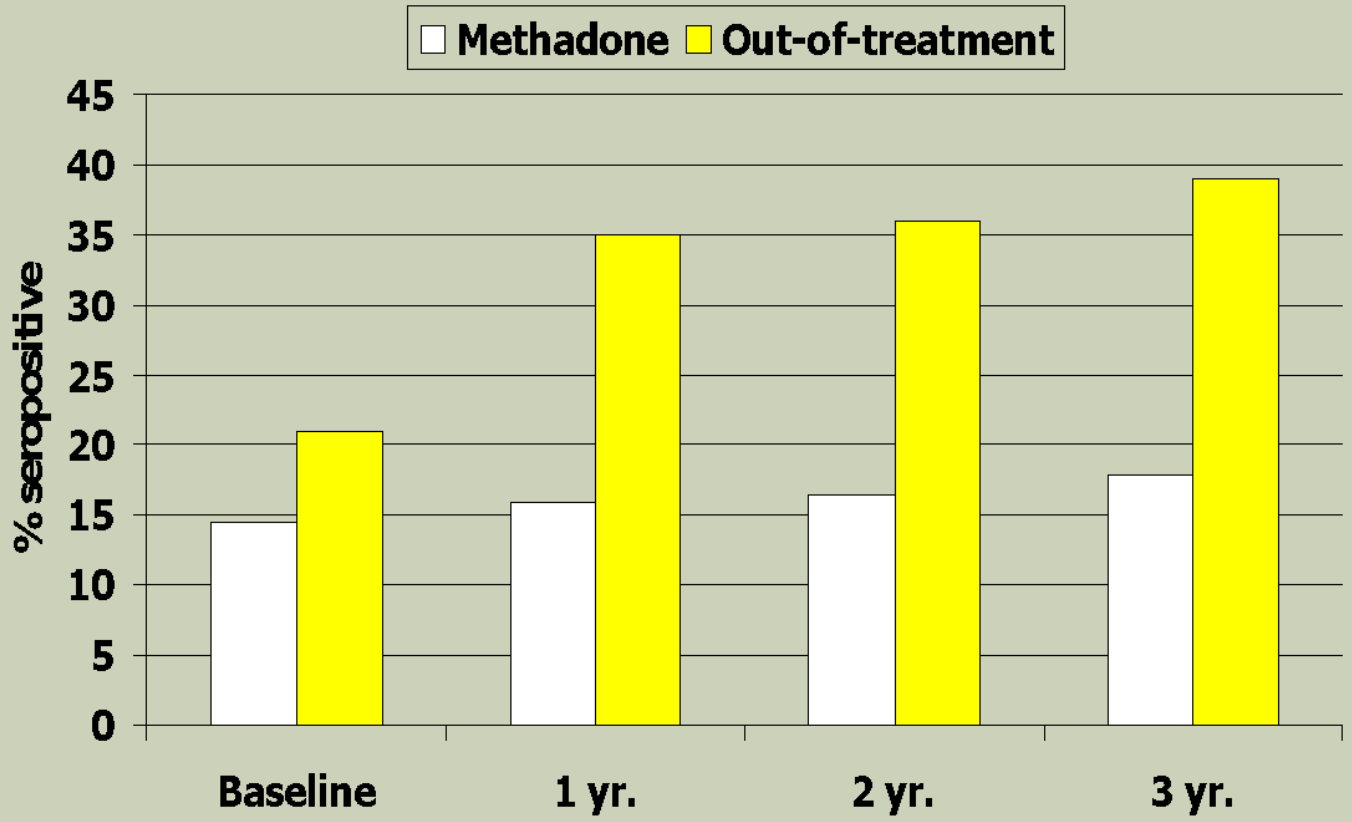


METHADONE TREATMENT DECREASES HIV SEROINCIDENCE

METZGER ET AL. J AIDS 1993;6:1049.



METHADONE: PROS/CONS

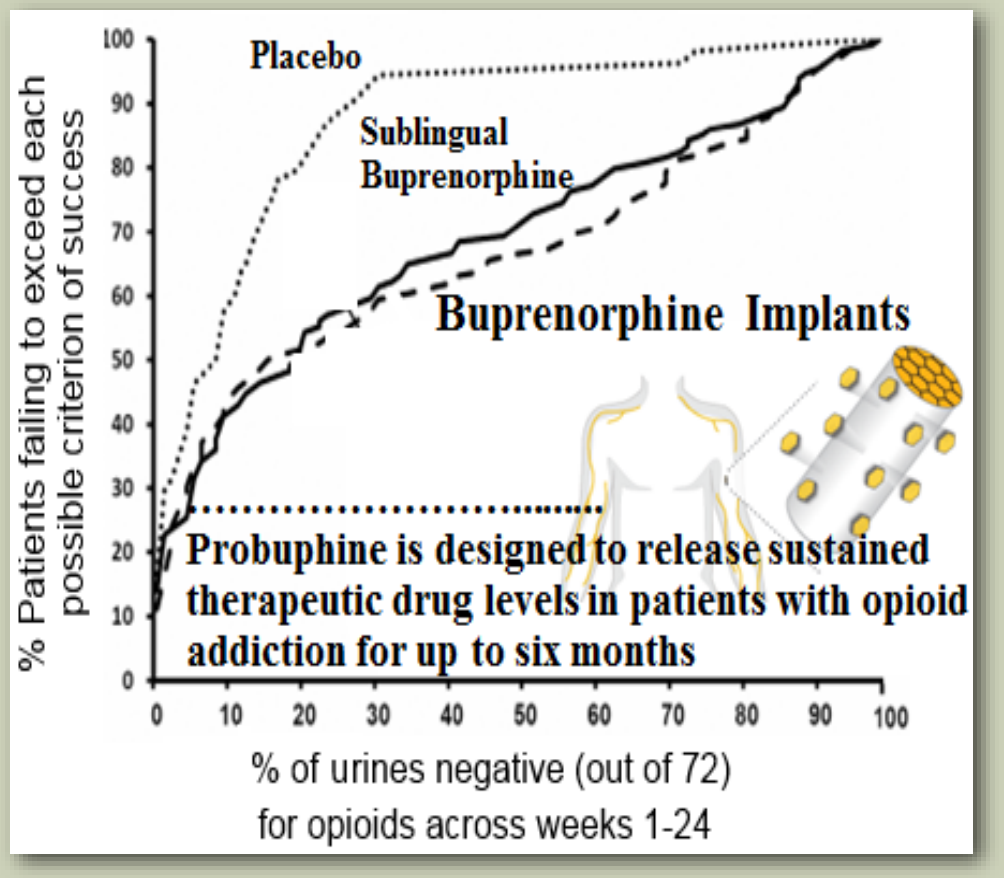
- Pros
  - Increased retention in treatment
  - Decreased opioid use
  - Decreased HIV transmission
  - Highly structured treatment
    - Psychiatric comorbidity
    - Polysubstance use
    - Frequent relapses
  - Some analgesic benefit*
- Cons
  - QTc prolongation
  - High overdose risk
  - Many drug-drug interactions
    - Benzodiazapines
    - HIVmeds
    - Seizure medications
  - Polysubstance use
  - Daily dosing

BUPRENORPHINE (SUBUTEX™) / NALOXONE (SUBOXONE™) (4:1 COMBINATION)

- Partial opioid agonist (plateau effect)
- Long half-life
- Typically once daily, but BID or TID is safe
- 24mg usually the highest effective dose
- Less euphoric effect than other opioids
- Paired with antagonist (naloxone) to prevent abuse through injection
- Office based prescribing with DEA waiver or "Xlicense"
  - One day or online training
  - Treat up to 30 patients first year, then up to 100 patients

BUPRENORPHINE IMPLANTABLE

- Implanted buprenorphine may improve compliance
  - Trial: buprenorphine implants vs. placebo for 6 months



Rosenthal et al., Addiction 2013;105.

