Pharmacotherapy of Opioid Use Disorder (OUD)

Julie Kmiec, DO
Assistant Professor of Psychiatry
University of Pittsburgh School of Medicine

kmiecj@upmc.edu

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- I have no disclosures

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Objectives

- By the end of this lecture, participants should be able to
  - Discuss the prevalence of OUD and medical complications of this disorder
  - Discuss the possible risks and benefits of methadone and regulations regarding providing treatment with methadone
  - Understand the pharmacology of buprenorphine, as well as possible risks and benefits of this medication
  - Discuss the role of naltrexone in treatment of opioid use disorder, risks and benefits, as well as barriers to starting this medication

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Opioid use disorder over the years

- NESARC data for US adults comparison of 2001-2002 to 2012-2013 (NESARC-III)
  - Nonmedical prescription opioid use increased by 161%
  - Nonmedical prescription opioid use disorder increased by 125% (Saha et al., 2016)

  - Lifetime heroin use increased almost 5 times
  - Lifetime prevalence of heroin use disorder increased approximately 3-fold (Martins et al., 2017)

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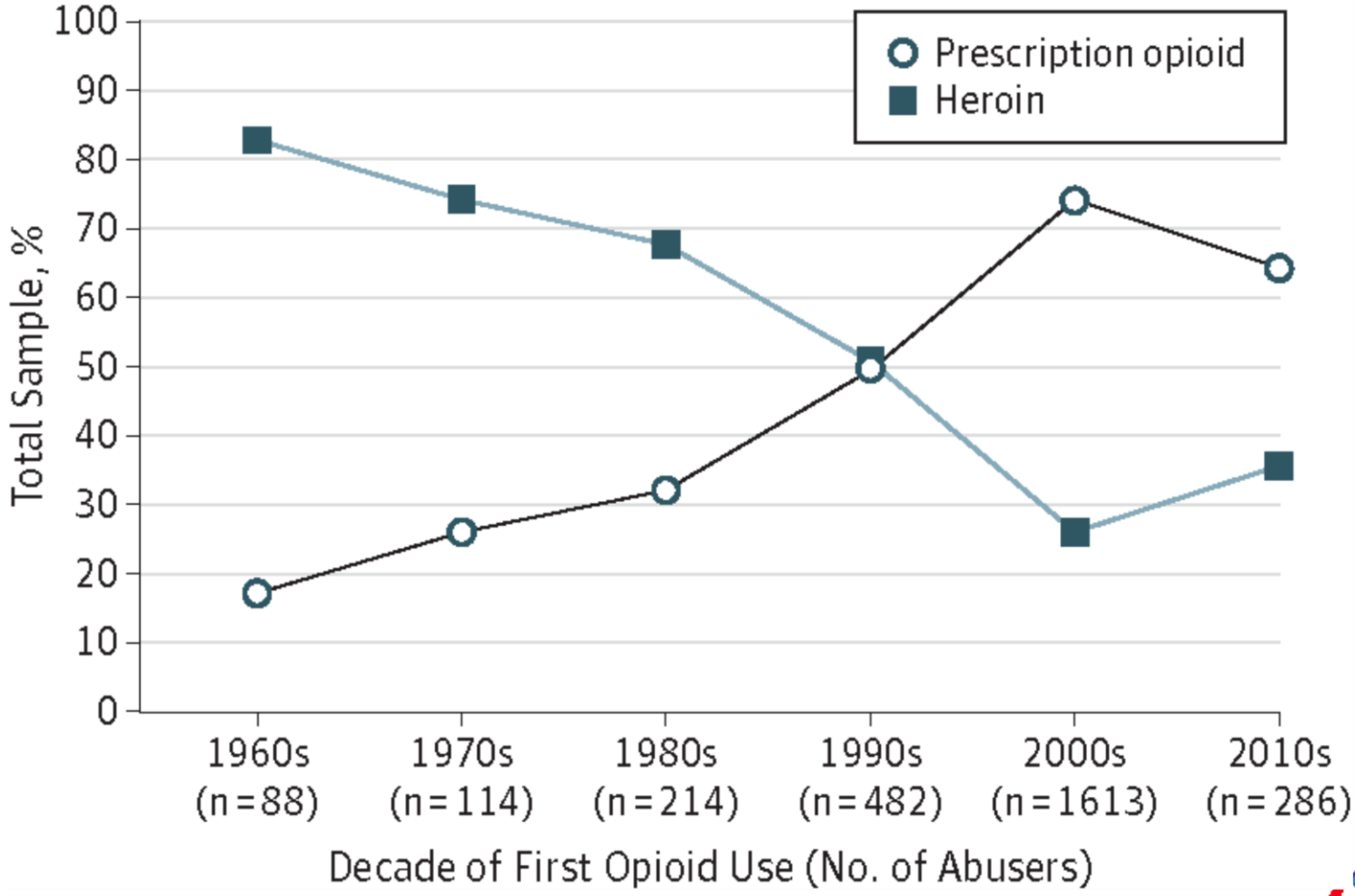
The changing face of heroin use in the last 50 years



