Opioids

Immersion Training in Addiction Medicine Program 2018

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Daniel P. Alford, MD, MPH
Professor of Medicine
Associate Dean, Continuing Medical Education
Director, Clinical Addiction Research and Education (CARE) Unit

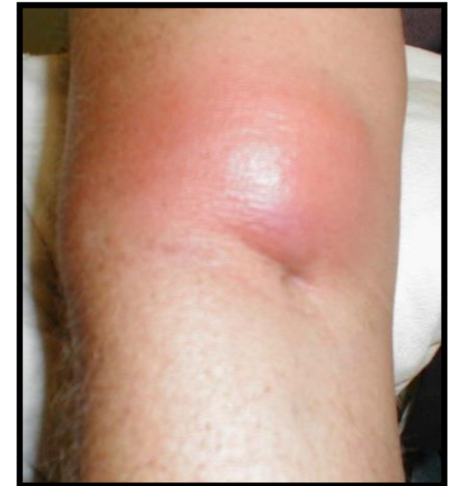
Boston University School of Medicine

EXCEPTIONAL CARE. WITHOUT EXCEPTION.

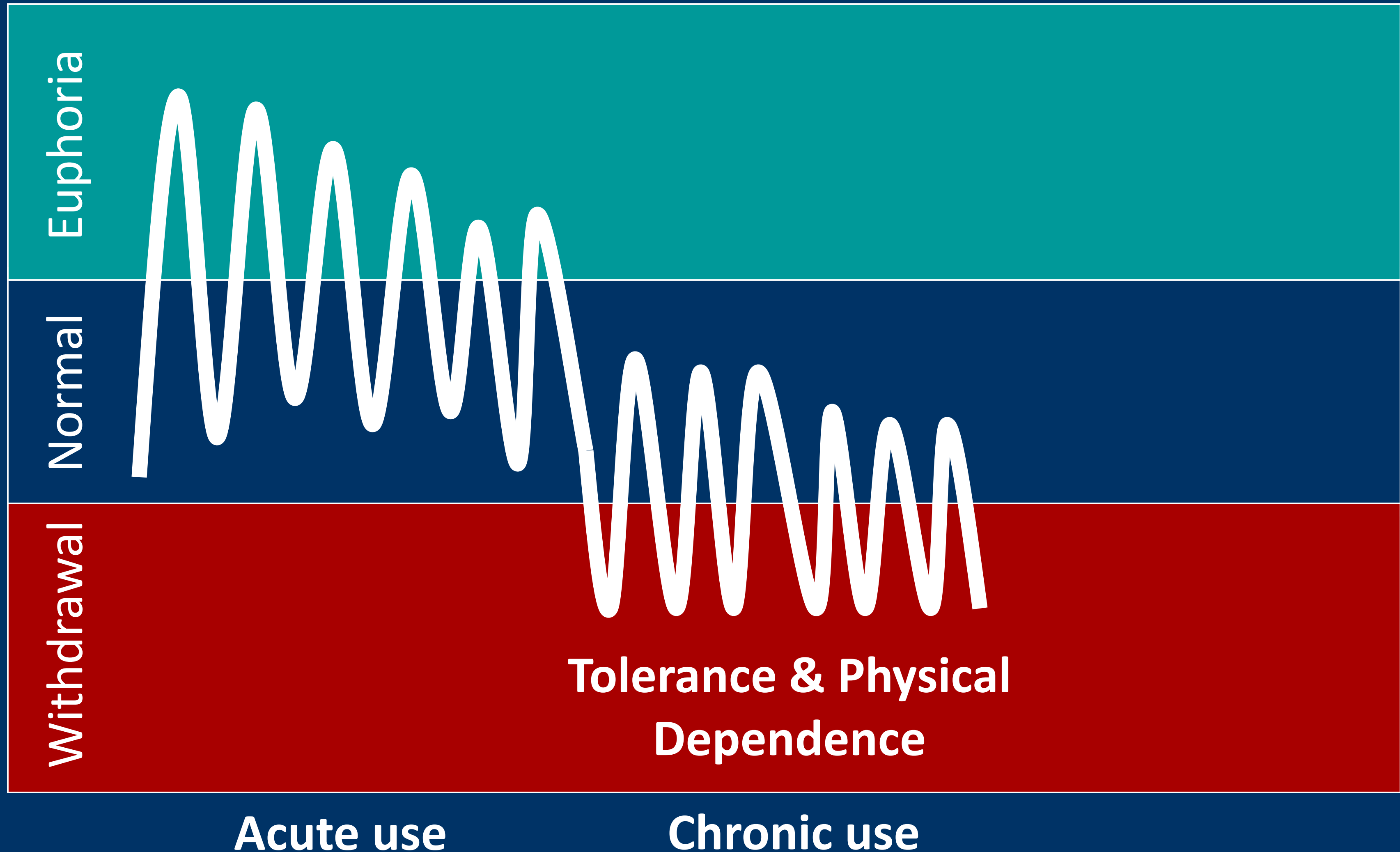
Grayken Center for Addiction
Boston Medical Center

Case

- 32 yo male brought in after "heroin overdose"
- Brisk response to IV naloxone 0.4 mg
- Re-sedation after 1 hr requiring repeat naloxone
- Antecubital abscess and cellulitis at injection site
- Admitted for "drug overdose", "persistent altered mental status" and "arm cellulitis"



Natural History of Opioid Use Disorder



Alford DP. http://www.bumc.bu.edu/care/

Case continued

Substance use history

- ½ gram of heroin/day
- Intranasal use for 6 months then IV for 7 years
- Had been in recovery for 2 years by going to NA but relapsed 3 months ago
- History of 10 detox's, no treatment with medications
- No other drug, alcohol or tobacco use

- HIV and hepatitis C negative
- Unemployed electrician
- Lives with wife (in recovery) and 2 young children
- **Now complaining of opioid withdrawal**
  - **How will you assess and treat him?**

Opioid Withdrawal Assessment

Grade	Symptoms / Signs
0	Anxiety, Drug Craving
1	Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia
2	Dilated pupils, Gooseflesh, Muscle twitching & shaking, Muscle & Joint aches, Loss of appetite
3	Nausea, extreme restlessness, elevated blood pressure, Heart rate > 100, Fever
4	Vomiting / dehydration, Diarrhea, Abdominal cramps, Curled-up body position

Clinical Opiate Withdrawal Scale (COWS): *pulse, sweating, restlessness & anxiety, pupil size, aches, runny nose & tearing, GI sx, tremor, yawning, gooseflesh*

(score 5-12 mild, 13-24 mod, 25-36 mod sev, 36-48 severe)

How is acute opioid withdrawal treated on your inpatient service?

A. Clonidine

B. Methadone

C. Buprenorphine

D. Don’t know

E. Other

Inpatient Goals

- Prevent/treat acute opioid withdrawal
  - Inadequate treatment may prevent full treatment of medical/surgical condition
- Don’t expect to cure OUD during hospitalization
  - Withholding opioids will not cure patient’s OUD
  - Giving opioids will not worsen patient’s OUD
- Diagnose and treat medical illness
- Initiate addiction treatment referral

Inpatient Goals

- **Methadone** or **buprenorphine** *(more expensive)* are the best choices!

- Other option…multidrug regimen

  Clonidine*, Tizanidine*, Lofexidine (hyperadrenergic state)

  \+ **NSAIDS** (muscle cramps and pain)

  \+ **Benzodiazepines** (insomnia)

  \+ **Dicyclomine** (abdominal cramps)

  \+ **Bismuth subsalicylate** (diarrhea)

* Off label use

Inpatient Dosing Guidelines

Methadone

- Start w/ **20** mg
- Reassess q 2-3 h, give additional **5-10** mg until withdrawal signs abate
- Don't exceed **40** mg/24 hrs

Buprenorphine

- Start with **4** mg
- Reassess q 2-3 h, give additional **4** mg until withdrawal signs abate
- Don't exceed **12** mg/24 hrs

- Monitor for CNS and respiratory depression
- Give same dose each daily including day of discharge
  - Allows 24-36 hour withdrawal-free period after d/c
- **Don't give a methadone prescription**
- **Can give a buprenorphine prescription if you are waivered**

Case continued

Hospital course

- Arm abscess I and D, cellulitis treated with IV Vancomycin
- Opioid withdrawal management
  - Day 1 Methadone 20 mg
  - Day 2
    - Very anxious, demanded increase in methadone
    - Off the floor for 2+ hours
    - Repeat urine drug test was positive for "**opiates**"

All of the following are possible explanations for her <u>opiate positive</u> drug test <u>EXCEPT</u>?