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Buprenorphine Diversion

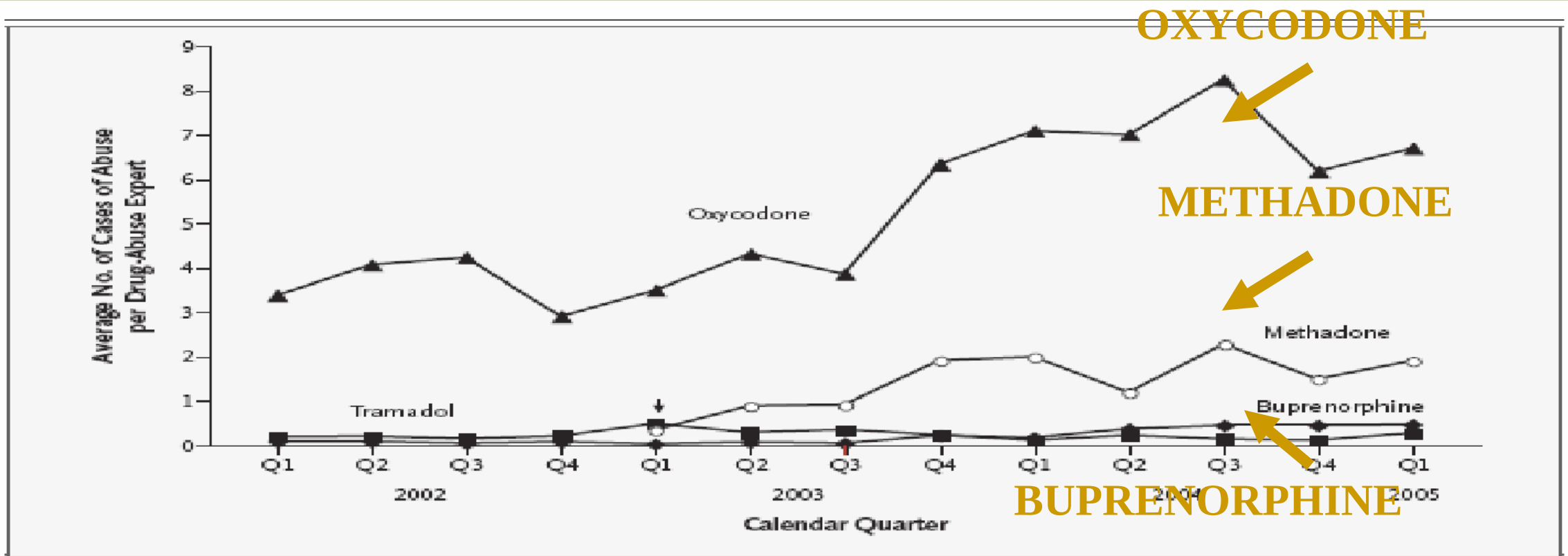


Figure 1. Average Number of Cases of Abuse of Buprenorphine Products, Methadone, Tramadol, and Oxycodone per Drug-Abuse Expert.
The arrow indicates the launch date of buprenorphine for use in office-based treatment of opioid dependence. Q denotes quarter.

Cicero, NEJM 2005

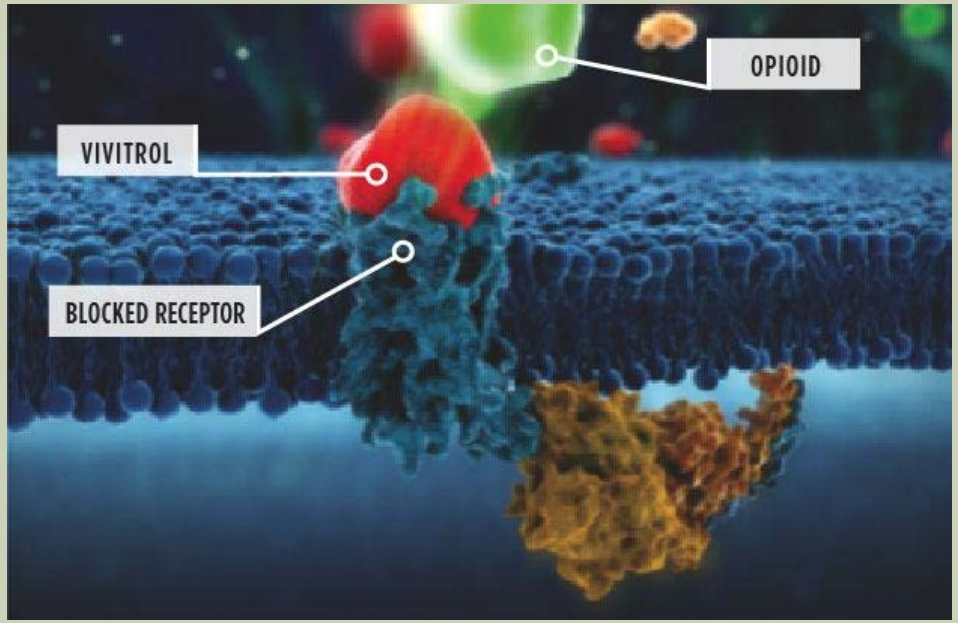
BUPRENORPHINE: PROS/CONS

- Pros
  - Effective for pain and OUD
  - Increased retention in treatment
  - Low overdose risk
  - Office-based prescribing (OBOT)
  - Minimal drug interactions
    - Except benzos, etoh
  - No cardiac toxicity
  - Less neonatal abstinence syndrome compared to methadone
- Cons
  - Training required to prescribe
  - Cost
  - Can complicate pain treatment
  - Potential for precipitated withdrawal
  - Can be diverted