Cicero et al., 2014

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Increase in heroin as initiating opioid of abuse

Addictive Behaviors 74 (2017) 63–66

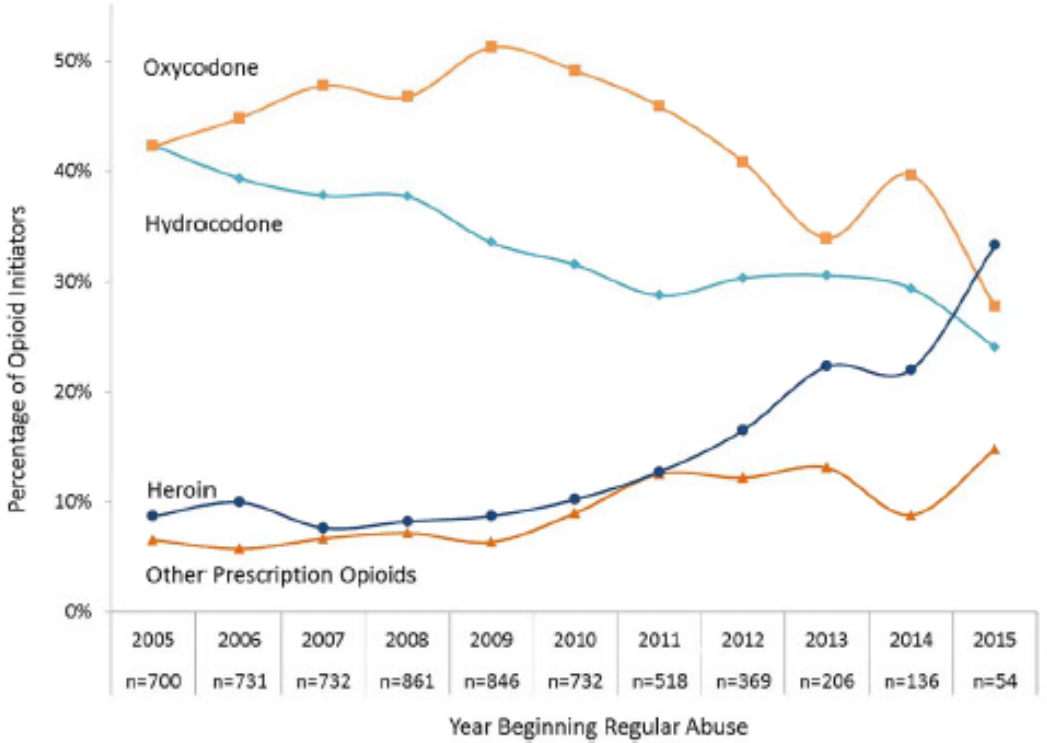

Fig. 1. First opioid of regular use among opioid initiates from 2005 to 2015 (N = 5885). Cochran-Armitage trend tests showed significant changes for heroin (< .0.001), hydrocodone (< 0.001), other prescription opioids (< 0.001), but not oxycodone (p = 0.13).

