Overview of Medication Assisted Treatment Methadone, Buprenorphine and Naltrexone

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Medication Assisted Treatment Summit
Massachusetts Medical Society
Monday, October 31, 2016

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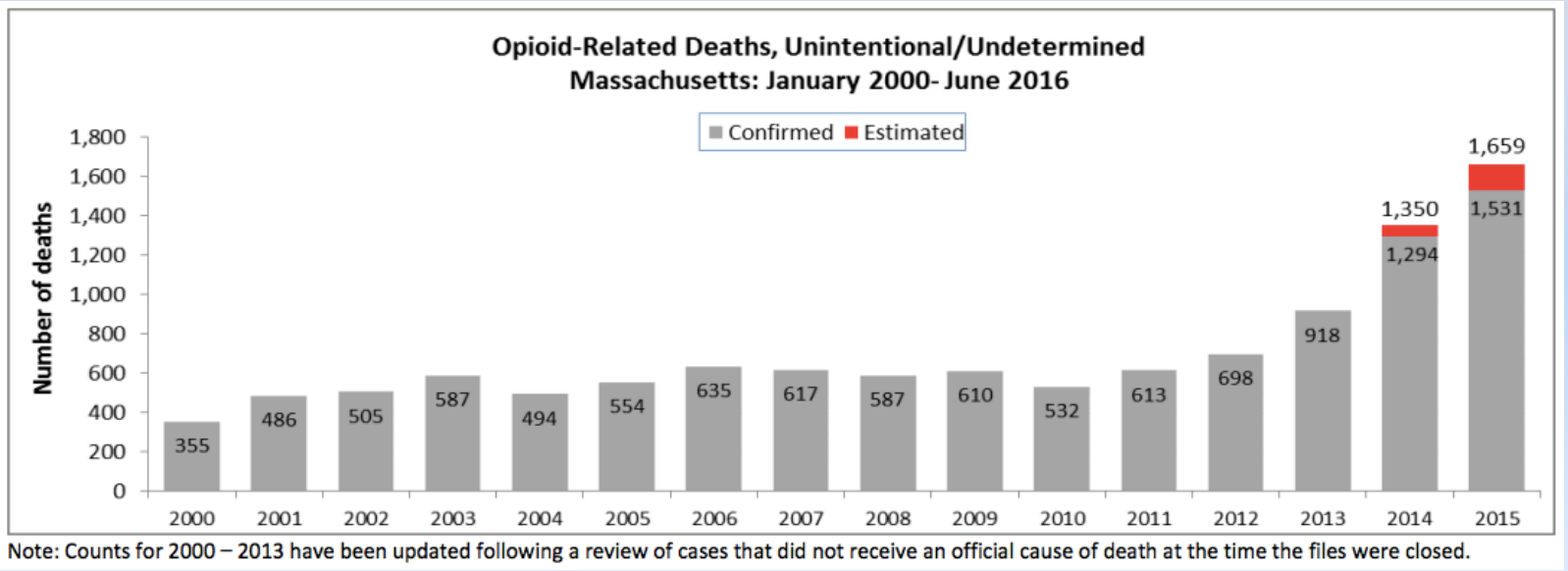
Disclosures –

Alexander Y. Walley, MD, MSc

- The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:
  - None

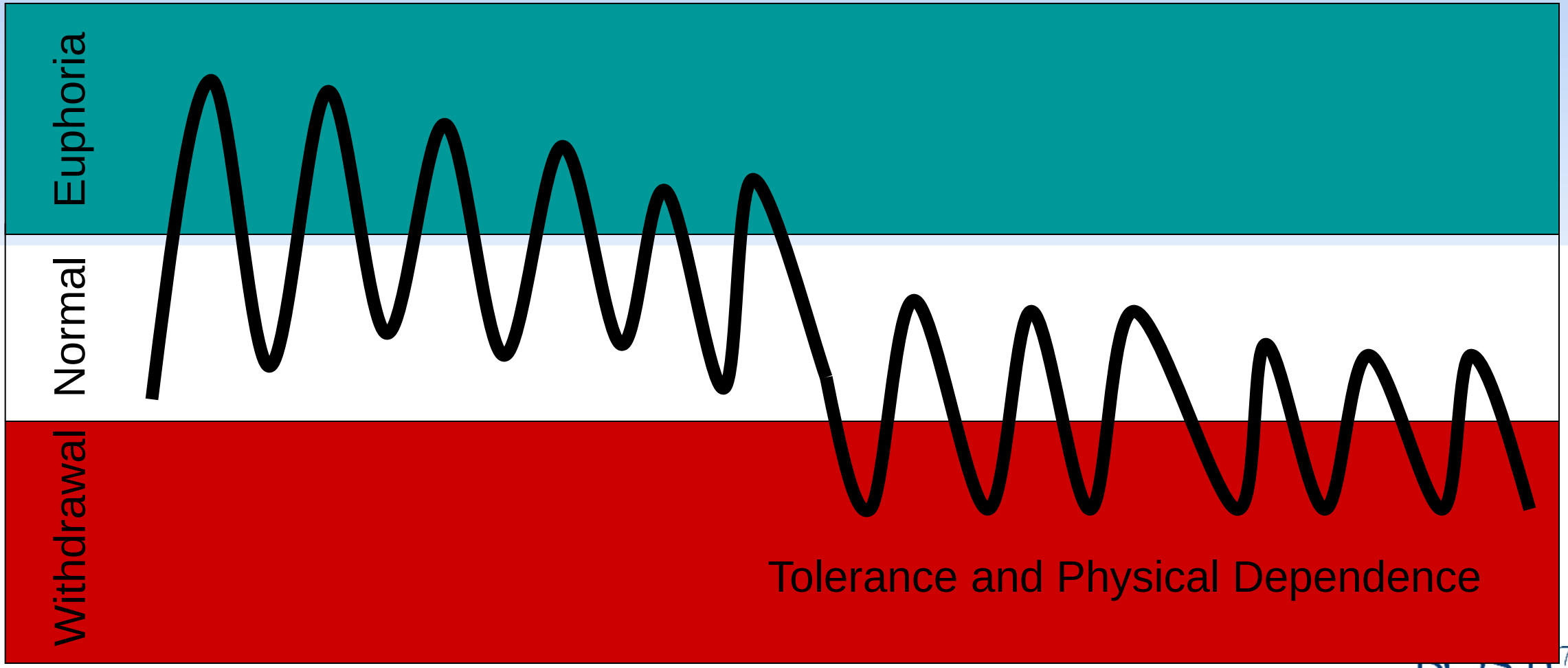
3 priority areas for the opioid crisis

US DHHS March 26, 2015

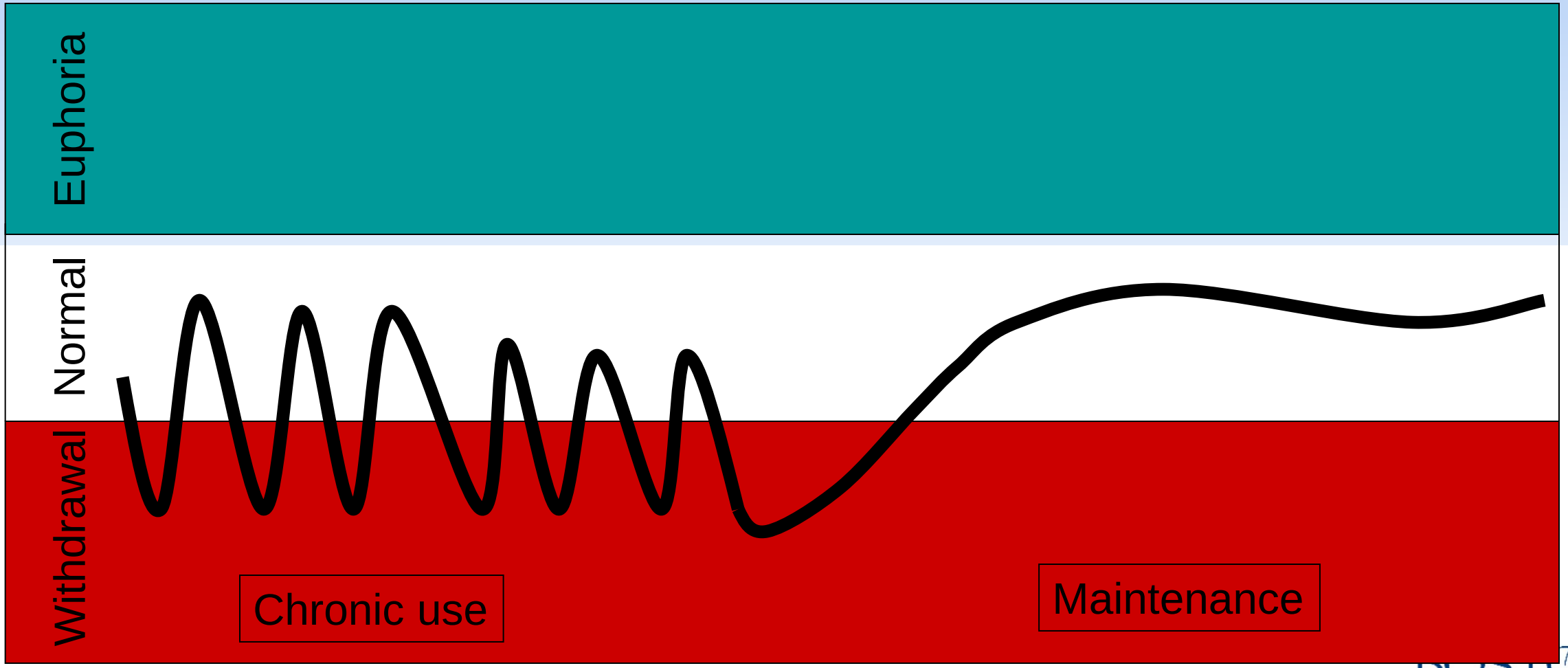


1. Provide training and educational resources to assist health professionals in making informed prescribing decisions
2. Increase use of naloxone
3. Expand the use of “Medication-Assisted Treatment”
   - *Just call it treatment* – Friedmann, Schwartz ASCP 2012.