NALTREXONE: OPIOID ANTAGONIST

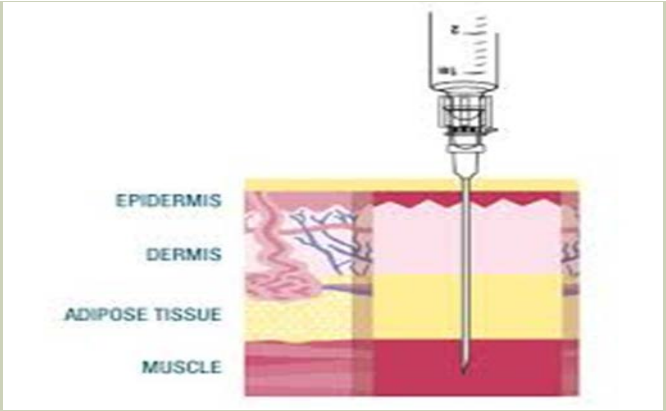
Two formulations approved in US
Oral Naltrexone (1984), 50mg once daily
Extended Release Naltrexone, (2010) Q 28 days

Blocks all Opioid receptors
Not controlled
Blocks euphoric effects of opioids
Also treats alcohol dependence
ER Naltrexone has important use in criminal justice



XR-NALTREXONE FOR OPIOID USE DISORDER

- Intramuscular injection lasts 28d
- Efficacious compared to placebo:
  - Comer: 60 U.S. heroin users at 8 weeks[1]
  - Krupitsky: 250 Russian heroin users at 24 wks[2]
    - Naltrexone ER: 45 (35.7%) vs Placebo 25 (22.8%)
    - RR 1.58, 95% CI (1.06 – 2.36), p = 0.0224
    - NNT 7.8
    - Fair quality study, high attrition, young white males only



[1] Comer Arch Gen Psych 2006, [2]Krupitsky Lancet 2011, [3] Wang J Leuk Bio 2006, [4] Gekker Drug Alc Dep 2001, [5] Quin J Cell Biochem 2011

Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders

Primary Outcome:
Median Time to Relapse
10.5 vs 5 wks
HR 0.49
(95% CI 0.36-0.68)
P <0.0001

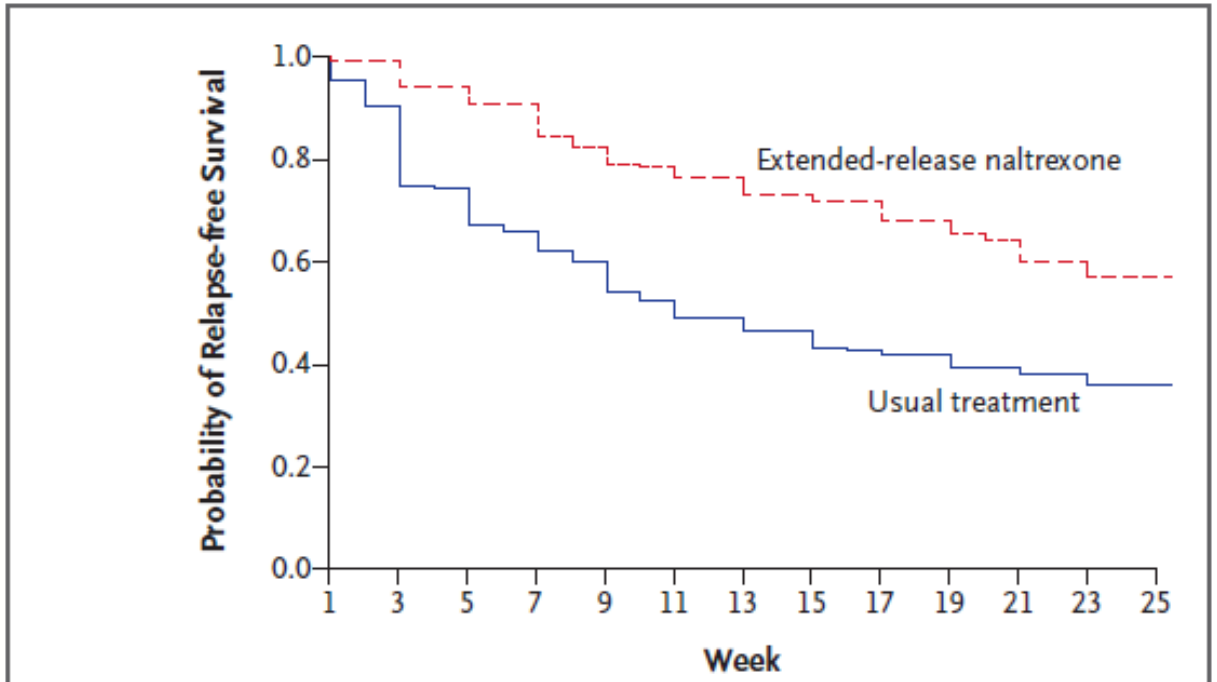
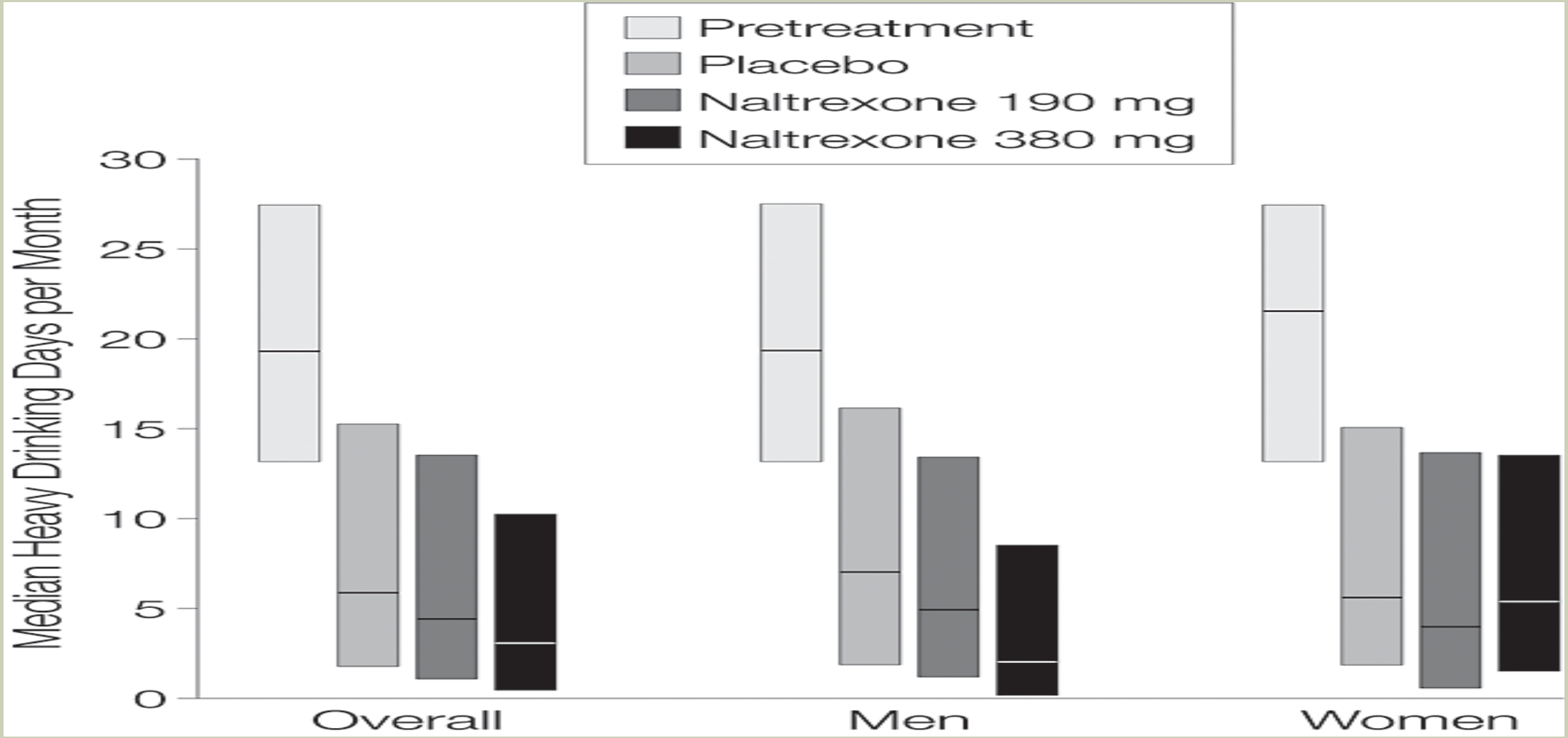