1. Illicit opioid (heroin) use during hospitalization
2. Heroin use prior to admission
3. Hydromorphone (Dilaudid) given for pain last night
4. Methadone given during hospitalization

Opioids

Opiates: Codeine and Morphine

Morphine

Diacetylmorphine (Heroin)

Oxymorphone

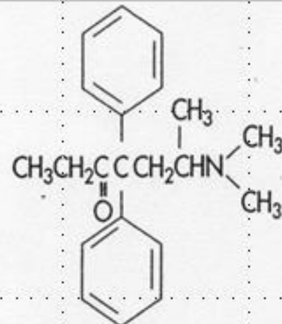
Natural (Opiates) and Semisynthetic

Hydrocodone

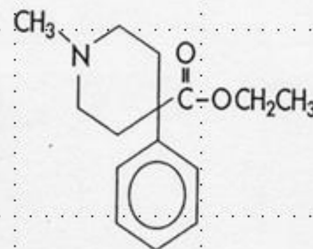
Hydromorphone

Oxycodone

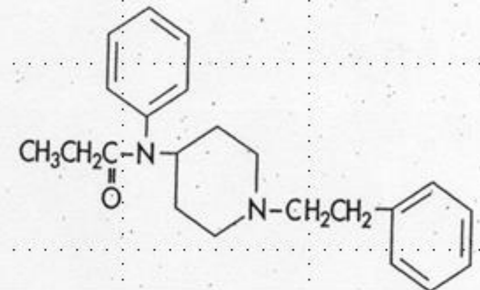
Synthetic



Methadone



Meperidine



Fentanyl

Case continued

6 months later

- He presents to your primary care clinic requesting treatment for his heroin addiction
- He has been using heroin since the day he left the hospital

Case continued

Recommended options from primary care

- Narcotics Anonymous (NA)
- Clonidine + NSAID + benzodiazepine + …
- Naltrexone (po or injectable) after abstinence
- Buprenorphine maintenance (if waivered)
- Overdose prevention education and naloxone
- Referral
    - Detoxification program
    - Methadone maintenance
    - Buprenorphine maintenance (if not waivered)
    - Needle exchange
    - Acupuncture
    - Outpatient counseling

Opioid Detoxification Outcomes

- Low rates 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

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

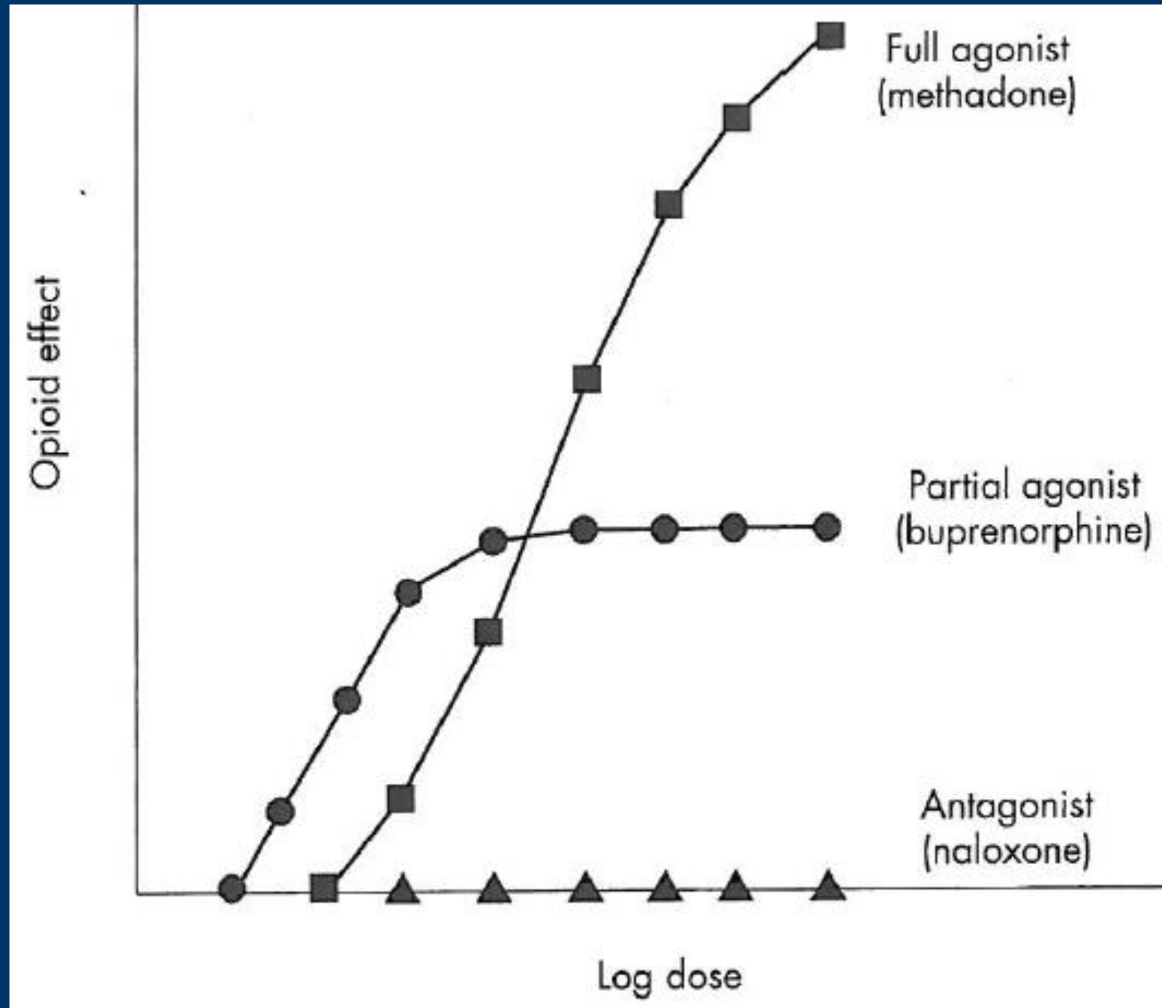
Reasons for Relapse

- Protracted abstinence syndrome
  - Secondary to derangement of endogenous opioid receptor system
  - Symptoms
    - Generalized malaise, fatigue, insomnia
    - Poor tolerance to stress and pain
    - Opioid craving
- Conditioned cues (triggers)
- Priming with small dose of drug

Medications for OUD Treatment

- Goals
  - Alleviate physical withdrawal
  - Opioid blockade
  - Alleviate drug craving
  - Normalized deranged brain changes and physiology
- Some options
  - **Naltrexone** (opioid antagonist)
  - Opioid Agonist Therapy
    - **Methadone** (full opioid agonist)
    - **Buprenorphine** (partial opioid agonist)

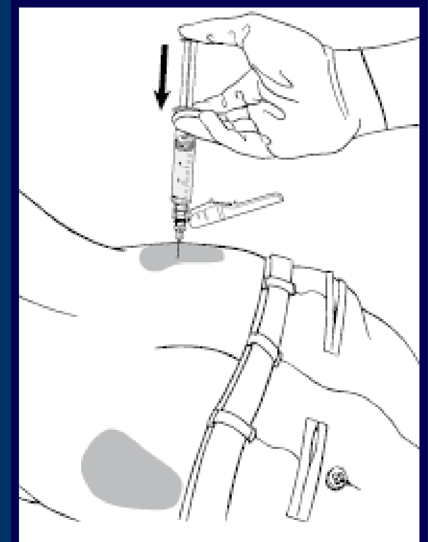
Mu Opioid Receptor Activation
Full Agonist, Partial Agonist, Antagonist