Why do people use opioids?



Maintenance Treatment for Opioid Use Disorder



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A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine. With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity, apart from constipation. This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential.

ough review of evidence available in 1957,[1] concluded that "The advisability of establishing clinics or some equivalent system to dispense opiates to addicts cannot be settled on the basis of objective facts. Any position taken is necessarily based in part on opinion, and on this question opinions are divided." With respect to previous trials of maintenance treatment, the Council found that "Assessment of the operations of the narcotic dispensaries between 1919 and 1923 is difficult because of the paucity of published material. Much of the small amount of data that is available is not sufficiently objective to be of great value in formulating any clear-cut opinion of the purpose of the clinics, the way in which they operated, or the results attained." No new studies bearing on the question

In a Comprehensive Rehabilitation Program…

- Increases overall survival
- Increases treatment retention
- Decreases illicit opioid use
- Decreases hepatitis and HIV seroconversion
- Decreases criminal activity
- Increases employment
- Improves birth outcomes

Dole VP, Nyswander M. JAMA 1965 Aug 23;193(8):646-50.

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Goals of medication treatment for opioid use disorder

1. Relief of withdrawal symptoms
   - Low dose methadone (30-40mg), buprenorphine
2. Opioid blockade
   - High dose methadone (>60mg), buprenorphine, naltrexone
3. Reduce opioid craving
   - High dose methadone (>60mg), buprenorphine, naltrexone
4. Restoration of reward pathway
   - Long term (>6 months)
   - methadone, buprenorphine, naltrexone

Opioid Detox Outcomes

- Low rate of retention in treatment
- High rates of relapse post treatment
  - < 50% abstinent at 6 months
  - < 15% abstinent at 12 months
  - Increased rates of overdose due to decreased tolerance

So, how long should maintenance treatment last?

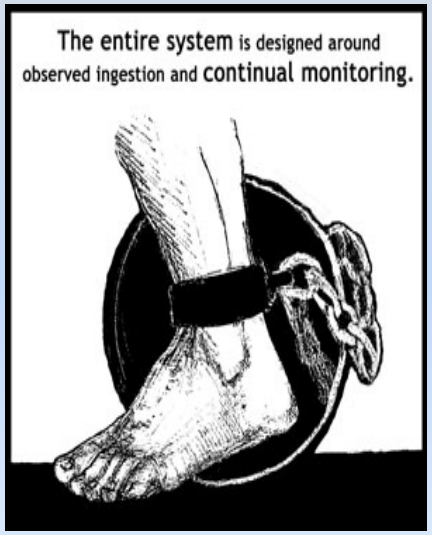
Long enough

O'Connor PG JAMA 2005
Mattick RP, Hall WD. Lancet 1996
Stimmel B et al. JAMA 1977

Methadone Maintenance Treatment

Regulated and Structured

- *Narcotic Addict Treatment Act 1974*



- Daily nursing assessment
- Weekly individual and/or group counseling
- Random supervised toxicology screens
- Medical director oversight
- Methadone dosing
  - Observed daily ⇒ “Take homes”

- Separate system outside primary care or community mental health
- Limited access
- Inconvenient and punitive
- Mixes stable and unstable patients
- Lack of privacy
- No ability to “graduate”
- Stigma

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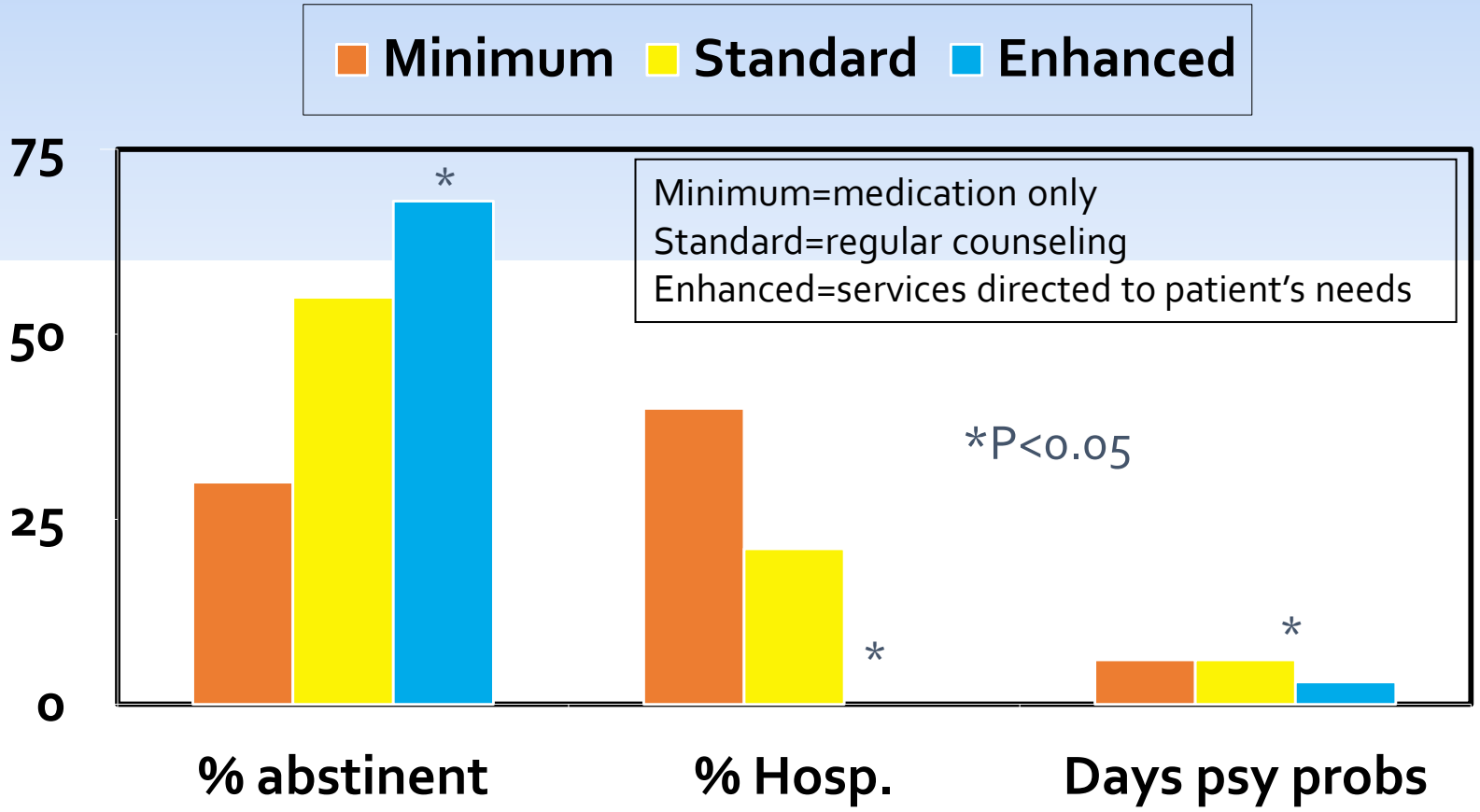
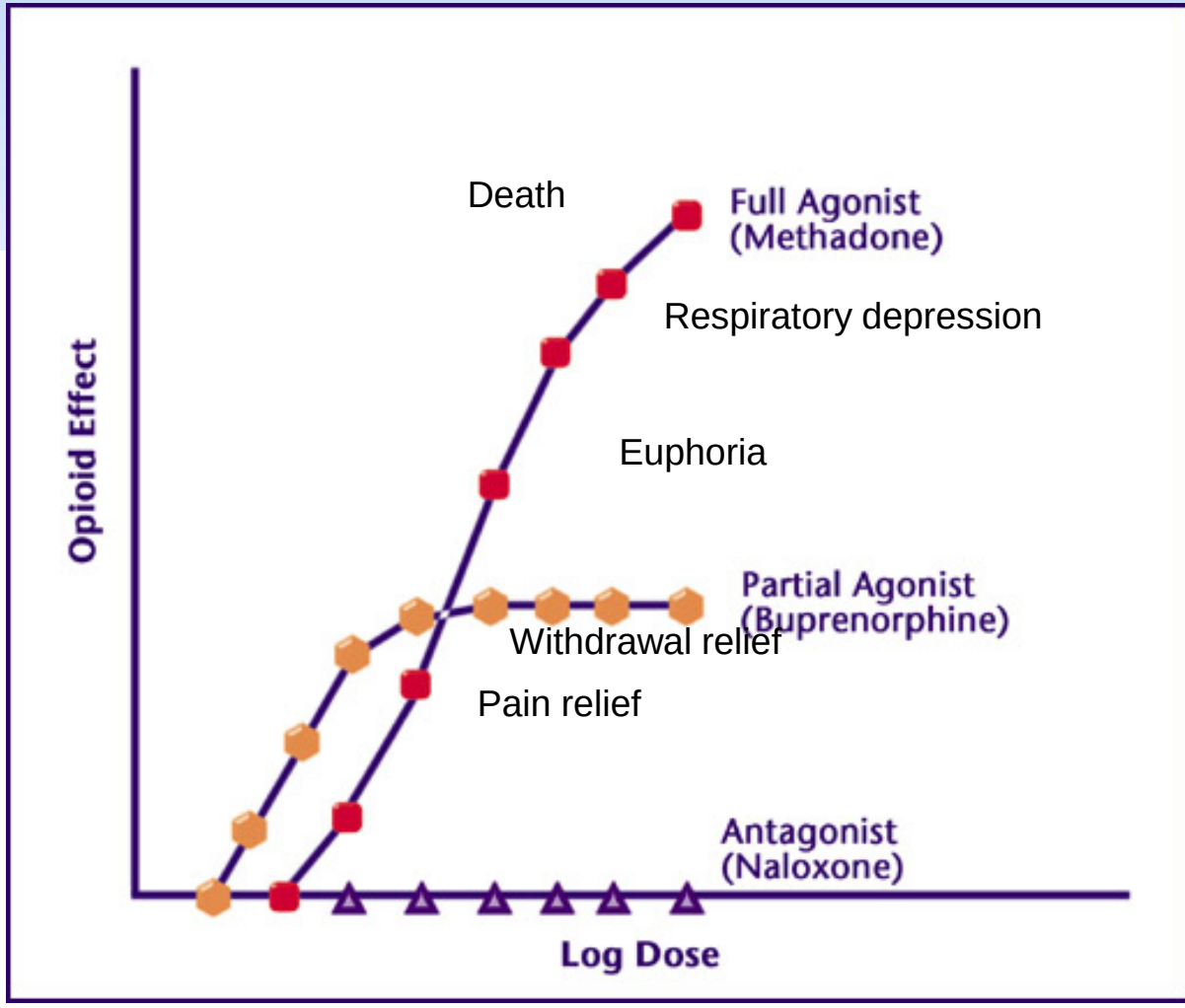
Effects of Enhanced Services for Patients on Methadone Maintenance