Figure 2. Kaplan–Meier Curves for Relapse-free Survival.

Lee, J, et al. NEJM, 374; 13. 2016

Median Heavy Drinking Days per Month for Each Treatment Group Overall and by Sex



Garbutt, J. C. et al. JAMA 2005;293:1617-1625.

NALTREXONE: PROS/CONS

- Pros
  - Not controlled
  - Treats etoh and opioid use disorders
  - No ability to feel effects of opioids
  - Few drug interactions
- Cons
  - Must be opioid free for 5-7 days
  - Can complicate pain treatment
  - May affect liver function
  - Pain at injection site
  - Cost
  - Overdose risk when dose wears off

METHADONE VS. BUPRENORPHINE

- Low dose Buprenorphine (2-6mg) was less effective than methadone in retaining people in treatment.

- Buprenorphine (>7 mg/day) was not different from methadone (≥40 mg/day) in retaining people in treatment or in suppression of illicit opioid use.

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014, Issue 2.

MEDICATION EFFICACY FOR OPIOID USE DISORDER

	Treatment Program Retention	Opioid Misuse	Criminal Activity
Methadone	↑ (n=3)[a]	↓ (n=6)[a]	No Effect (n=3)[a]
Buprenorphine	↑ (n=4)[b]	↓ (n=2)[b]	No effect (n=2) [a]
PO NTX	No effect (n=2)[c]	↓ (n=4)[c]	↓ (n=2)[c]
XR NTX	↑ (n=2)[d]	↓ (n=3)[d,e]	↓ (n=1)[e]

[a]Mattick RP, et al. Cochrane Database Syst Rev 2011;
[b]Mattick RP, et al. Cochrane Database Syst Rev 2013;
[c]Minozzi S, et al. Cochrane Database Syst Rev 2011;
[d]Krupitsky E et al. Lancet. 2011, Comer SD et al. Arch Gen Psychiatry 2006, [e]Lee J et al, NEJM, 2016.

TREATMENT RETENTION AND TAPERS

- There is no evidence for a pre-determined length of treatment

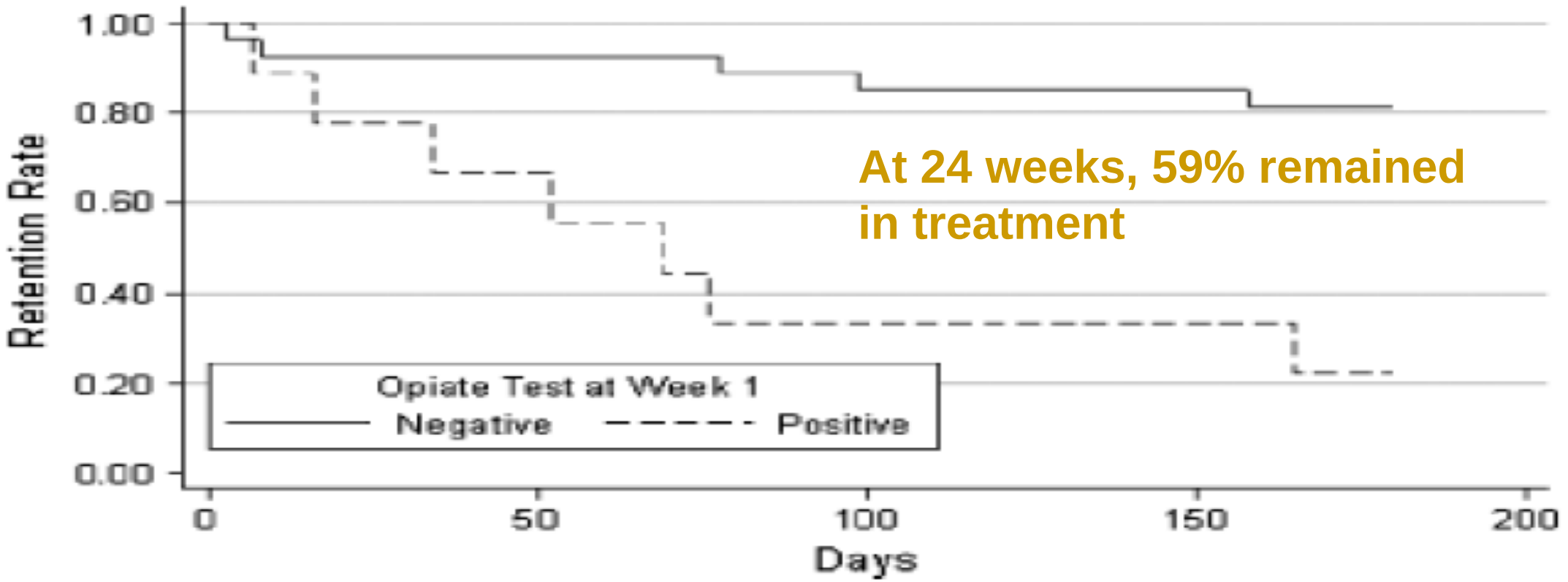
Longer Retention = Better Outcomes

- Patients benefit from MAT for a minimum >1-2 years of sobriety before attempting to taper, with dosing reassessments every 6 months
- Predictors
  - Not demographics alone
  - Age of initiation
    - Sometimes correlated with age of presentation to treatment
  - Addiction history severity
    - Length of severity (i.e. heroin use, injection history)
    - Premorbid functioning
  - Combination of counseling + MAT
  - Abstinence at the beginning of treatment