Office-Based Buprenorphine Treatment of Opioid Use Disorder, 2nd edition. Renner JA, Levounis P, LaRose AT eds. American Psychiatric Association Publishing, Inc, Arlington, VA, 2018

Naltrexone

- Pure opioid antagonist
- Oral naltrexone
  - Well tolerated, safe
  - Duration of action 24-48 hours
  - FDA approved 1984
- Injectable XR naltrexone
  - FDA approved 2010
  - IM w/ customized needle/month
  - Patients physically dependent must be opioid free for a minimum of 7-10 days before treatment



Oral Naltrexone

- Meta-analysis of 13 RCTs 1,158 participants
- Naltrexone maintenance treatment versus placebo or other treatments
- No statistically significant difference were noted for all the primary outcomes considered.
- Only 28% of people were retained in treatment in the included studies
- More effective than placebo in sustaining abstinence in studies where patients were legally mandated to take the drug

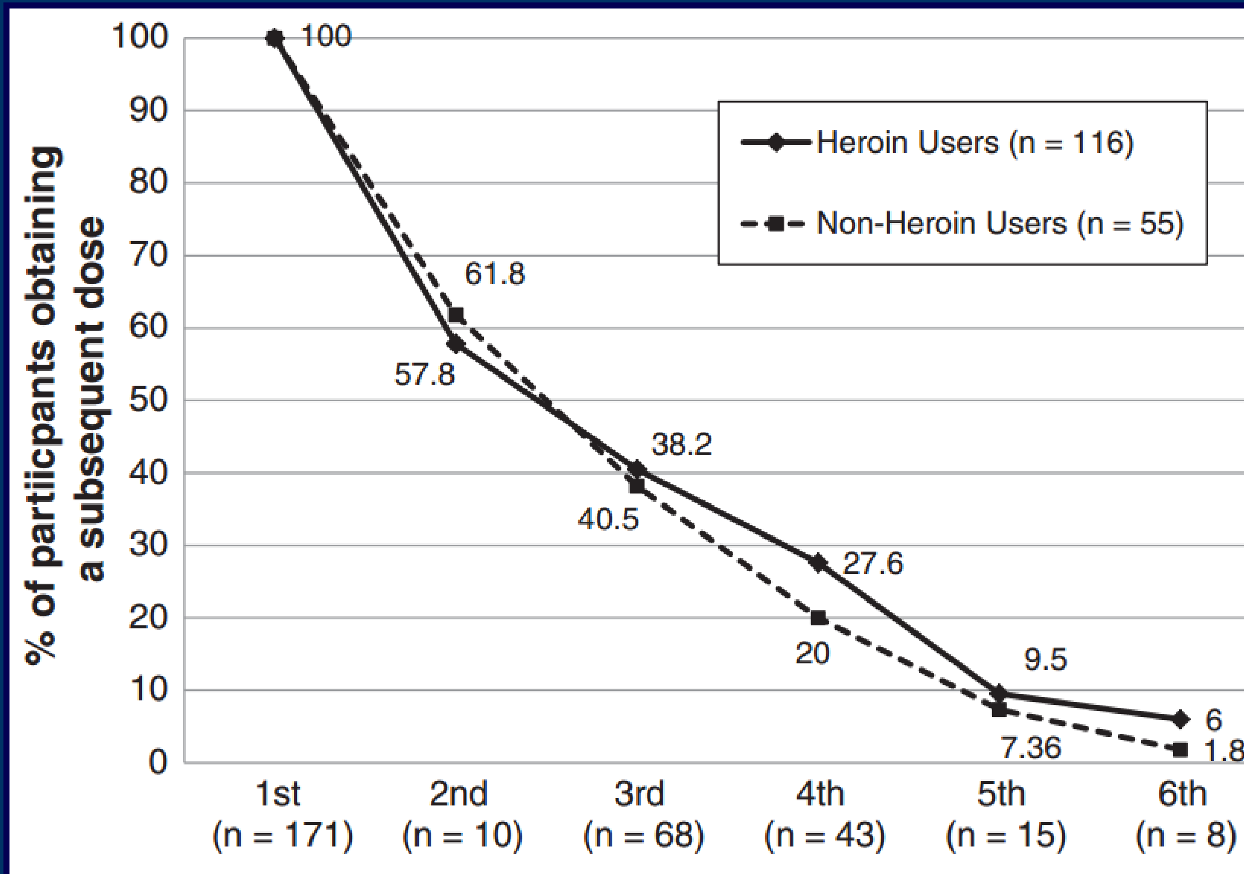
Minozzi S et al. *Cochrane Database Syst Rev* 2011

Injectable Naltrexone (XR-NTX)

- Multicenter (13 sites in Russia) funded by Alkermes
- DB RPCT, 24 wks, n=250 w/ opioid dependence
- All offered biweekly individual drug counseling
- Results
  - Weeks of confirmed abstinence (90% vs 35%)
  - Craving (-10 vs +0.7)

Krupitsky E, et al. *Lancet,* 2011

XR-NTX Retention



Mean doses (max 6)

- Heroin users 2.3
- Non-heroin opioid users 2.5

Drop out risk factors

- Homelessness
- Opioid injection use (regardless of opioid-type)
- Mental illness

N=171

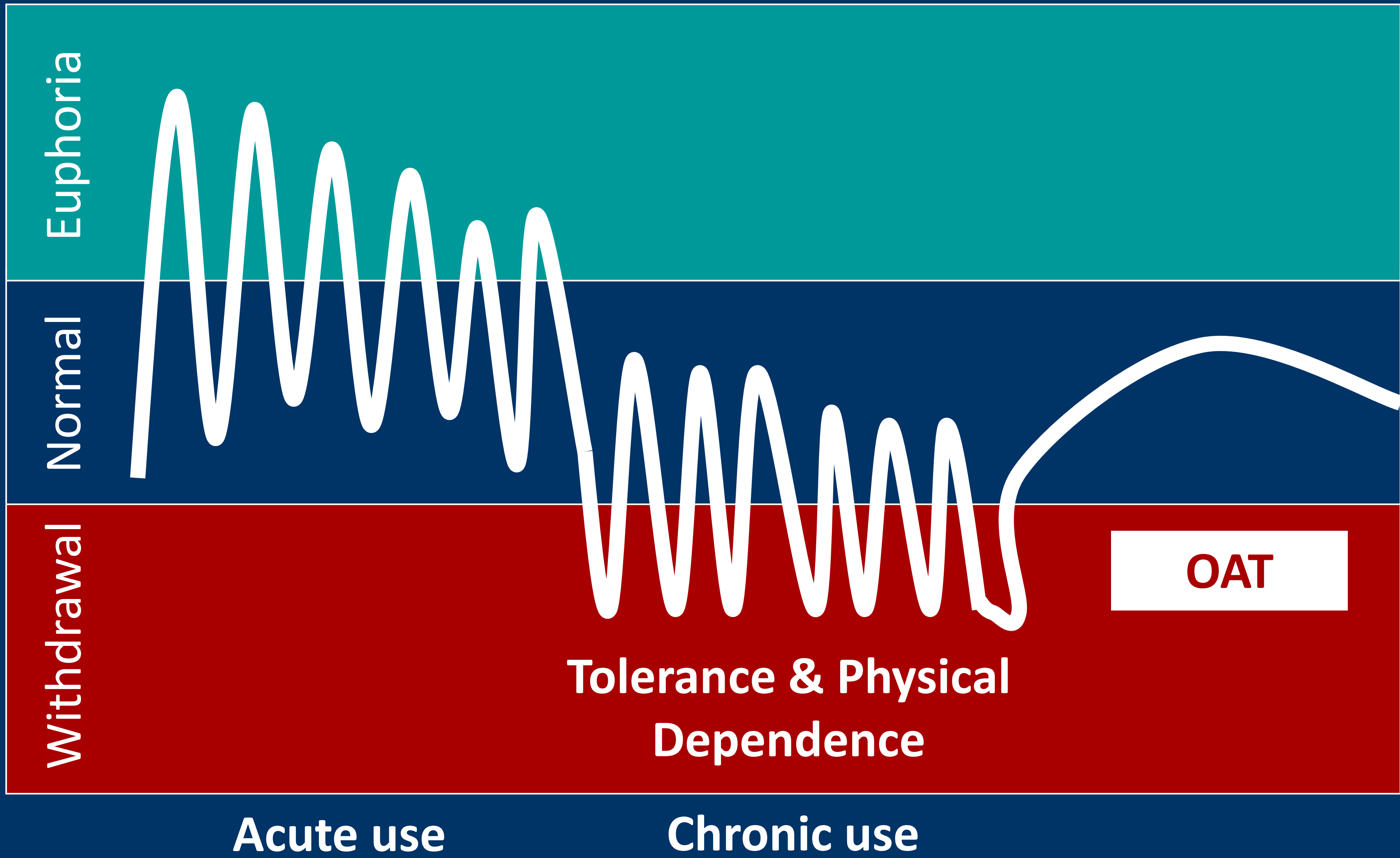
Cousins SJ et al. *J Sub Abuse Treat* 2016