McLellan et al. JAMA 1993

How does buprenorphine work?

- High affinity, but low activity at the mu opioid receptor
  - Low activity is enough activity to TREAT WITHDRAWAL and REDUCE CRAVINGS
  - Low activity results in a CEILING EFFECT
    - Euphoria is unusual
    - Overdose occurs only with other drugs of abuse
    - Opioid dependent patients FEEL NORMAL
  - High affinity means it is a BLOCKER, more active opioids can not stimulate the receptor in presence of buprenorphine

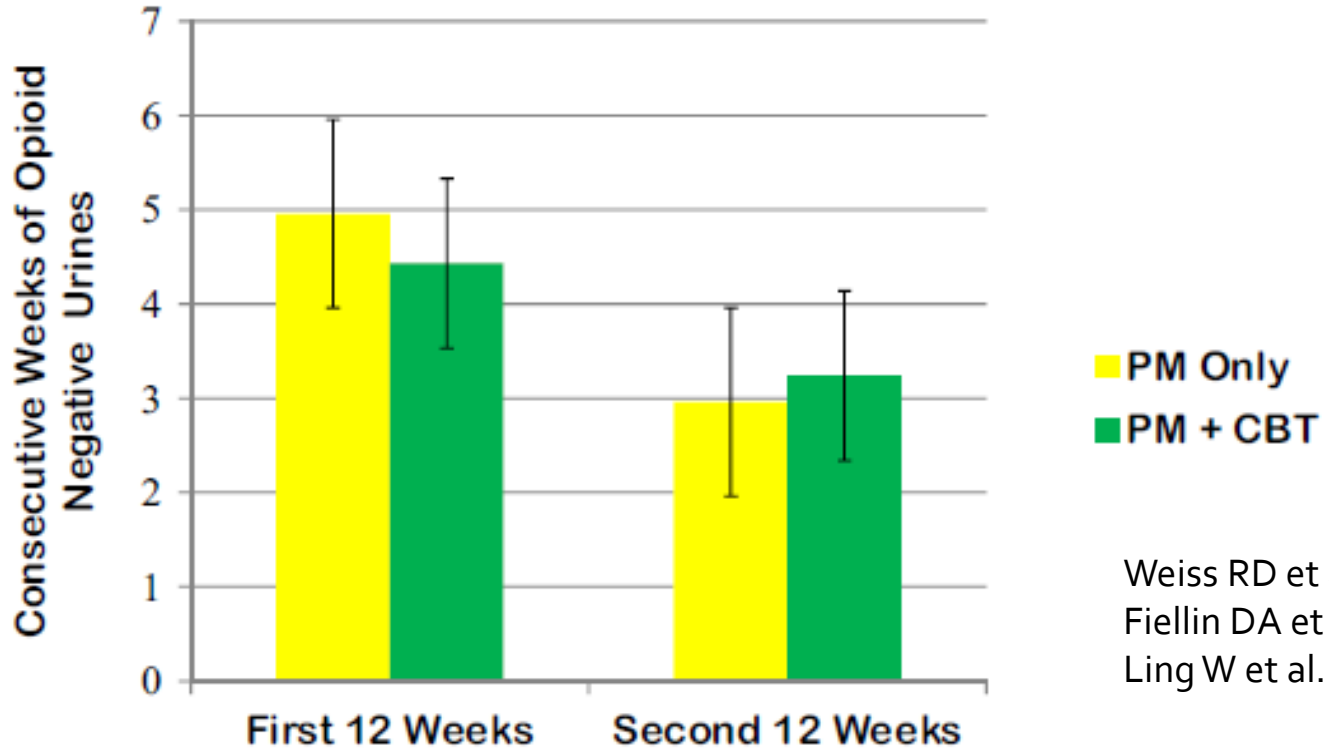


How do buprenorphine + naloxone work?

- Buprenorphine has good sublingual and IV bioavailability but poor GI bioavailability
- Naloxone (Narcan) has good IV bioavailability, but poor GI and sublingual bioavailability
- The combination results in decreased abuse and diversion for IV use

Does behavioral therapy improve outcomes in OBOT?

3 RCTs show that additional behavioral therapy (i.e., CBT, drug counseling) does NOT significantly improve outcomes over that achieved by buprenorphine PLUS medical management or "medical counseling"



Weiss RD et al. *Arch Gen Psychiatry.* 2011.
Fiellin DA et al. *Am J Med.* 2013.
Ling W et al. *Addiction*. 2013.