TAPERING

- **Typically patients with continuous sobriety for 1-2+ years have the best outcomes**
  - Treatment <6 months has worse outcomes
- **There is no evidence to support stopping MAT**
  - 95% of methadone patients do not achieve abstinence when attempting to taper off (Nosyk, et al. 2013)
  - Over 90% of buprenorphine patients relapse within 8 weeks of taper completion (Weiss, et al. 2011)
- **Successful patients are commonly maintained on**
  - Methadone for 24+ months, Buprenorphine for 18+ months

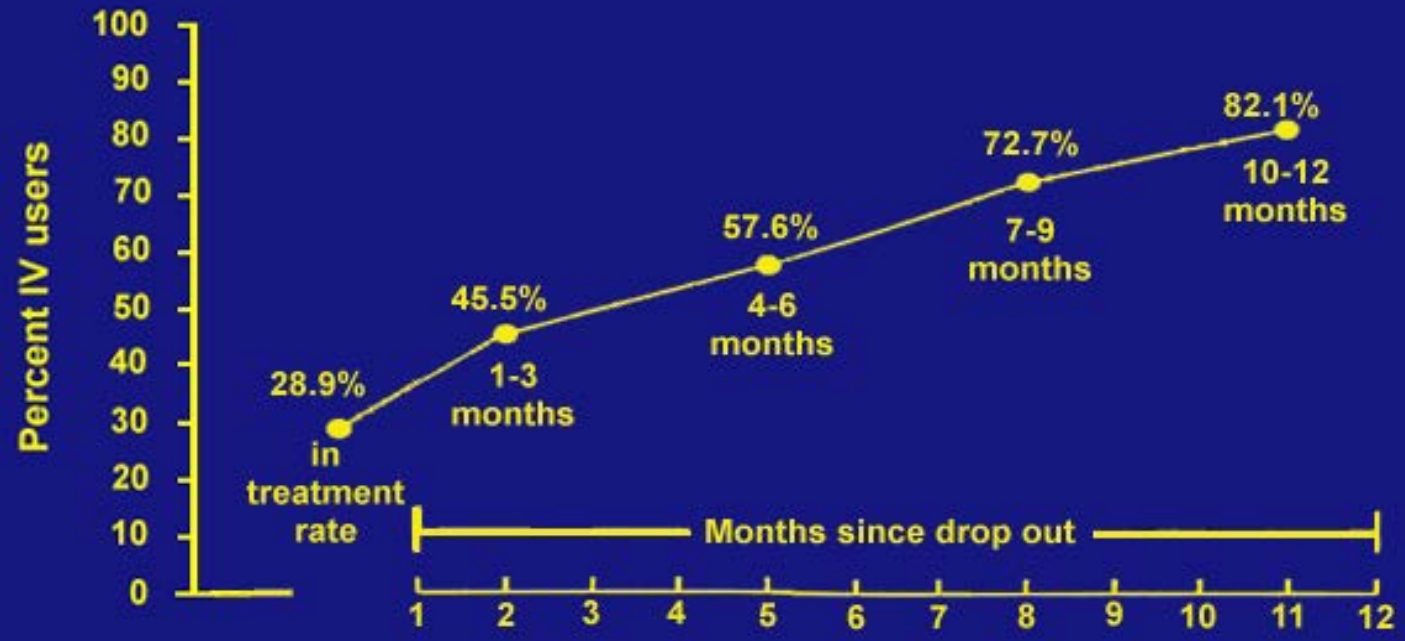
Opioid Dependence Treatment in Primary Care



At 24 weeks, 59% remained in treatment

FIGURE 1. Program retention time by week 1 opiate test.

Stein, JGIM 2005



Relapse to intravenous drug use after methadone maintenance treatment for 105 male patients who left treatment.

From the Effectiveness of Methadone Maintenance Treatment (p. 182). by J. C. Ball and A. Ross, 1991, New York: Springer-Verlag. Copyright 1991 by Springer-Verlag New York, Inc. Reprinted with permission.

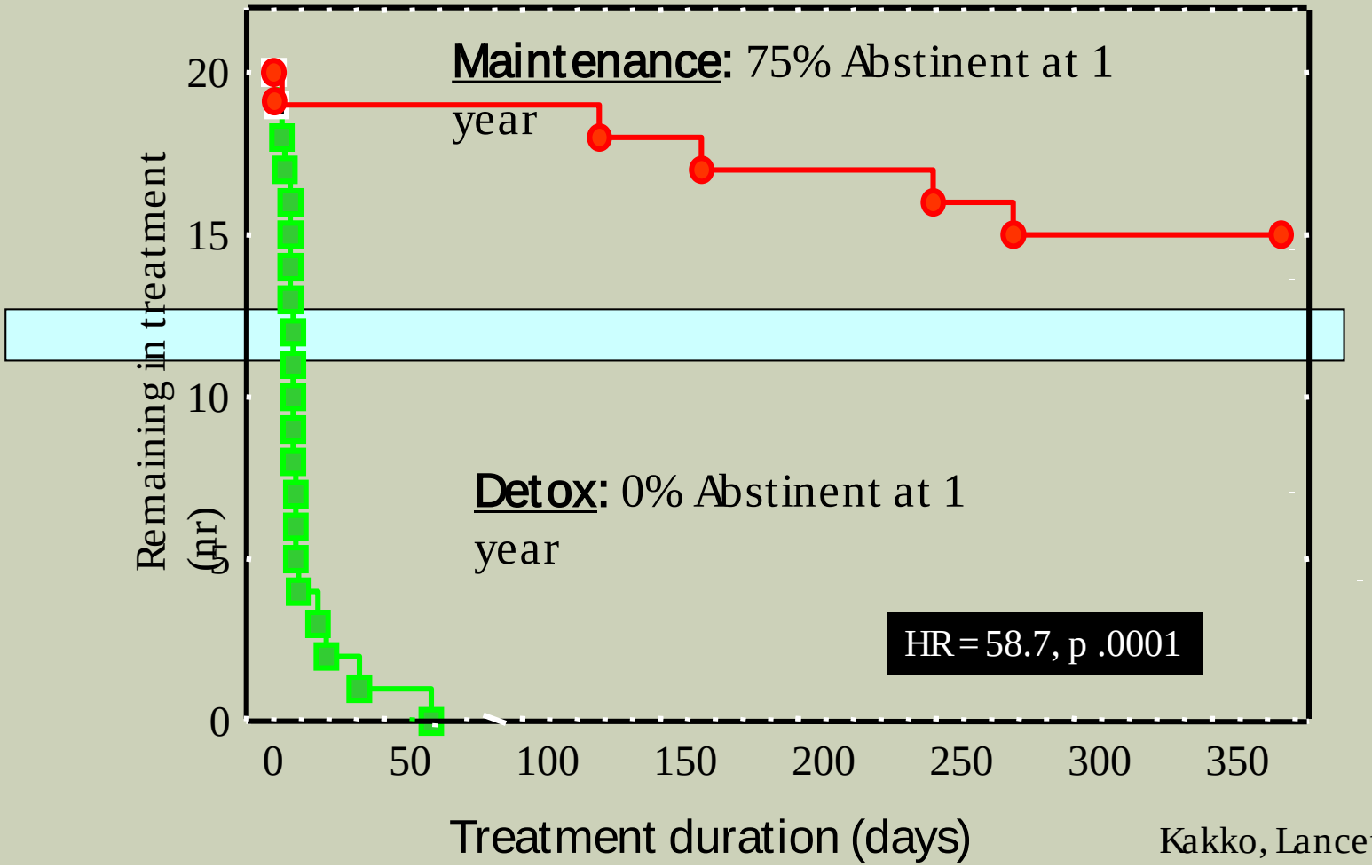
DETOX VS. MAINTENANCE: WHICH IS BETTER?