XR-NTX and Linkage to Primary Care

- 62 adults with OUD
- Received 1st XR-NTX during inpatient detoxification, then referred to 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

Opioid Agonist Treatment (OAT)



Alford DP. http://www.bumc.bu.edu/care/

Methadone Hydrochloride

- Full opioid agonist
- PO onset of action 30-60 minutes
- Duration of action
  - 24-36 hours to treat OUD
  - 6-8 hours to treat pain
- Proper dosing for OUD
  - 20-40 mg for acute withdrawal
  - > 80 mg for craving, “opioid blockade”

Methadone Maintenance Treatment
Highly Structured

- Methadone dosing
  - Observed daily ⇒ “Take homes”
- Daily nursing assessment
- Weekly individual and/or group counseling
- Drug testing
- Psychiatric services
- Medical services

A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

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

JAMA 1965

Extensive Research on Effectiveness

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

Methadone Maintenance Limitations

- Highly regulated - *Narcotic Addict Treatment Act 1974*
    - Created methadone clinics (Opioid Treatment Programs)
    - Separate system not involving primary care or pharmacists
- Limited access
- Inconvenient and highly punitive
- Mixes stable and unstable patients
- Lack of privacy
- No ability to “graduate” from program
- **Stigma “I don’t believe in methadone”**

Drug Addiction Treatment Act (DATA) 2000

2000: Qualified physician (e.g., 8 hours of training) to prescribe scheduled III - V, narcotic FDA approved for OUD treatment limit 30 patients per practice

2005: Limit to 30 patients per physician

2007: Limit to 100 patients per physician after 1 year

2016: Limit to 275 patients (HHS Final Rule (Regulation) 2016) after 1 year at 100 patients

Comprehensive Addiction and Recovery Act (CARA) 2016

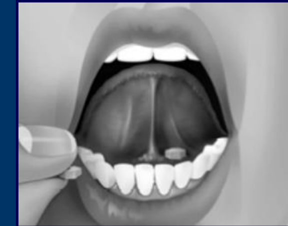
Expands to qualified NPs and PAs

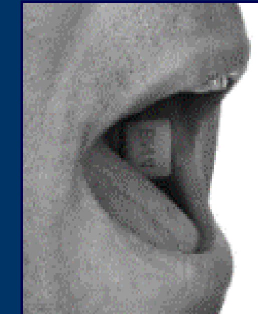
- Require 24 hours of training
- Must be supervised by qualifying physician if required by state law
- 30 patients for at least 1 year then up to 100 patients

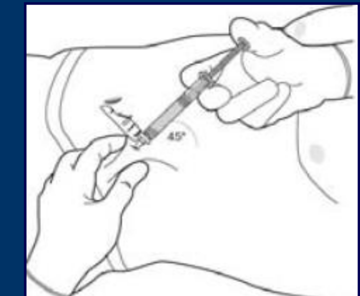
Buprenorphine Formulations

For OUD (off-label for pain)

Drug	Formulations	Maintenance	Cost/6 m
Buprenorphine			
generic	2, 8 mg SL tabs	16 mg/d	$1,083
Probuphine	74.2 mg SD implant	4 implants/6m	$4,950
Sublocade	100 mg SQ injection	100 mg/m	$9,480
Buprenorphine/Naloxone			
generic	2/0.5, 8/2 mg SL tabs	16/4 mg/d	$2,339
Bunavail	2.1/0.3, 4.2/0/7, 6.3/1 mg buccal film	8.4/1.4 mg/d	$2,793
Suboxone	2/0.5, 4/1, 8/2, 12/3 mg SL film	16/4 mg/d	$2,933
Zubsolv	1.4/0.36, 5.7/1.4 mg SL tab	11.4/2.8 mg/d	$2,989

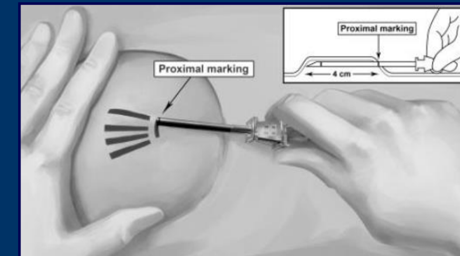






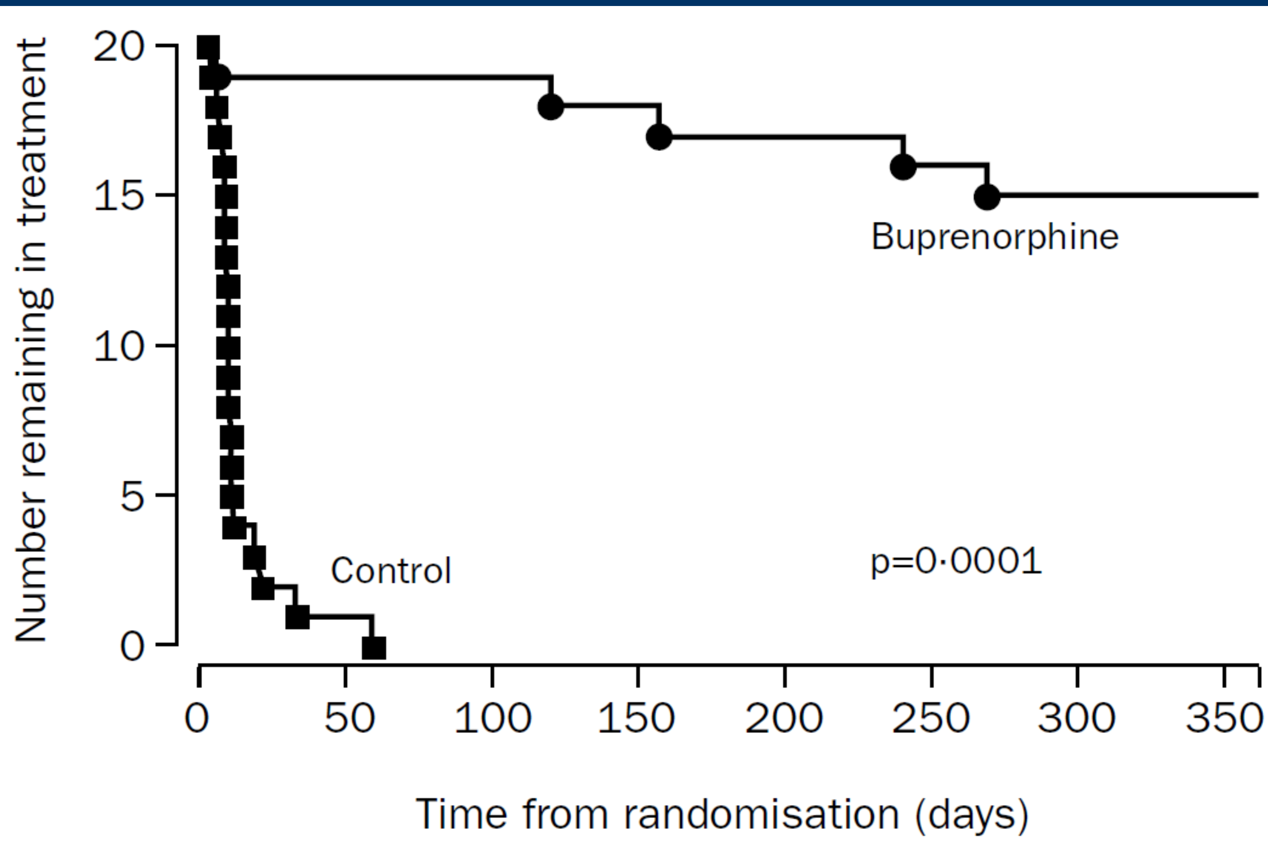
For Pain NOT OUD

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



The Medical Letter 2/2018

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 Summary

Studies (RCT) show buprenorphine (**16-24 mg**) more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:

- Retention in treatment
- Abstinence from illicit opioid use
- Decreased opioid craving
- Decreased mortality
- Improved occupational stability
- Improved psychosocial outcomes

Johnson et al. *NEJM* 2000
Fudala PJ et al. *NEJM* 2003
Kakko J et al. *Lancet* 2003
Sordo L et al. *BMJ* 2017
Mattick RP et al. *Conchrane Syst Rev* 2014
Parran TV et al. *Drug Alcohol Depend* 2010

Annals of Internal Medicine REVIEW

Primary Care–Based Models for the Treatment of Opioid Use Disorder

A Scoping Review

P. Todd Korthuis, MD, MPH; Dennis McCarty, PhD; Melissa Weimer, DO, MCR; Christina Bougatsos, MPH; Ian Blazina, MPH; Bernadette Zakher, MBBS; Sara Grusing, BS; Beth Devine, PhD, PharmD, MBA; and Roger Chou, MD 2016

12 representative models for integrating into primary care settings across diverse health care settings

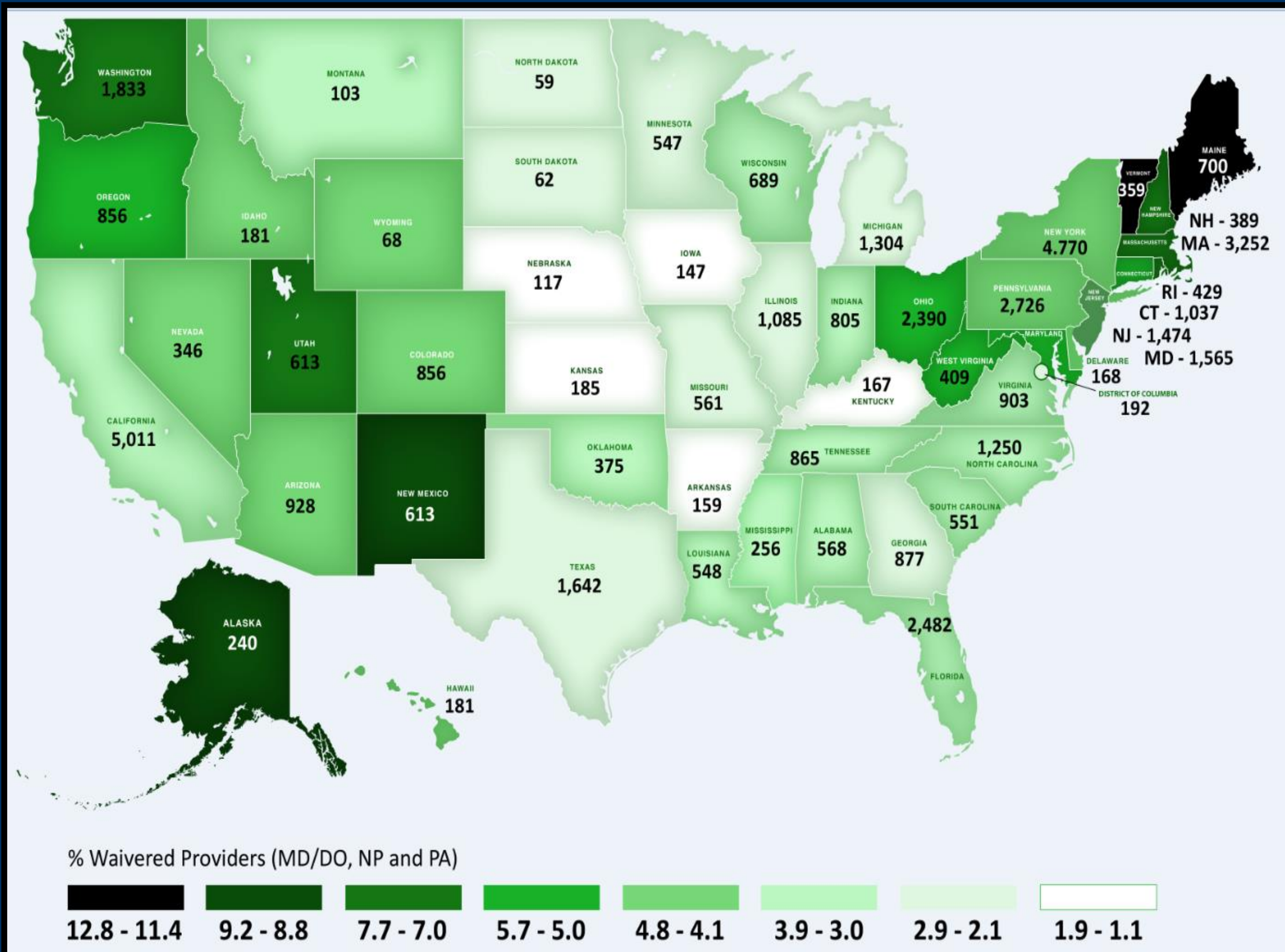
Nurse Care Manager Collaborative Care

At 12 months,

- 51% of patients remained in treatment or successfully tapered
- Urine negative for opioids and cocaine in 91% of patients who remained in treatment

Alford DP et al. *Arch Intern Med.* 2011

Percent DATA Waivered Clinicians by State



% DATA Waivered by Profession

All Physicians: 4.4%
(42,015/951,061)

PCPs: 9.2%
(42,015/456,389)