Cicero et al., 2017

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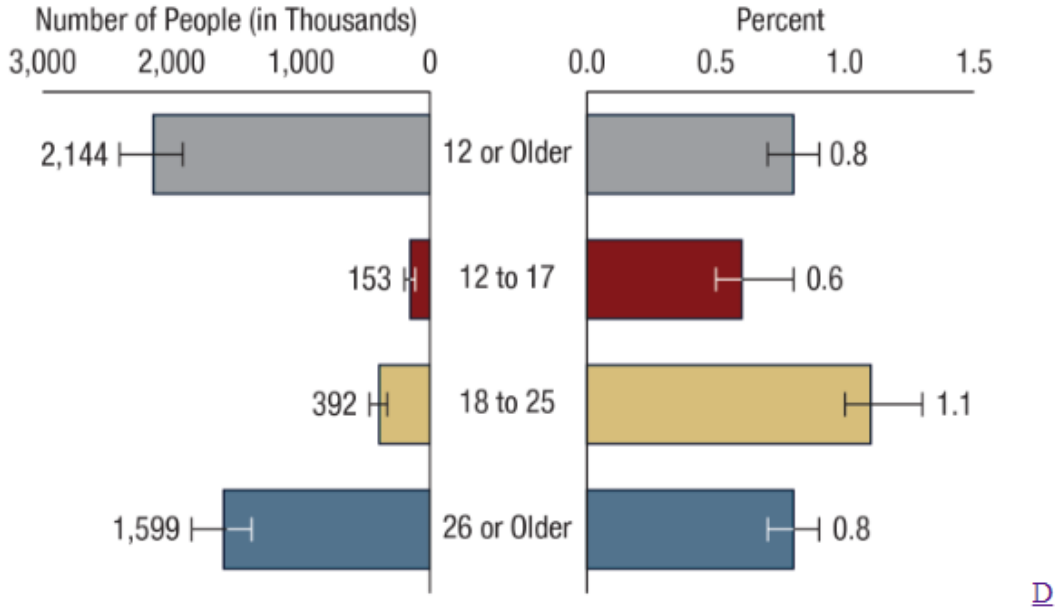
Figure 41. Opioid Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: 2016



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Note: Opioid use disorder is defined as meeting DSM-IV criteria for heroin use disorder or pain reliever use disorder in the past 12 months.

Substance Abuse and Mental Health Services Administration. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

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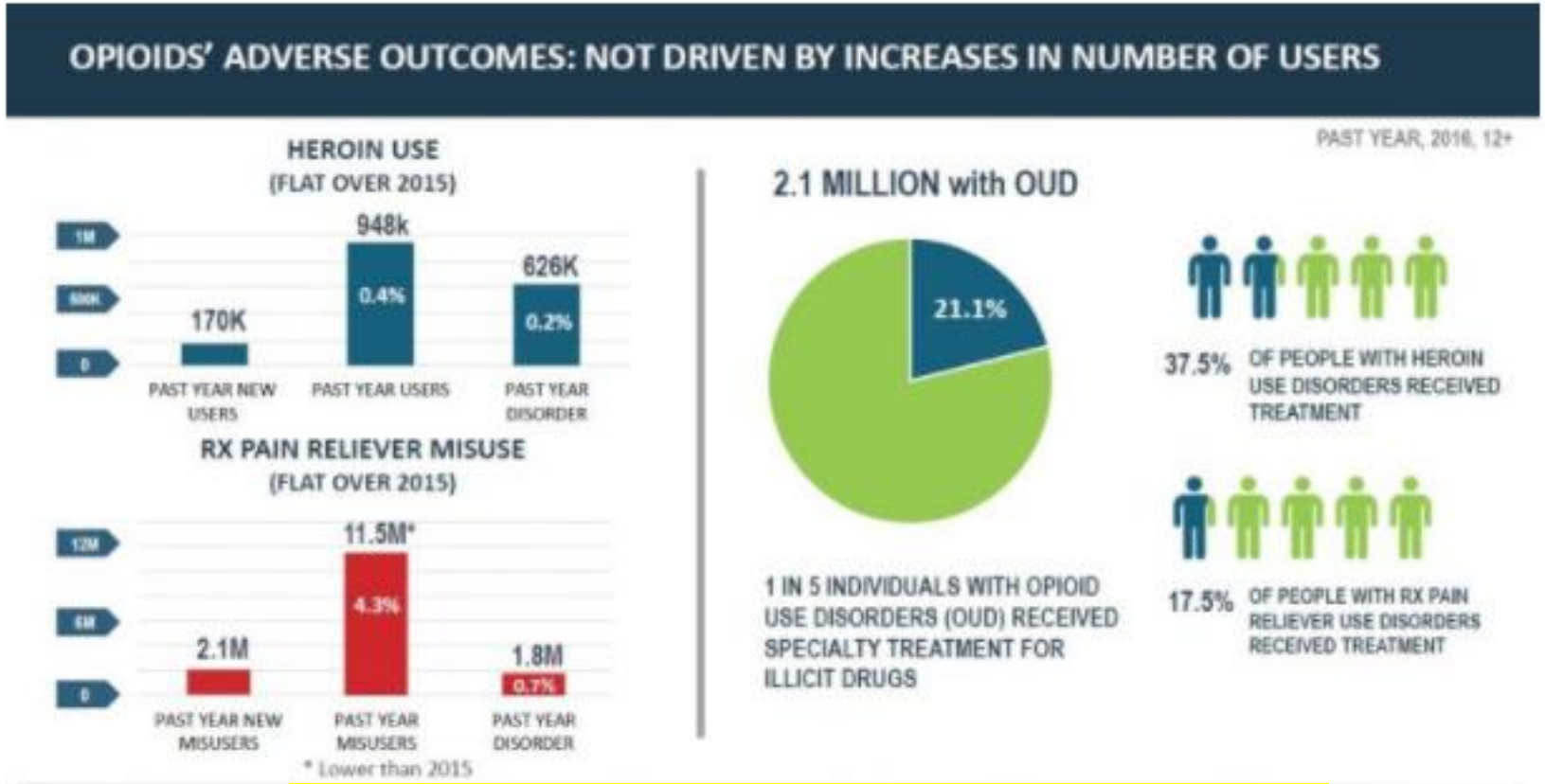