- Multi-site trial of buprenorphine/nx for 653 patients with prescription opioid use disorder in 10 primary care clinics
- Detox phase followed by maintenance phase for those who relapse
- "Success" = minimal or no use on UDS &self-report

Success at 12 Weeks:	
Detox Phase:	**6.6%**
Maintenance Phase:	**49.2%**

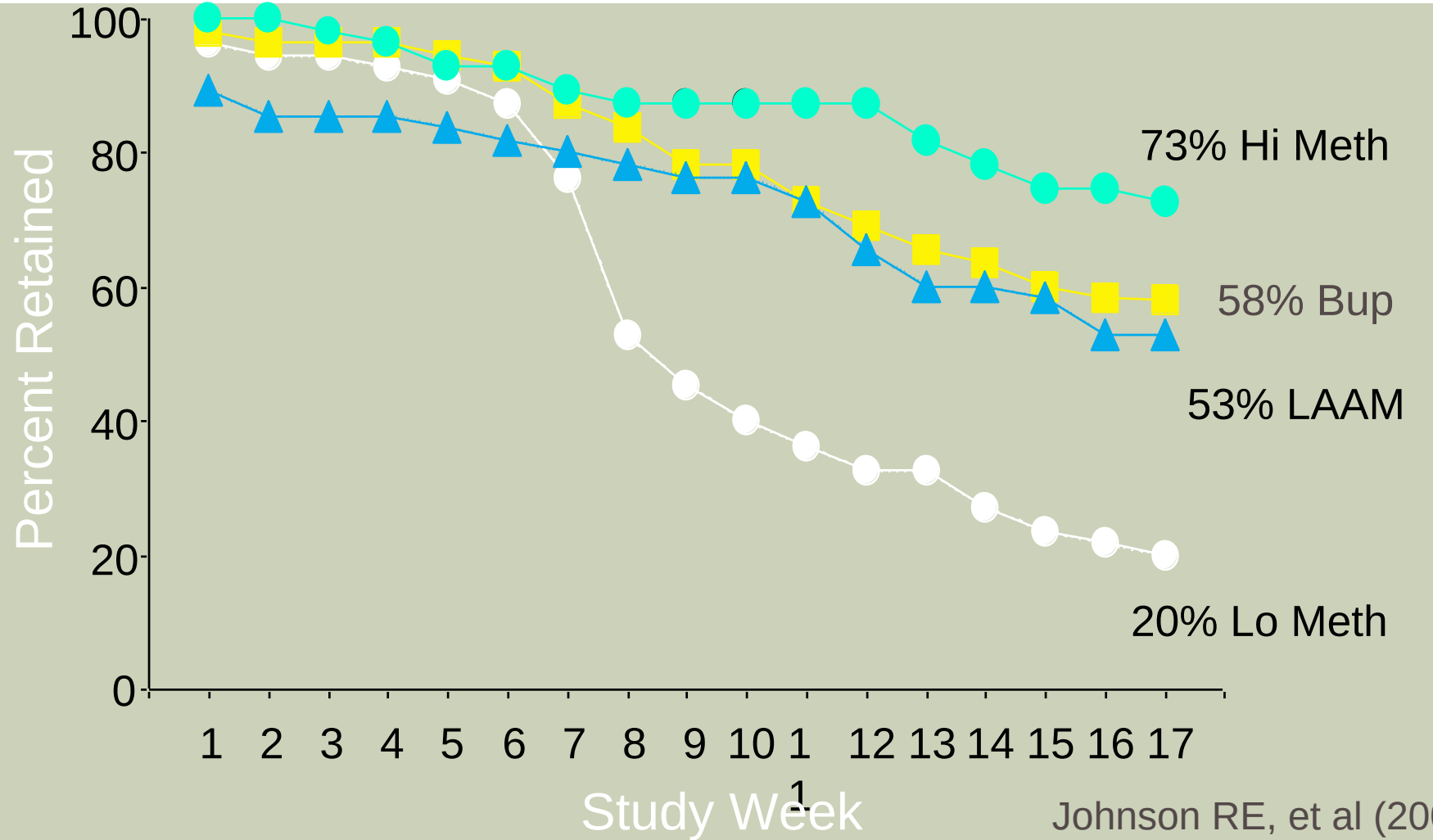
[1] Weiss Arch Gen Psych 2011

Treatment Retention: Buprenorphine Detox vs. Maintenance



Kakko, Lancet 2003

BUPRENORPHINE, METHADONE, LAAM: TREATMENT RETENTION



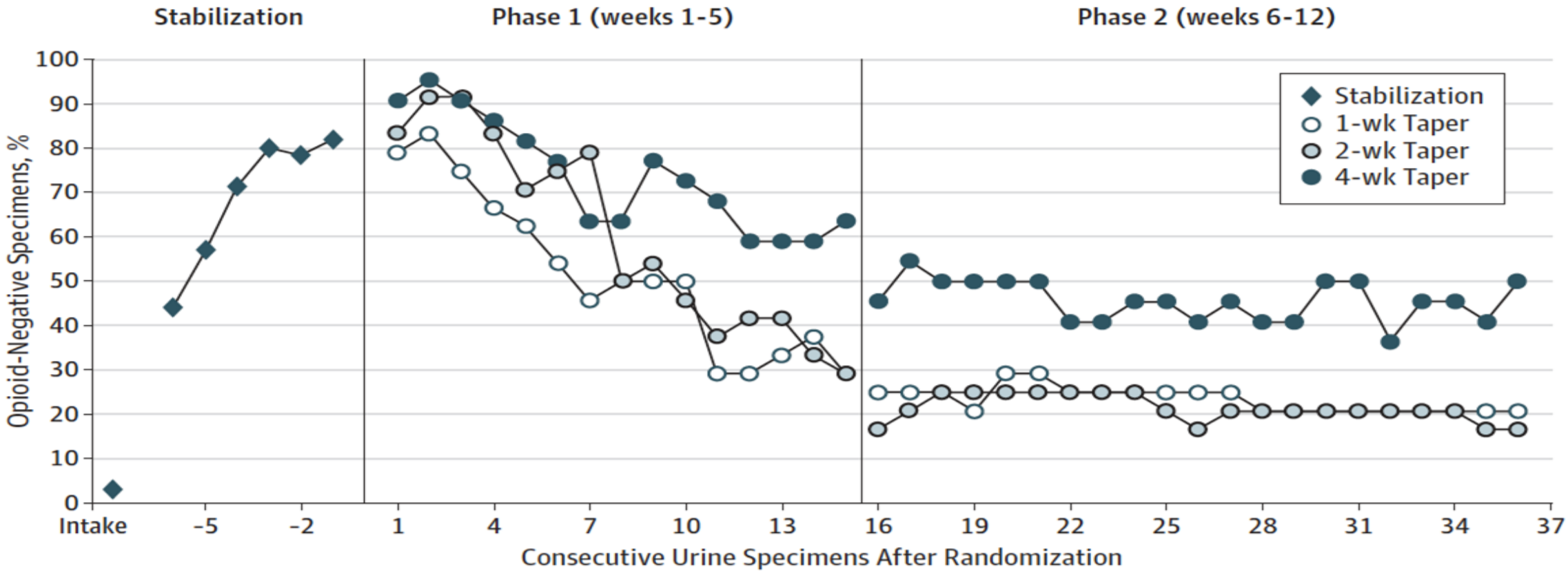
Johnson RE, et al (2000)