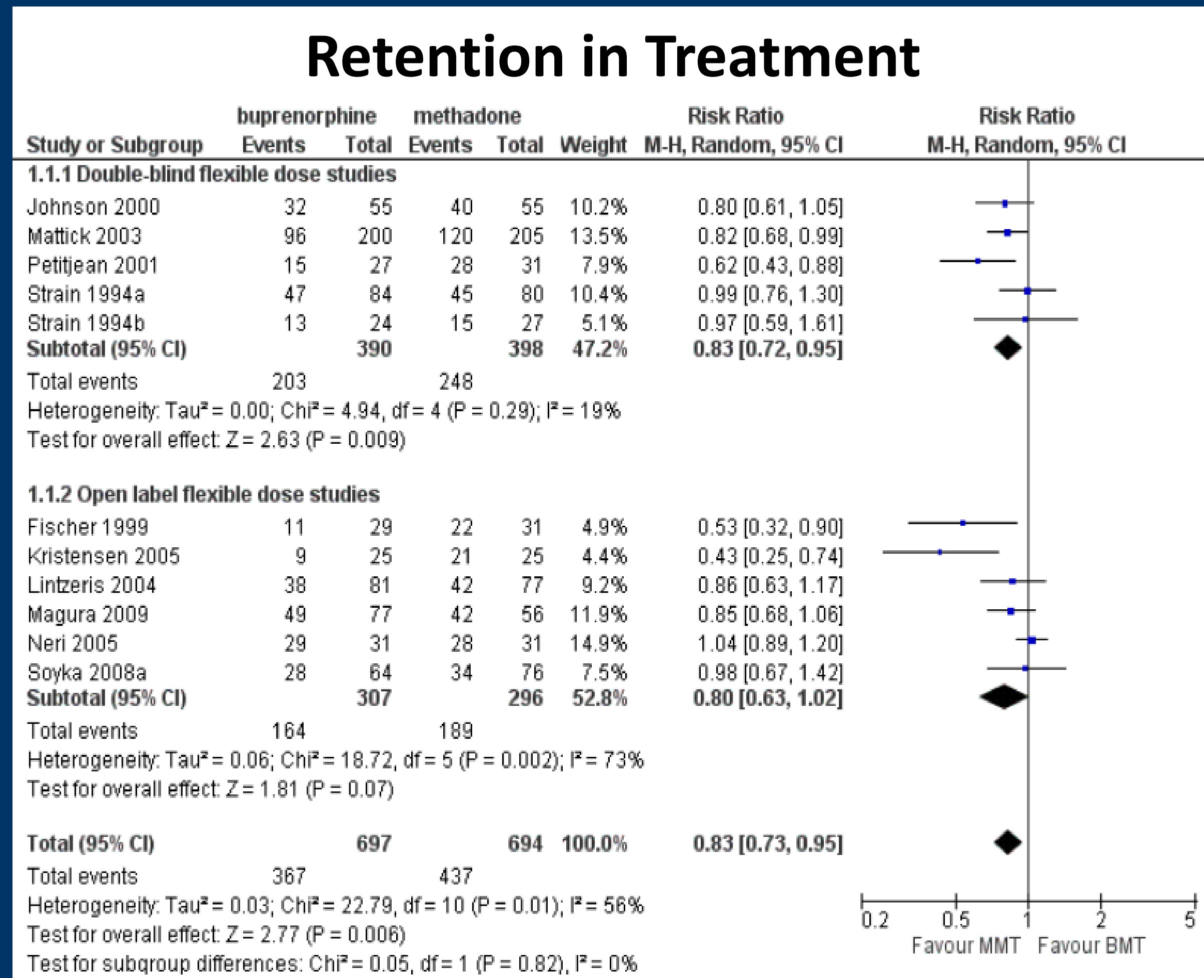
NPs: 3.2%
(5,284/164,794)

PAs: 1.6%
(1,389/88,006)

SAMHSA 2018
Image by Andrew Parakevas, BUSM CME

Methadone vs. Buprenorphine for OUD

- Buprenorphine less effective than methadone in retention using flexible doses, 5 studies, n=788 *(high quality evidence)*
- For those retained no difference in decrease opioid use, 8 studies, n=1027 *(moderate quality of evidence)*



Retention in Treatment

Study or Subgroup	buprenorphine Events	buprenorphine Total	methadone Events	methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Double-blind flexible dose studies						
Johnson 2000	32	55	40	55	10.2%	0.80 [0.61, 1.05]
Mattick 2003	96	200	120	205	13.5%	0.82 [0.68, 0.99]
Petitjean 2001	15	27	28	31	7.9%	0.62 [0.43, 0.88]
Strain 1994a	47	84	45	80	10.4%	0.99 [0.76, 1.30]
Strain 1994b	13	24	15	27	5.1%	0.97 [0.59, 1.61]
Subtotal (95% CI)		**390**		**398**	**47.2%**	**0.83 [0.72, 0.95]**
Total events	203		248			
Heterogeneity: Tau² = 0.00; Chi² = 4.94, df = 4 (P = 0.29); I² = 19%						
Test for overall effect: Z = 2.63 (P = 0.009)						
1.1.2 Open label flexible dose studies						
Fischer 1999	11	29	22	31	4.9%	0.53 [0.32, 0.90]
Kristensen 2005	9	25	21	25	4.4%	0.43 [0.25, 0.74]
Lintzeris 2004	38	81	42	77	9.2%	0.86 [0.63, 1.17]
Magura 2009	49	77	42	56	11.9%	0.85 [0.68, 1.06]
Neri 2005	29	31	28	31	14.9%	1.04 [0.89, 1.20]
Soyka 2008a	28	64	34	76	7.5%	0.98 [0.67, 1.42]
Subtotal (95% CI)		**307**		**296**	**52.8%**	**0.80 [0.63, 1.02]**
Total events	164		189			
Heterogeneity: Tau² = 0.06; Chi² = 18.72, df = 5 (P = 0.002); I² = 73%						
Test for overall effect: Z = 1.81 (P = 0.07)						
Total (95% CI)		**697**		**694**	**100.0%**	**0.83 [0.73, 0.95]**
Total events	367		437			
Heterogeneity: Tau² = 0.03; Chi² = 22.79, df = 10 (P = 0.01); I² = 56%						
Test for overall effect: Z = 2.77 (P = 0.006)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						