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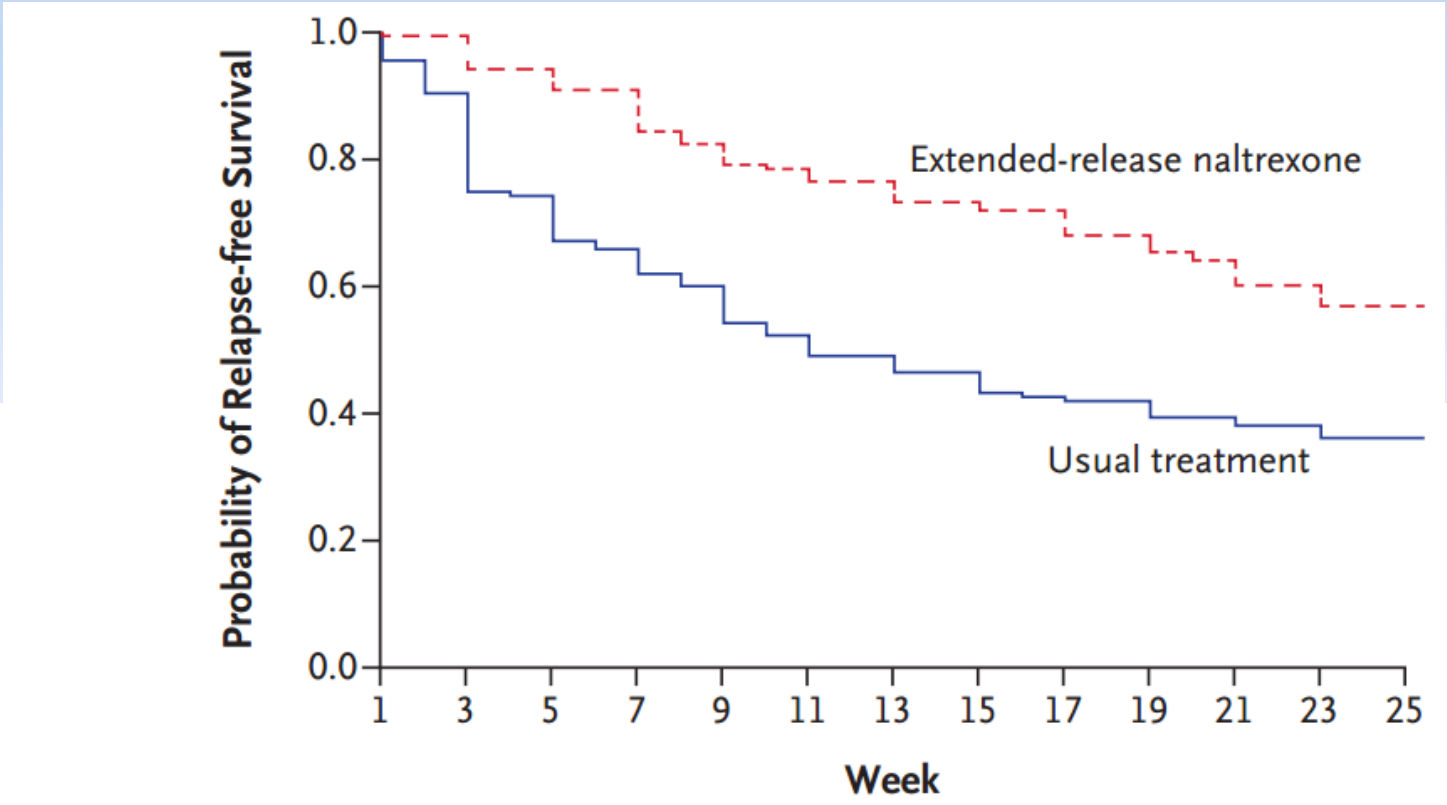
Naltrexone

Krupitsky E, et al. Lancet, 2011

Outcomes	NTX	placebo
Trial completion	53%	38%
Abstinence at 24 weeks	90%	35%
Change in craving score	-10.1	0.7

- Pure opioid antagonist
- Injectable naltrexone (Vivitrol®)
  - Monthly IM injection
  - FDA approved 2010
  - Patients must be opioid free for a minimum of 7-10 days before treatment
- Oral naltrexone
  - Well tolerated, safe
  - Duration of action 24-48 hours
  - FDA approved 1984
  - 2008 Cochrane Review
    - No clear benefit in treatment retention or relapse at follow up over placebo
    - Physicians > 80% abstinence at 18 months

XR-NTX to Prevent Opioid Relapse in Criminal Justice Offenders



No. at Risk													
Extended-release naltrexone	153	144	139	129	121	117	112	110	104	100	92	87	87
Usual treatment	155	116	104	96	84	76	72	67	65	61	59	56	56

- longer median time to return to ≥ 10 d of opioid use
  - 10.5 w vs 5 w
- lower rate of return to such use
  - 43% vs 64%
- higher rate opioid-neg urine
  - 74% vs 56%

Lee JD et al. N Engl J Med 2016

N=308

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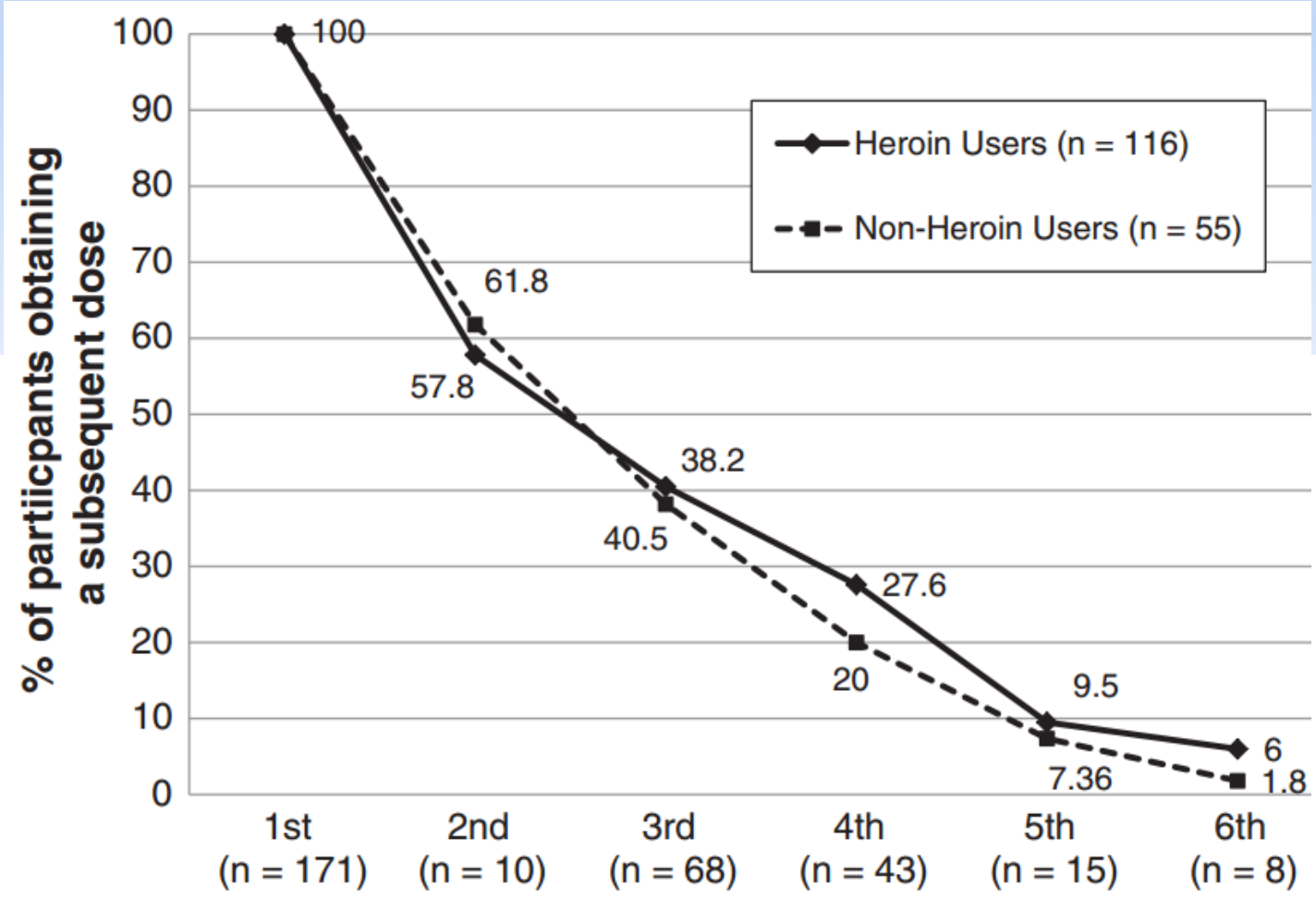
XR-NTX Retention
SUD Treatment Centers



- mean # XR-NTX injections heroin users was 2.3, vs 2.5 by non-heroin opioid users
- Homelessness, opioid injection use (regardless of opioid-type), and mental illness were less likely to be retained in XR-NTX treatment