BENTZLEY 2015 (REVIEW ON BUP DISCONTINUATION)

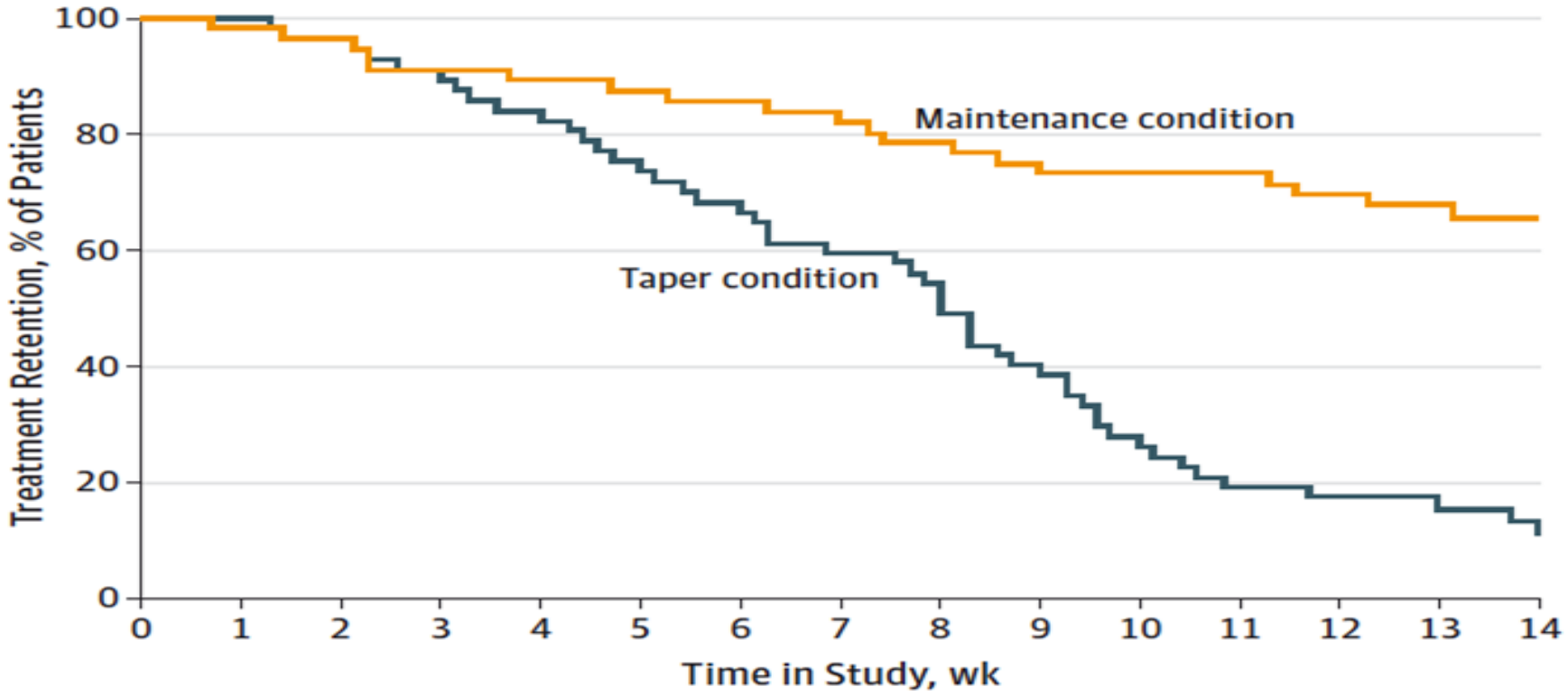
Study (N)	Heroin	Duration (taper)	Avg Dose	Treatment Abstinent	F/u	Post taper Abstinence
Sigmon 2013 (70)	50%	2 wks (1 v. 2)	11.5mg	82%	9 wks	17% (21%)
Weiss 2011 (323)	26%	12 wks (4)	20.8g	54%	8 wks	10%
Ling 2009 (516)	83%	4 wks (1 v. 4)	20.3mg	37%	4 wks	18% (18%)
Woody 2008 (55)	76%	8 wks (4)	15.1mg	54%	24 wks	34%

SIGMON ET AL. 2013

Figure 3. Effects of Buprenorphine Taper Duration on Illicit Opioid Abstinence Achieved



FIELLIN 2014: BUP TAPER V MAINTENANCE



Mean buprenorphine dosage, mg/d															
Maintenance condition	14.9	15.1	15.2	15.3	15.3	16.0	15.9	16.2	16.2	16.6	16.8	16.2	16.1	15.8	14.6
Taper condition	15.6	15.6	15.4	15.3	14.2	9.7	5.7	3.1	0.6	0.2	0	0	0	0	0

PATIENT 1

- LS is a 48 year old female, call center communications supervisor who started snorting heroin at age 17.
- On methadone several times- did not like " crowd at methadone program."
- Single mom who raised a son on her own, who just graduated college.
- She uses heroin 3x day " to not be sick"

- What other information do you need?

- How would you approach MAT in this patient?

PATIENT 2

- SB is a 34 year old male with Type I DM, HTN and retinopathy.
- Recently moved to Pittsburgh. Works as concierge at downtown hotel.
- Using heroin since age 21- snort and IV. Active in NA, but keeps relapsing.
- Was on methadone- made too drowsy.
- Heard about buprenorphine and interested in finding out more.

- What other information do you need?

- How would you approach MAT in this patient?