Mattick RP et al. *Cochrane Database Systematic Reviews* 2014

Methadone vs Buprenorphine in OTP

9 OTPs
n=1,267
RCT
buprenorphine vs methadone
6 month retention

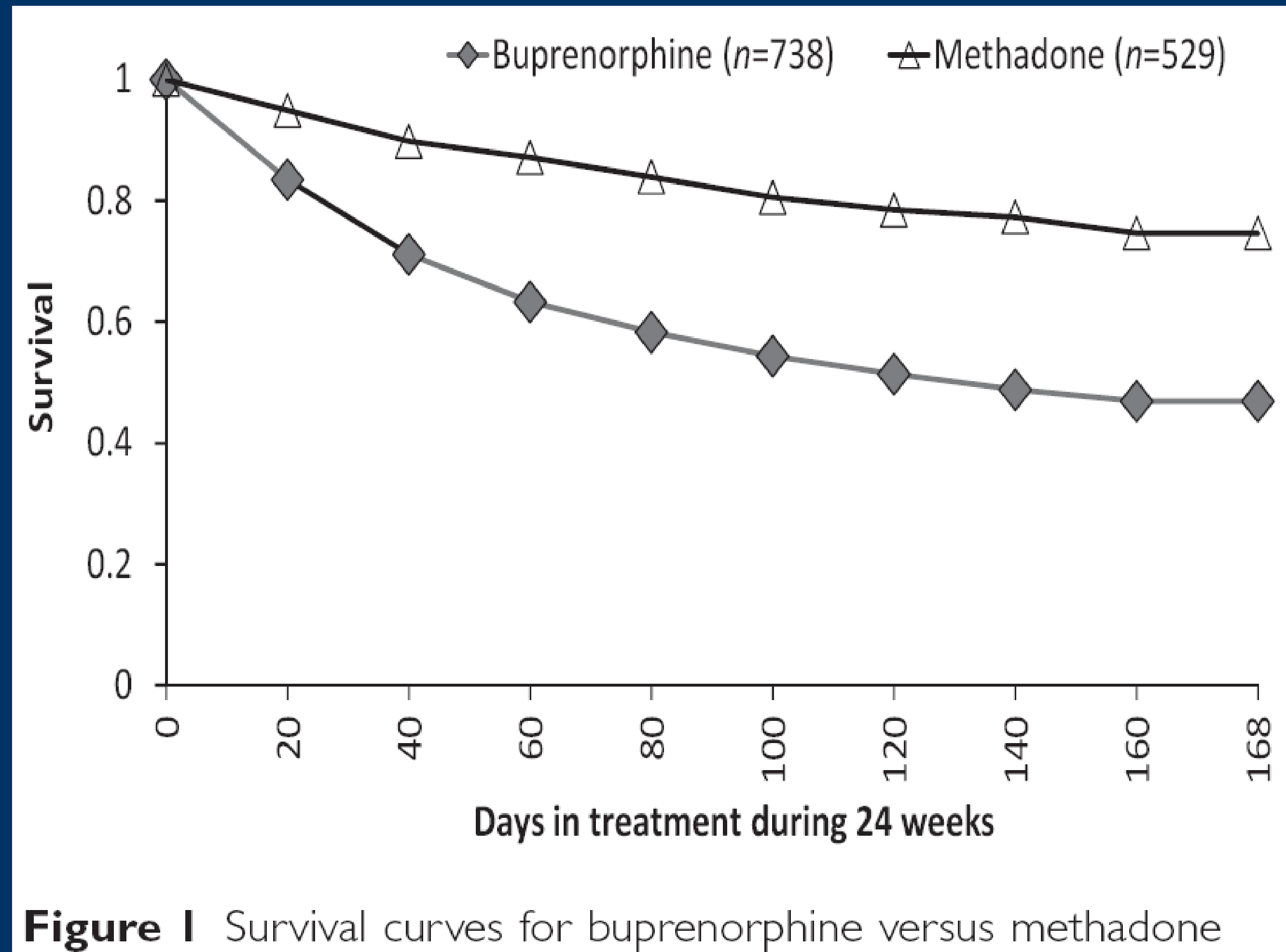
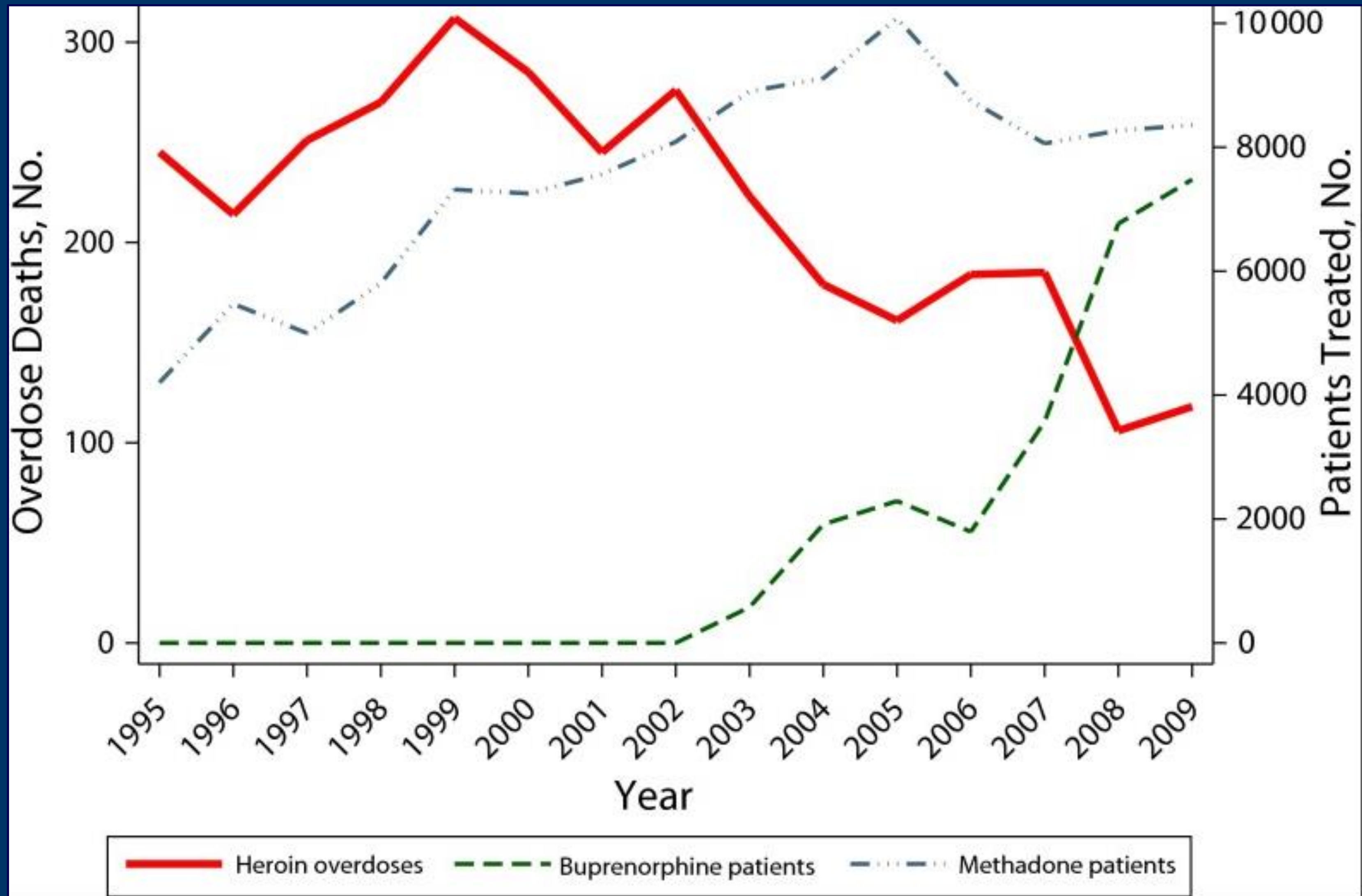


Figure 1 Survival curves for buprenorphine versus methadone

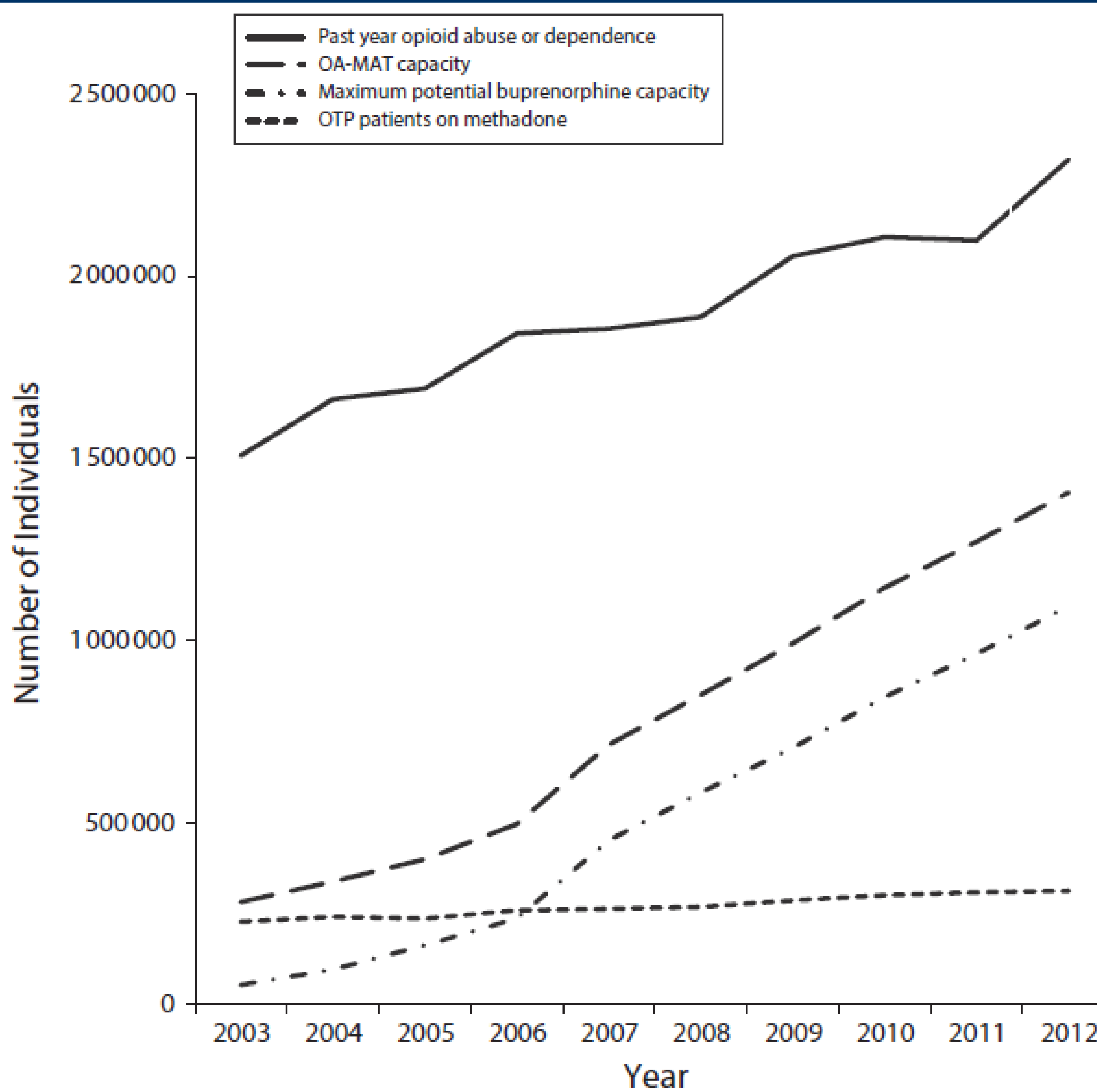
Hser Y et al. *Addiction.* 2014

OAT May Reduce Overdose Deaths



Schwartz R et al. *Am J Public Health* 2013

OUD and OAT Capacity



Gap=914,000

Jones CM et al. *Am J Public Health.* 2015

"Overcoming My Fear of Treating Opioid Use Disorder"