Cousins SJ et al. J Sub Abuse Treat 2016 N=171

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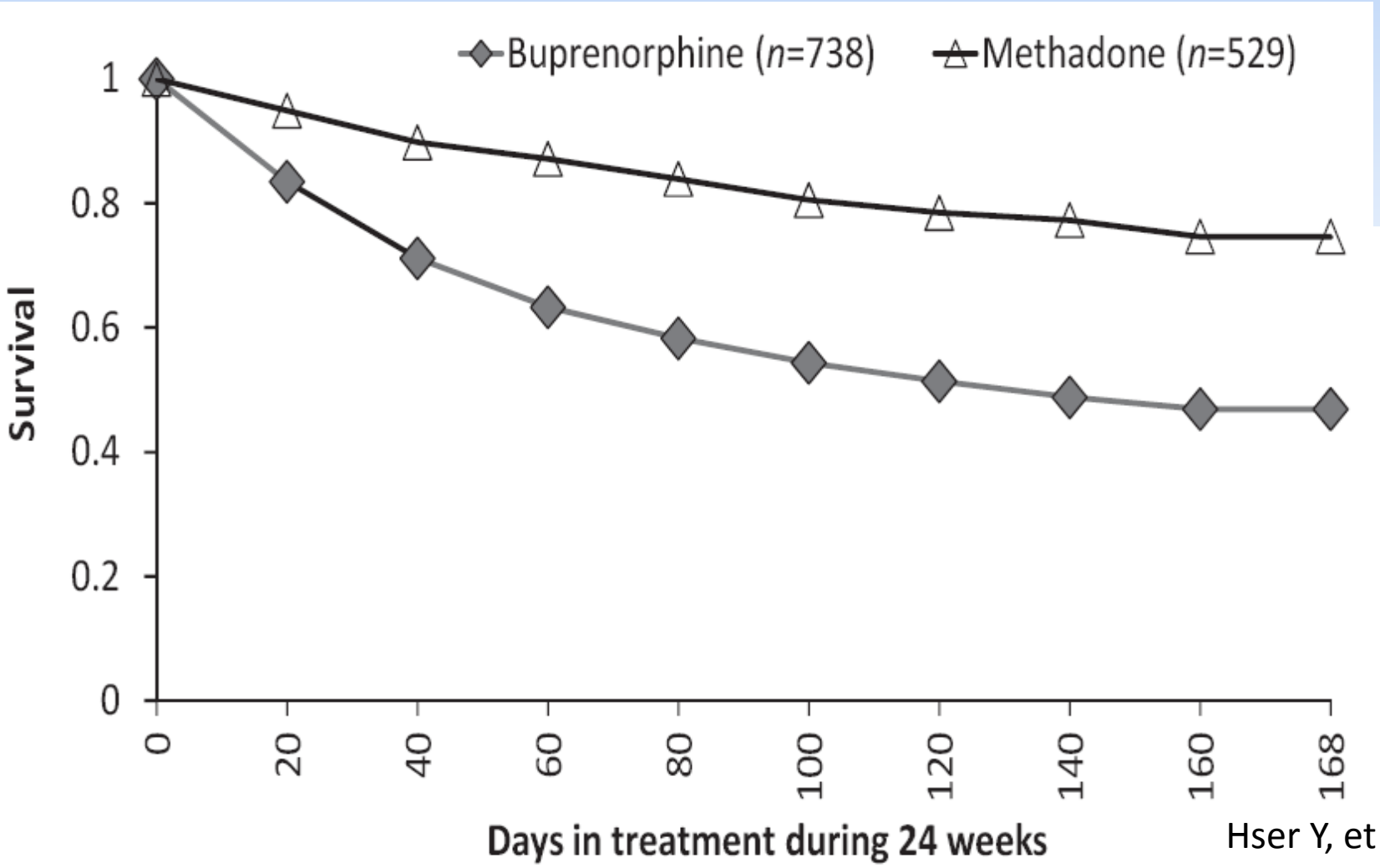
Methadone vs Buprenorphine: Proportion retained in treatment
- RCT buprenorphine vs methadone



9 OTPs
n=1,267

6 month retention

Hser Y, et al. Addiction. 2014

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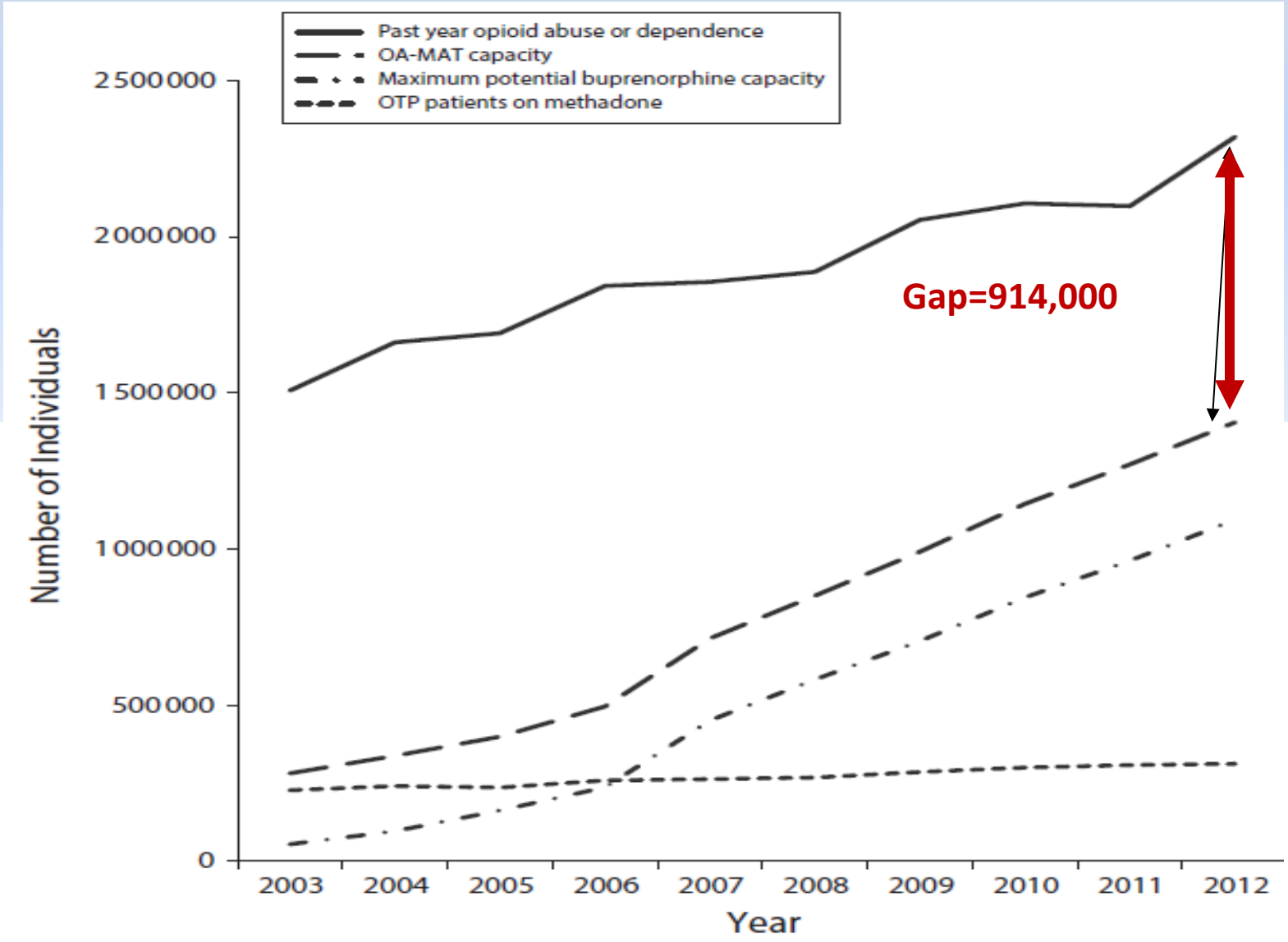
Matching Patients to Opioid Use Disorder Medications

- The choice between methadone, buprenorphine or naltrexone depends upon:
  - Patient preference - Past experience
  - Pharmacology
  - Access to treatment setting
  - Ease of withdrawal
  - Risk of overdose

OUD and MAT Capacity



Jones CM et al. Am J Public Health. 2015

Gap between # with past year OUD & combined buprenorphine & methadone capacity

Heroin maintenance for chronic heroin-dependent individuals (Review)

Ferri M, Davoli M, Perucci CA 2011 – 8 RCTs; 2007 patients

Cochrane Library

Cochrane Database of Systematic Reviews

For long-term, treatment refractory, opioid users

- *Heroin prescribed alongside flexible doses of methadone results in:*
  - *Less use of illicit substances*
  - *Less involvement in criminal activity*
  - *Less incarceration,*
  - *a possible reduction in mortality*
  - *Increased retention in treatment*
- *Due to the higher rate of serious adverse events, heroin should be prescribed for people who have failed maintenance treatment in clinical settings where proper follow-up is ensured.*

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Thank you!