PATIENT CONVERSATIONS

- Patients need advice on:
  - Getting through detox period successfully
  - Symptoms following induction on MAT
  - Necessary duration of treatment (i.e. 12+mo)
    - What will get in their way? Internal beliefs?
- What systems of care are needed to shepherd through this process successfully?

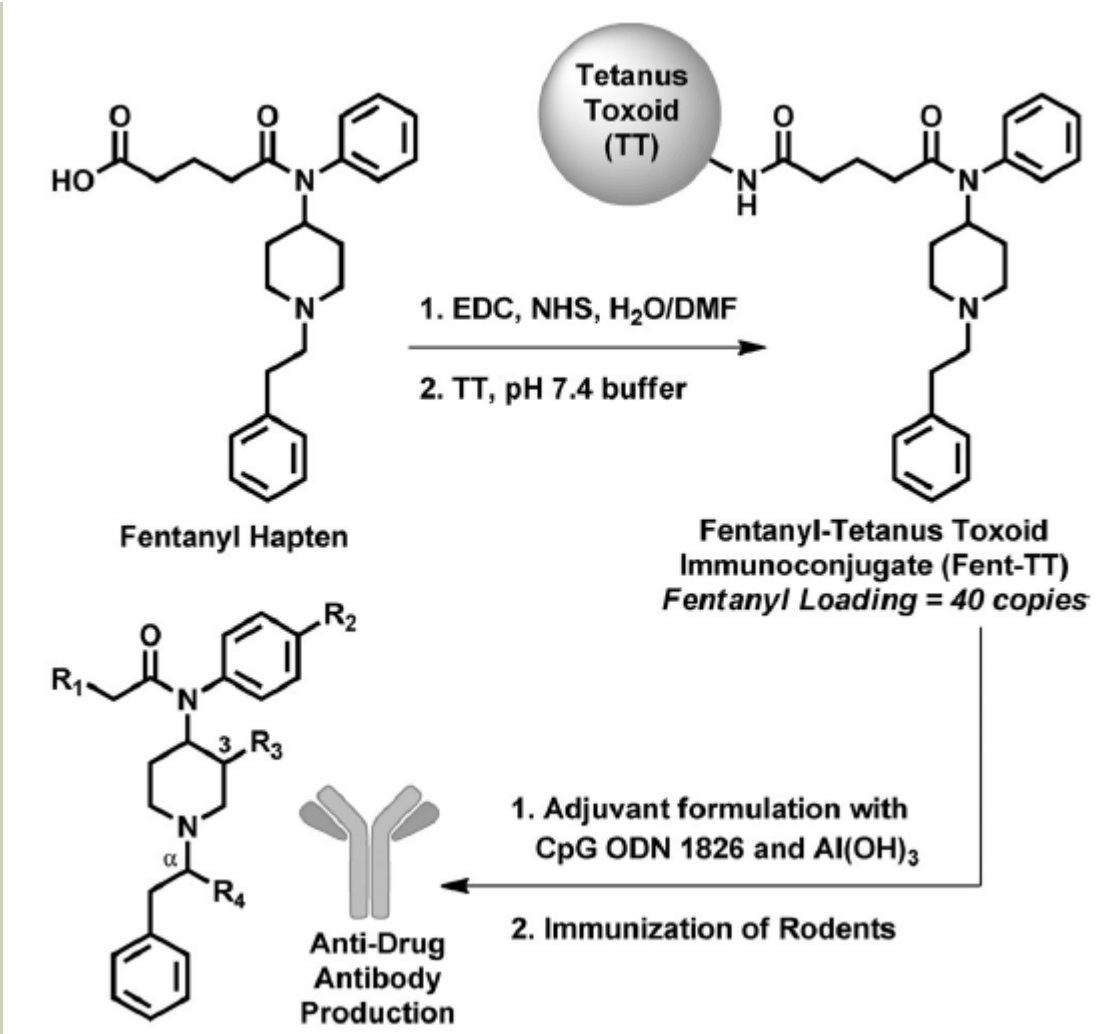
APPROPRIATENESS FOR OFFICE-BASED TREATMENT

- Patient is less likely to be an appropriate candidate for office-based treatment:
  - Dependence on high doses of benzodiazepines, alcohol, or other CNS depressants
  - Significant psychiatric co-morbidity
  - Multiple previous treatments (methadone) and relapses

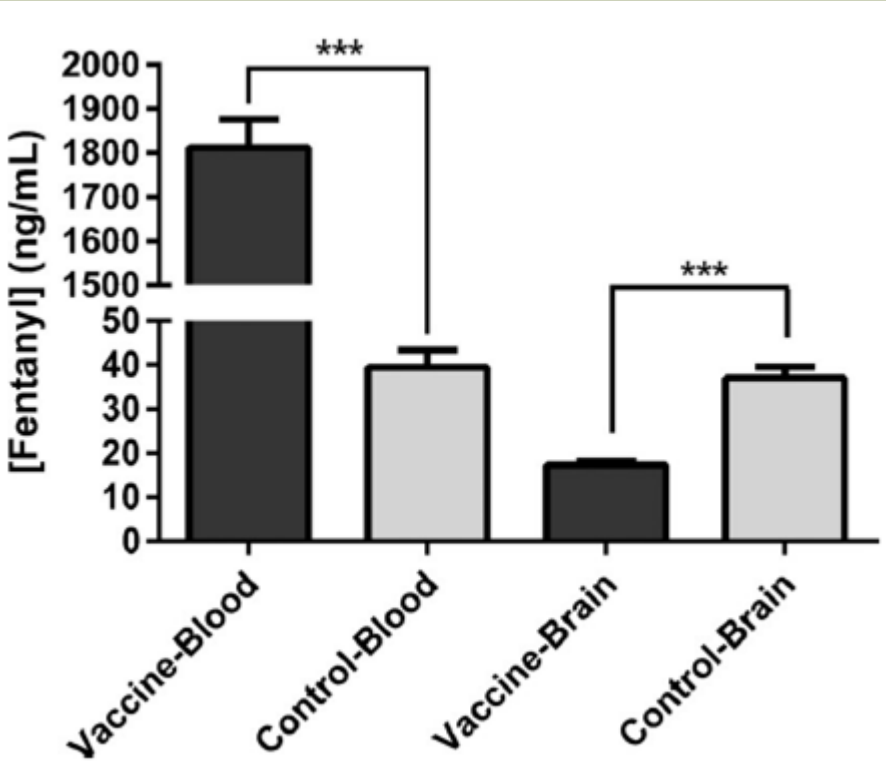
COMMON PITFALLS IN PRIMARY CARE

- Communication difficulties
  - With patient and addictions providers
- Knowledge gaps about MAT
- Use of methadone to treat opioid use disorder outside of a methadone clinic
- Referral to methadone clinics for patients with pain
- Prescribing drugs that interact with MAT

FUTURE DIRECTIONS



Biodistribution Of Fentanyl In Blood and Brain Samples



Bremer PT et al., Angew. Chem. Int. Ed. 2016, 55, 3772 –3775.

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QUESTIONS?