Dr. P was reluctant to obtain a waiver to prescribe buprenorphine for the treatment of OUD until her patient (Ms. L) with longstanding OUD died from a fatal opioid overdose…

- "Caring for these patients has become the most meaningful part of my practice."
- "Providing some sense of normalcy for patients whose lives are roiled by overdose and estrangement is the most profound therapeutic intervention I've engaged in as a caregiver."
- "I did not know what Ms. L. meant all those years ago when she said that she only wished to feel normal again. I wish that I'd listened more closely. I wish that I had not been afraid."

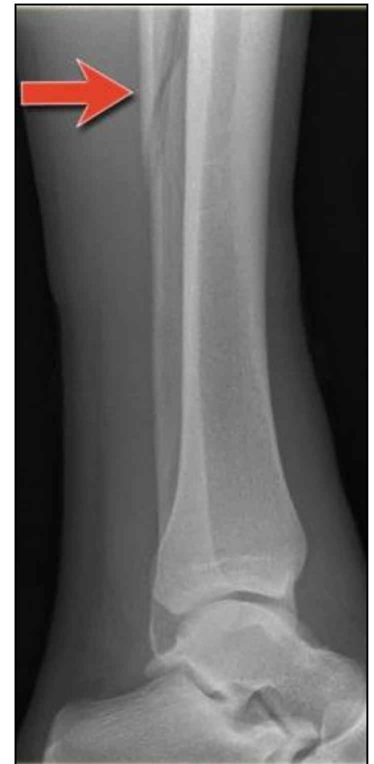
Provenzano AM. *N Engl J Med*. 2018

Case continued

2 years later…

- He has been successfully treated with buprenorphine/naloxone (16/4) SL qd and outpatient counseling with no relapses

- He presents to the ED with a fibula fracture sustained while playing soccer.
- How will you manage his acute pain?



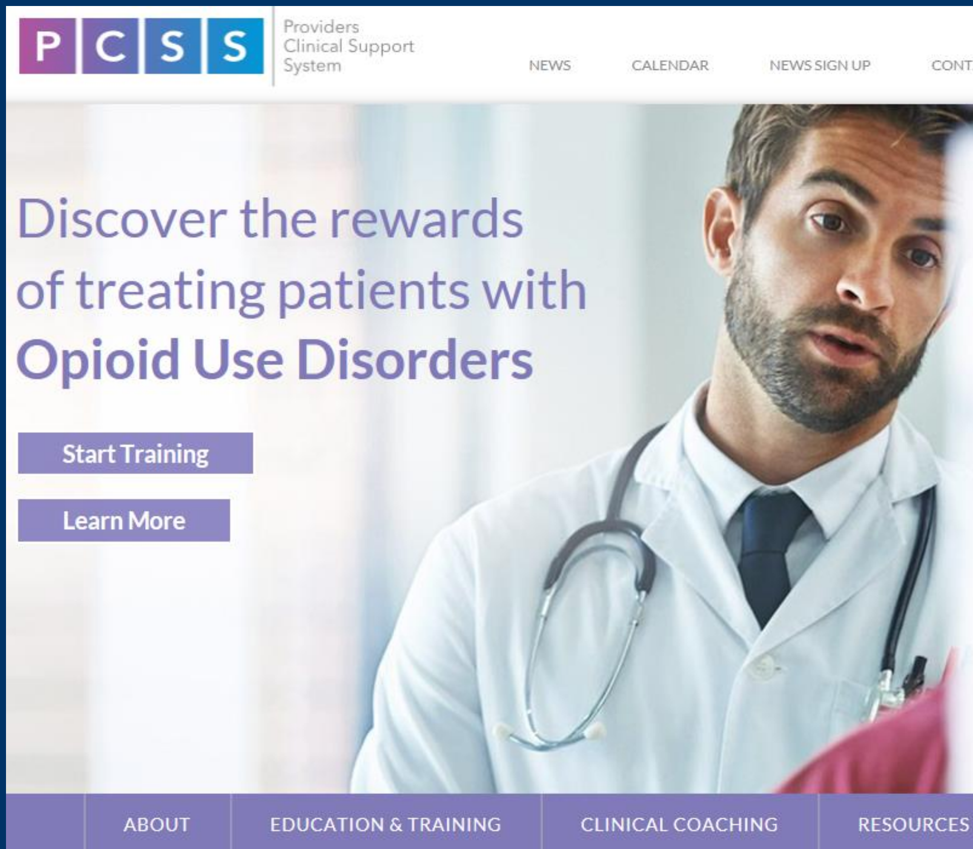
Opioid Agonist Treatment (OAT) and Acute Pain Management

- Patients with an OUD on OAT (i.e. methadone or buprenorphine) have less pain tolerance then matched controls
- Patients who are physically dependent on opioids (i.e. methadone or buprenorphine) must be maintained on a daily equivalence before ANY analgesic effect is realized with opioids used for acute pain management
- Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance

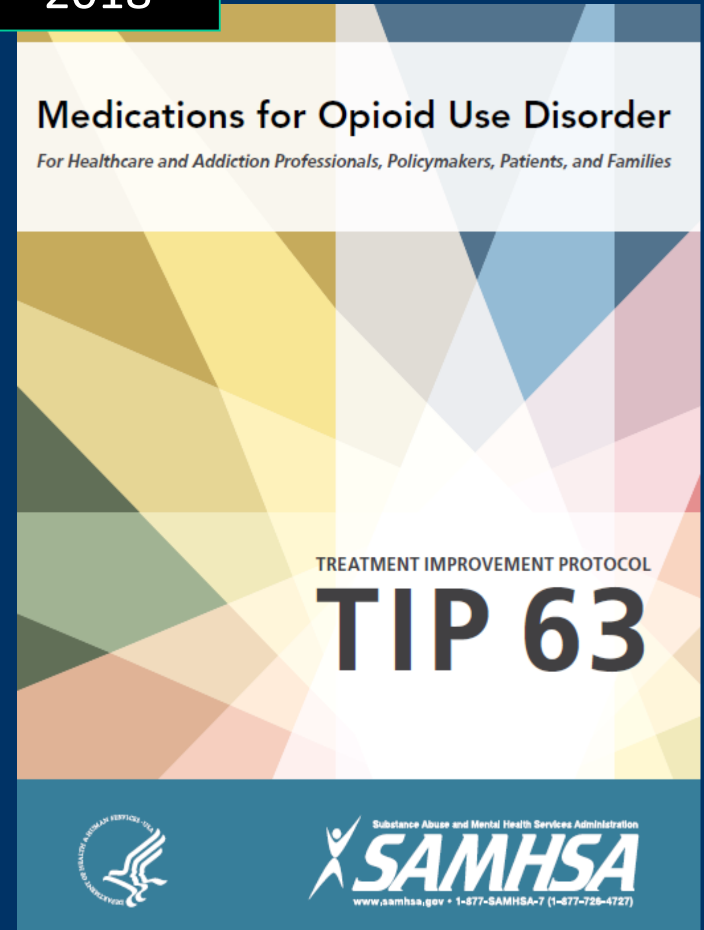
Alford DP, Compton P, Samet JH. *Ann Intern Med* 2006
Alford DP. *Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence* 2nd ed. American Psychiatric Publishing, Inc. (APPI) Arlington, VA. 2018

Resources

https://pcssnow.org/



2018



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