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Grateful for several slides and mentorship from Dan Alford

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DSM-5 defines a substance use disorder as the presence of at least 2 of 11 criteria:

- Impaired control:
  1. Taking more or for longer than intended
  2. Not being able to cut down or stop (repeated failed attempts)
  3. Spending a lot of time obtaining, using, or recovering from use
  4. Craving for substance
- Social impairment:
  5. Role failure (interference with home, work, or school obligations)
  6. Kept using despite relationship problems caused or exacerbated by use
  7. important activities given up or reduced because of substance use
- Risky use:
  8. Recurrent use in hazardous situations
  9. Kept using despite physical or psychological problems
- Pharmacologic dependence:
  10. Tolerance to effects of the substance*
  11. Withdrawal symptoms when not using or using less*

* Persons who are prescribed medications such as opioids may exhibit these two criteria, but would not necessarily be considered to have a substance use disorder

Mild = 2-3 criteria, Moderate = 4-5 criteria, Severe = 6 or more criteria

OUD Treatment Impact on Fatal Drug-Related Poisonings (DRP)

- Cohort study English National Drug Tx Monitoring System
- 151,983 treated for OUD 2005-2009
- Outcome: fatal DRP during periods in or out of treatment, adjusting for age, gender, substances used, injecting status
- Results
  - 1,499 fatal DRP
  - Risk increased while not enrolled in any treatment
  - **Risk 2x higher when enrolled only in a psychological treatment compared to those enrolled in OAT**

Pierce M et al. Addiction 2016

XR-NTX Adherence
Primary Care

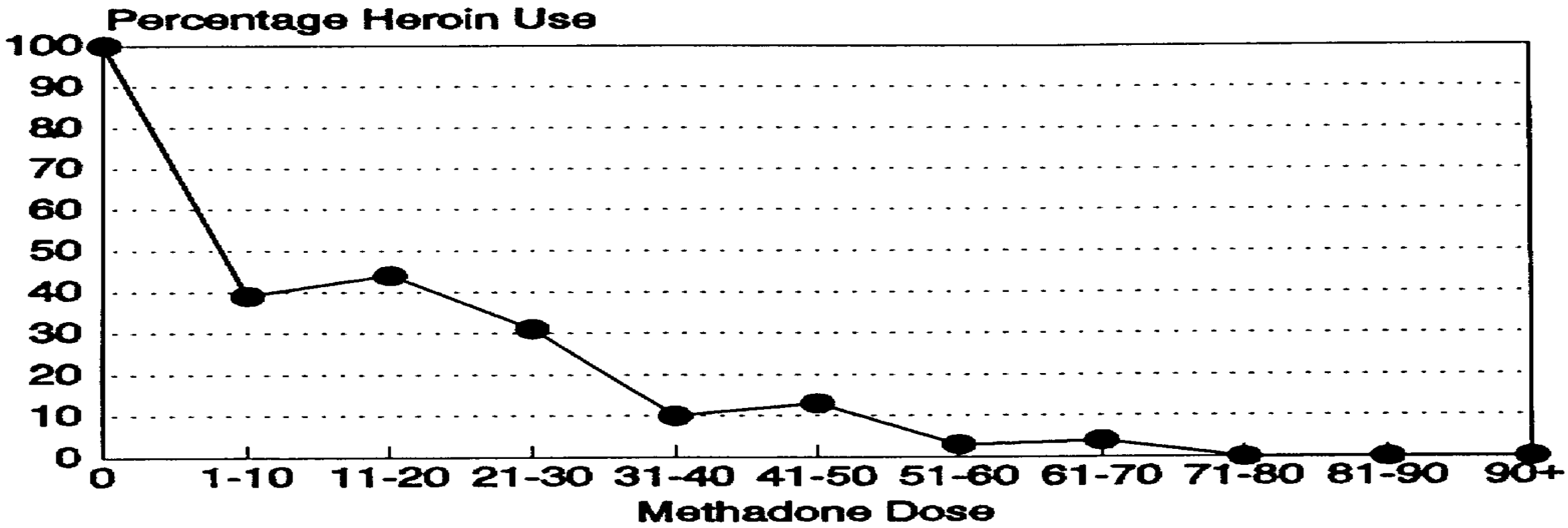
- 62 consecutive adults with OUD who received 1st injection of XR-NTX during inpatient detoxification 2013-2015, were referred to the adjacent primary care health center for 2nd injection 1 month later
- Results:
  - 55% followed up to receive 2nd XR-NTX injection
  - 32% received at least a 3rd XR-NTX injection
  - No demographic, treatment history, substance use behaviors, or aftercare plan variables associated with receipt of a 2nd injection

Stein MD, et al. J Subs Abuse Treat. 2016

Dose Response

Figure 1 - Heroin Use in Past 30 Days

407 MM Patients by Current Methadone Dose



SOURCE: Ball and Ross 1991, p. 248.

* Adapted from a study of 407 methadone maintenance patients.

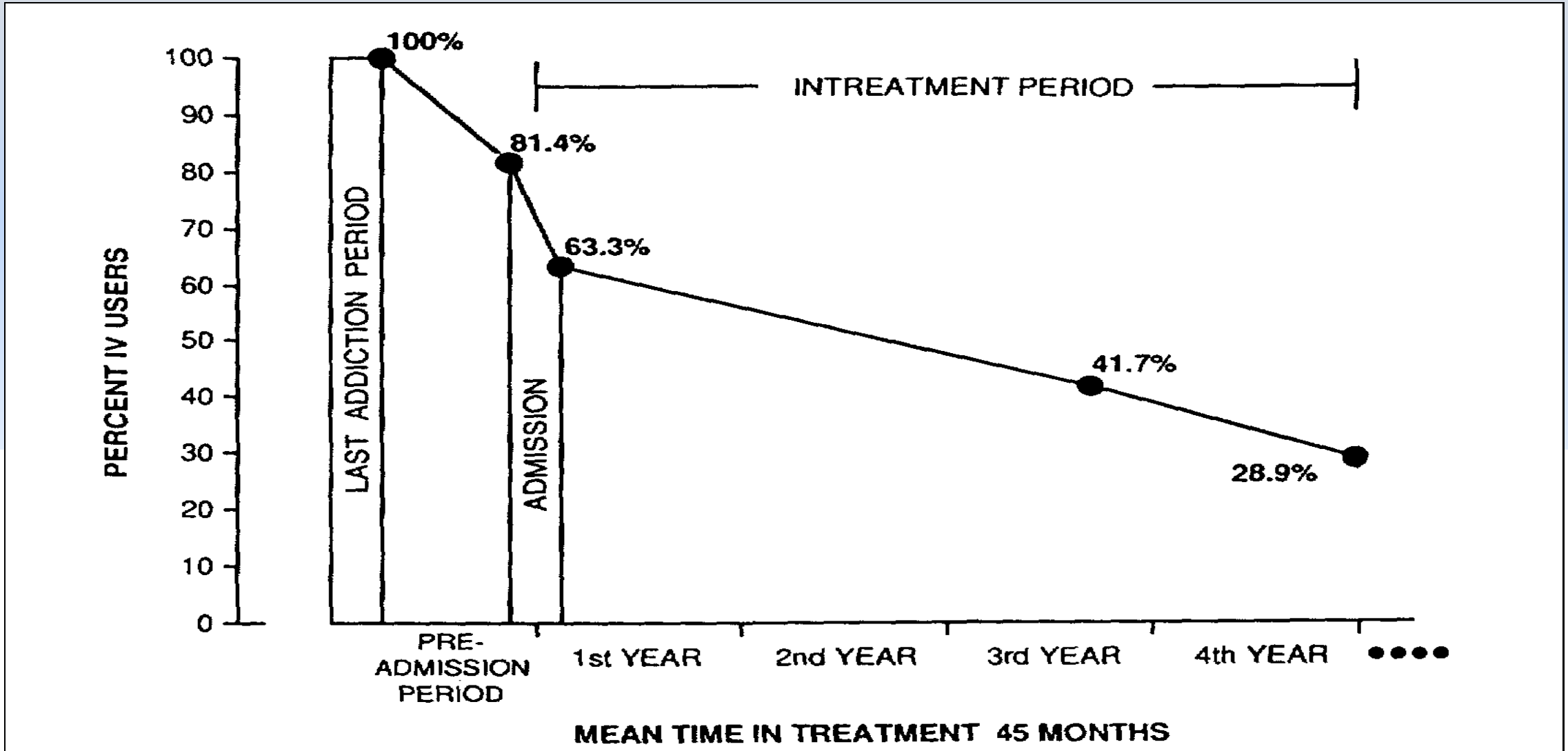


FIGURE 7.1. Impact of methadone maintenance treatment on intravenous drug use for 388 male methadone patients in six programs.

Ball JC, Ross A. The effectiveness of methadone maintenance treatment, 1991

Extensive Research on Effectiveness

In a Comprehensive Rehabilitation Program…

- Increases overall survival
- Increases treatment retention
- Decreases illicit opioid use
- Decreases hepatitis and HIV seroconversion
- Decreases criminal activity
- Increases employment
- Improves birth outcomes

JAMA 2005

MEDICAL NEWS & PERSPECTIVES

Methadone Treatment Marks 40 Years

Bridget M. Kuehn

FORTY YEARS AND COUNTLESS POlitical firestorms after it was first introduced, methadone maintenance for the treatment of opioid addiction remains a standard therapy in the field of addiction treatment.

The publication on August 23, 1965, of positive results from a small clinical trial of methadone as a treatment for heroin addiction in *JAMA* marked a sea change in the treatment of addiction (Dole and Nyswander. *JAMA*. 1965; 193:646-650). The study, conducted at Rockefeller University in New York City by Vincent P. Dole, MD, and the late Marie E. Nyswander, MD, suggested that a medication could be used to control the cravings and withdrawal that often lead to relapse in individuals with opioid addiction who attempt to quit.

The work, along with subsequent research by Dole, an endocrinologist, Nyswander, a psychiatrist, and colleagues established the concept of opioid addiction as a chronic disease, similar to diabetes, that as such required

now head of the Laboratory of the Biology of Addictive Diseases at Rockefeller University, explained that work conducted by the group in 1964 and published in 1966 established that methadone blocked the effects of heroin and stabilized patients, who prior to treatment oscillated between feeling

Ingbert Grüttner/The Rockefeller University

done treatment, the ap
always struggled for accep
the forces of public opini
tics. "There is a stigma ag
tions, addicts, and—sadly
providers," said Kreek, a
supporter of the methado

"THE FARM"

Methadone maintenance
resented a reversal of the t
approach to treating dru
said David F. Musto, MD
turer at Yale and expert
policy. A 1919 Supreme
sion had established tha
alone did not justify phys
ing addicts with opioids. B
cision, some physicians ha
acting opioids to treat indi
opioid addiction.

The Drug Enforcement
tion, in fact, considered D
illegal and had threatened
him prior to the 1965 pub
defy the US government wa
litical courage," said Jeron
who became the first natio

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Drug Addiction Treatment Act (DATA) 2000

2000: Drug Addiction Treatment Act (DATA) 2000

- Allows qualified physician to prescribe scheduled III - V, narcotic FDA approved for opioid maintenance or detoxification treatment limit 30 patients per practice

2002: Suboxone and Subutex FDA approved

2005: Limit to 30 patients per physician

2007: Limit to 100 patients per physician after 1 year

HHS Final Rule (Regulation) 2016

- Increased patient limit to **275 patients**
- Two pathways to increase limit
  - Hold additional credentialing
    - Boarded in addiction medicine or addiction psychiatry
  - Practice in "Qualified Practice Setting"
    - Coverage for patient emergencies after hours
    - Access to case-management
    - Use EHR, if required in practice setting
    - Registered for state PDMP
    - Accepts 1 form of 3rd party payment

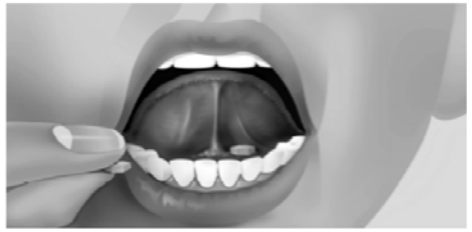
The Comprehensive Addiction and Recovery Act (CARA) 2016

- Expands prescribing privileges to NPs and PAs
  - Require 24 hours of training (8+16)
  - Must be supervised by or work in collaboration with a qualifying physician if required by state law
  - 30 patients for at least 1 year then up to 100 patients

Buprenorphine Formulations

For OUD

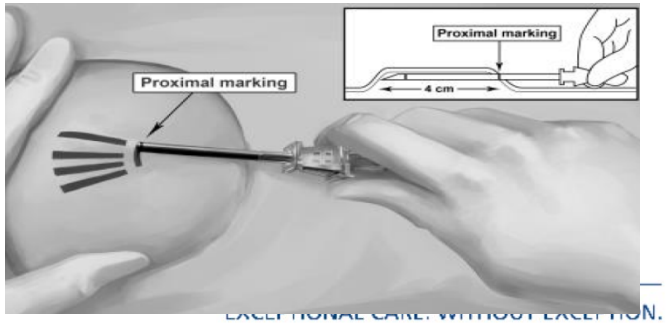
Drug		Formulations	Maintenance Dose	Cost/6 m
Buprenorphine				
	generic	2, 8 mg SL tabs	16 mg/d	$1,672
	Probuphine	74.2 mg SD implant	4 implants/6m	$4,950
	CAM2038 (phase 3)	SQ depot weekly or monthly	NA	NA
Buprenorphine/Naloxone				
	generic	2/0.5, 8/2 mg SL tabs	16/4 mg/d	$2,814
	Bunavail	2.1/0.3, 4.2/0/7, 6.3/1 mg buccal film	8.4/1.4 mg/d	$2,660
	Suboxone	2/0.5, 4/1, 8/2, 12/3 mg SL film	16/4 mg/d	$2,660
	Zubsolv	1.4/0.36, 5.7/1.4 mg SL tab	11.4/2.8 mg/d	$2,660



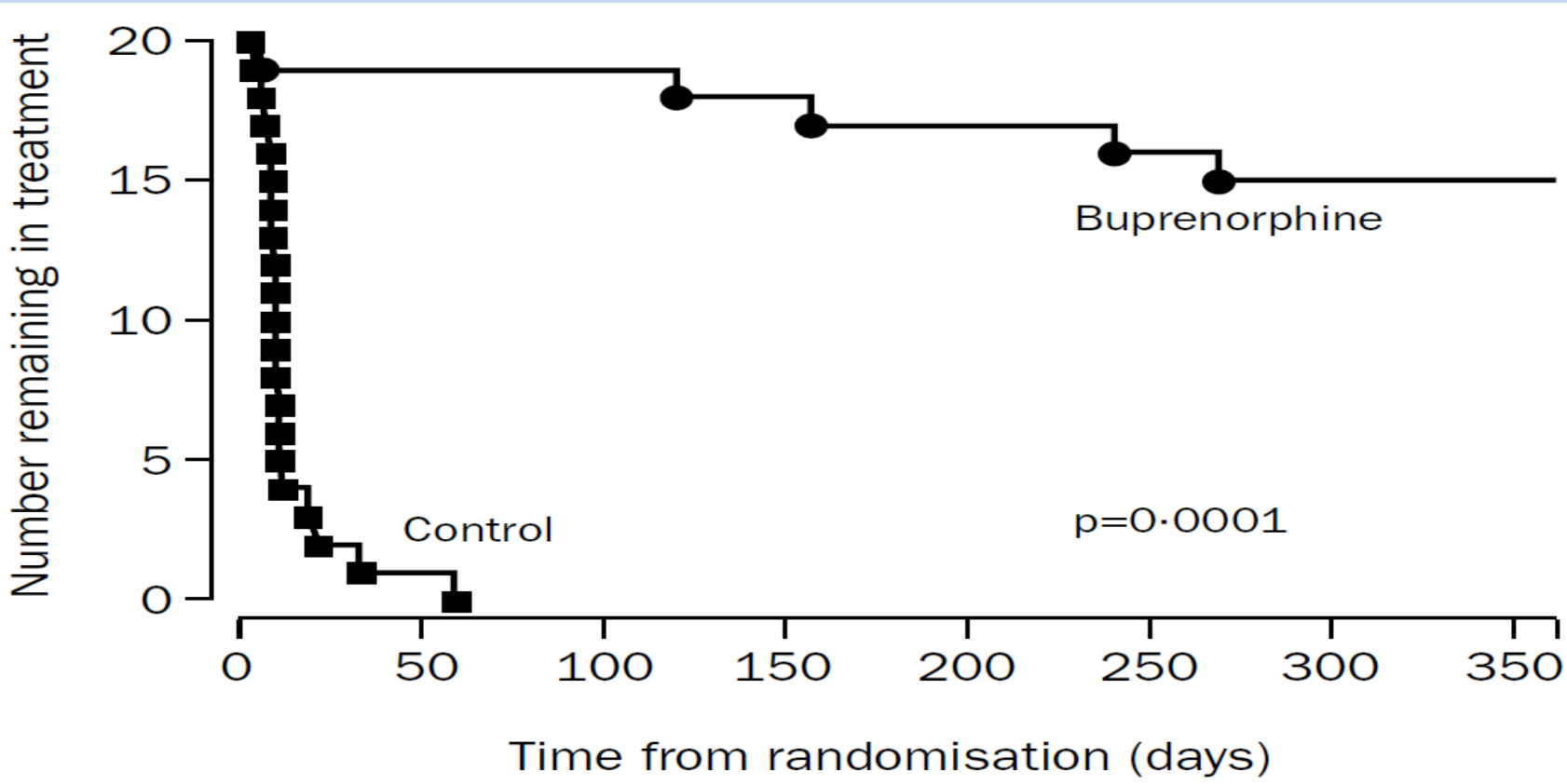
For Pain NOT OUD

The Medical Letter 2016

Drug	Formulations
Belbuca	Buccal q12h
Butrans	Transdermal 7-day patch
Buprenex	IM/IV q6h



Buprenorphine Maintenance vs Taper



Completion 52 wk trial:

- Taper 0%
- Maintenance 75%

Mean % urine neg:

- Maintenance 75%

Mortality

- **Taper 20%**
- **Maintenance 0%**

Kakko J et al. Lancet 2003

Buprenorphine Efficacy

- Studies (RCT) show buprenorphine more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:
  - Abstinence from illicit opioid use
  - Retention in treatment
  - Decreased opioid craving

Johnson et al. NEJM 2000
Fudala PJ et al. NEJM 2003
Kakko J et al. Lancet 2003

Unobserved "Home" Inductions

- Studies demonstrate that unobserved "home" inductions are both effective and safe
- Should be performed in properly selected patients.
- Providers and patient/significant other should be able to communicate during induction.
- Same protocol as in office-based induction

Alford DP et al. J Gen Intern Med. 2007
Lee JD et al. J Gen Intern Med 2008
Cunningham CO et al, J Subst Abuse Treat 2011
Sohler NL et al, J Subst Abuse Treat 2011
Lee JD et al. J Addict Med 2014

ED–Initiated Bup/Nx Treatment for OUD

- RCT n=329 patients w/OUD treated in an urban teaching hospital ED
  - 104→referral
  - 111 →brief intervention and referral
  - 114 →buprenorphine treatment

- Buprenorphine treatment…
  - increased engagement in outpt addiction treatment
  - reduced self-reported illicit opioid use
  - decreased inpatient addiction treatment services

D'Onofrio G, et al. JAMA. 2015

Buprenorphine Treatment for Hospitalized, Patients with OUD

- 72% randomized to linkage entered the primary-care based buprenorphine program within 6 months vs 12% of those assigned to the 5-day taper.
  - At 6-month follow-up, 17% randomized to linkage were enrolled vs 3% randomized to the 5-day taper.
- Compared with controls, participants randomized to the primary-care based buprenorphine program…
  - more likely to report no illicit opioid use in the past 30 days at each interval (38% versus 9%)
  - reported fewer days of illicit opioid use in the past 30 days (mean of 8 versus 14).

Liebschutz JM et al. JAMA Intern Med. 2014

Buprenorphine Diversion

86 programs
30 states
19,000 surveys

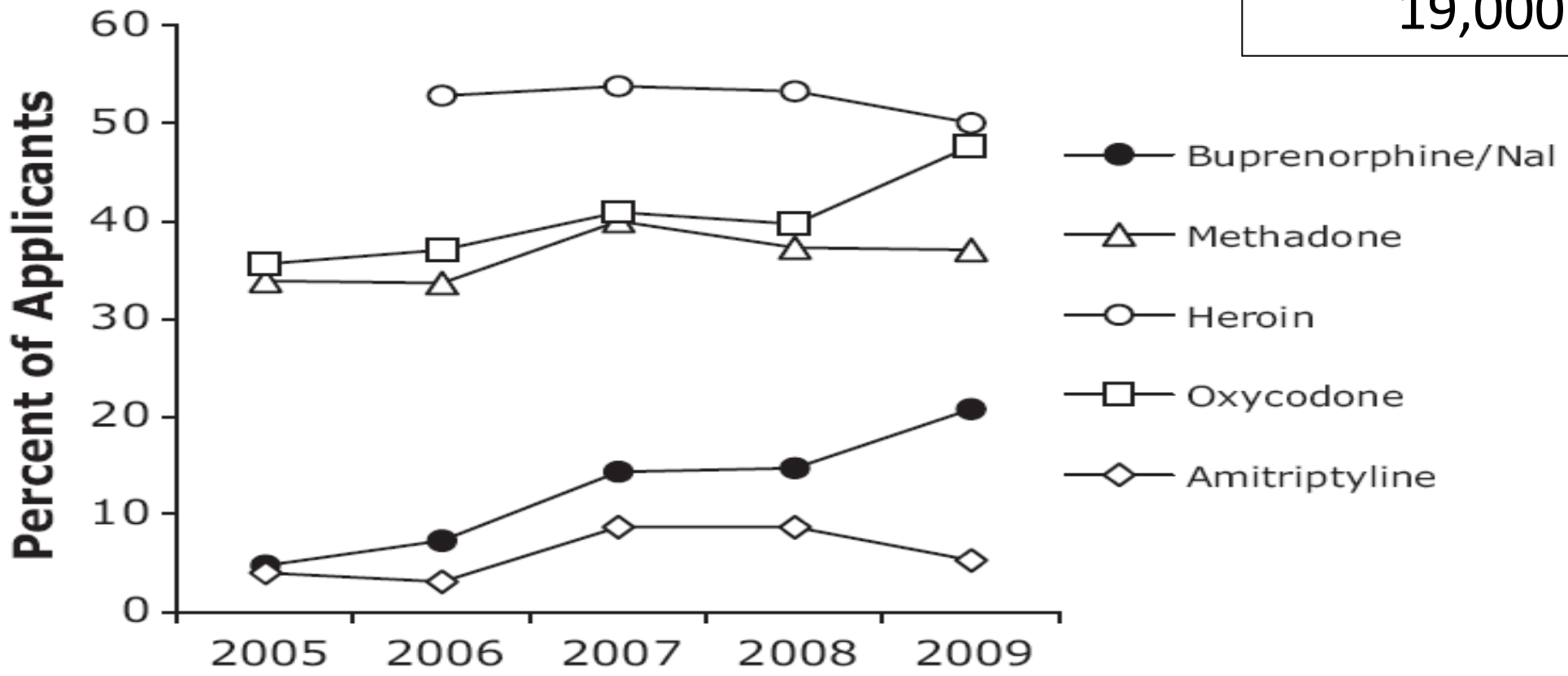


Fig. 1. Percent of applicants who used or knew someone who used the drug to get high (abuse) from 2005 to 2006.

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OAT and Pregnancy

- 3 RCTs (n = 223), 15 cohort OBSs (n = 1923)
- Compared to methadone, buprenorphine was associated with
  - lower risk of preterm birth
  - greater birth weight
  - larger head circumference
- No treatment differences for spontaneous fetal death, fetal/congenital anomalies and other fetal growth measures

Zedler BK et al. Addiction 2016

Overdose deaths decrease when agonist treatments increase

Methadone and Buprenorphine in Baltimore:

Schwartz et al. AJPH 2013.

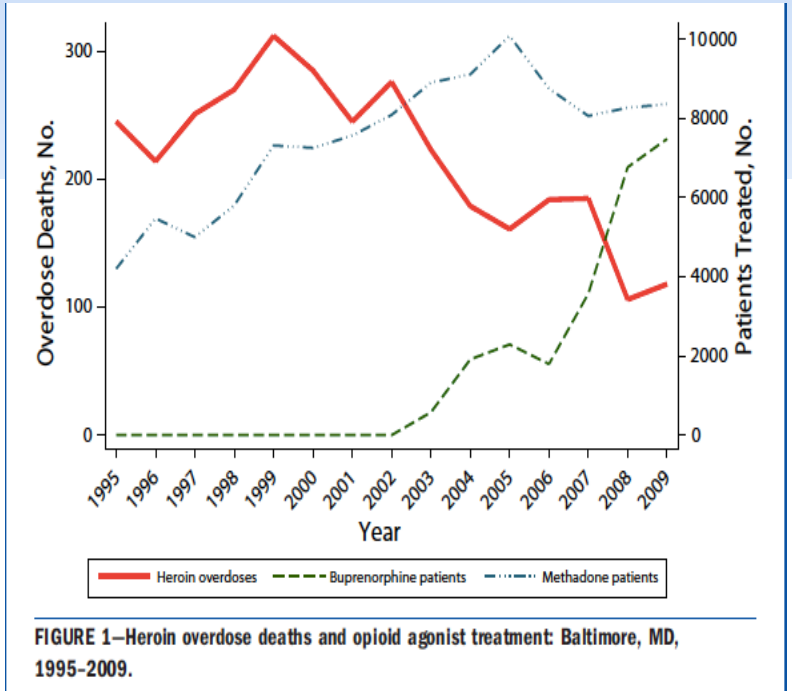
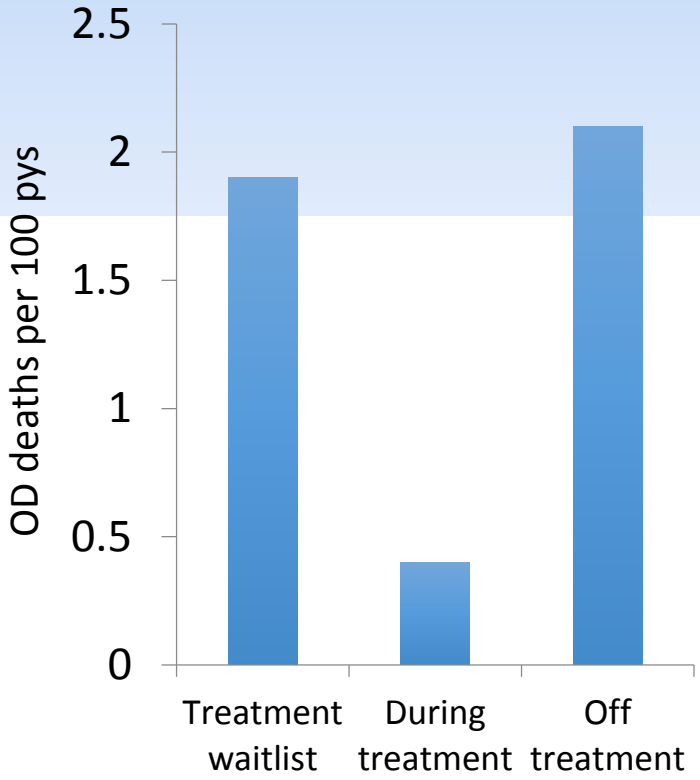


FIGURE 1—Heroin overdose deaths and opioid agonist treatment: Baltimore, MD, 1995–2009.

Methadone in Norway:

Clausen et al. Addiction 2009



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