Buprenorphine was offered in 27% of specialty care facilities (SAMHSA NSSATS 2016)

Specialty treatment

Hospital (IP only)

D&A rehab (IP or OP)

Mental health center

Nonspecialty treatment

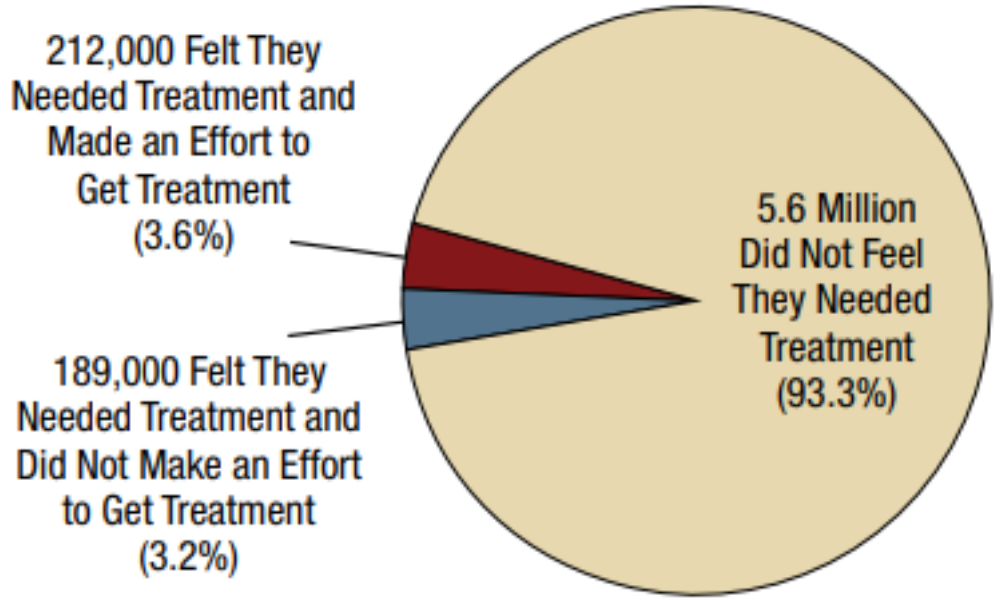
ED

Private doctor's office

Prison/jail

Self-help groups

Figure 15. Perceived Need for Illicit Drug Use Treatment among Adults Aged 18 or Older Who Needed but Did Not Receive Illicit Drug Use Treatment in the Past Year: 2016



6.0 Million Adults Needed but Did Not Receive Illicit Drug Use Treatment

Note: The percentages do not add to 100 percent due to rounding.

Park-Lee, E., Lipari, R. N., Hedden, S. L., Kroutil, L. A., & Porter, J. D. (2017, September). *Receipt of services for substance use and mental health issues among adults: Results from the 2016 National Survey on Drug Use and Health.* NSDUH Data Review. Retrieved from https://www.samhsa.gov/data

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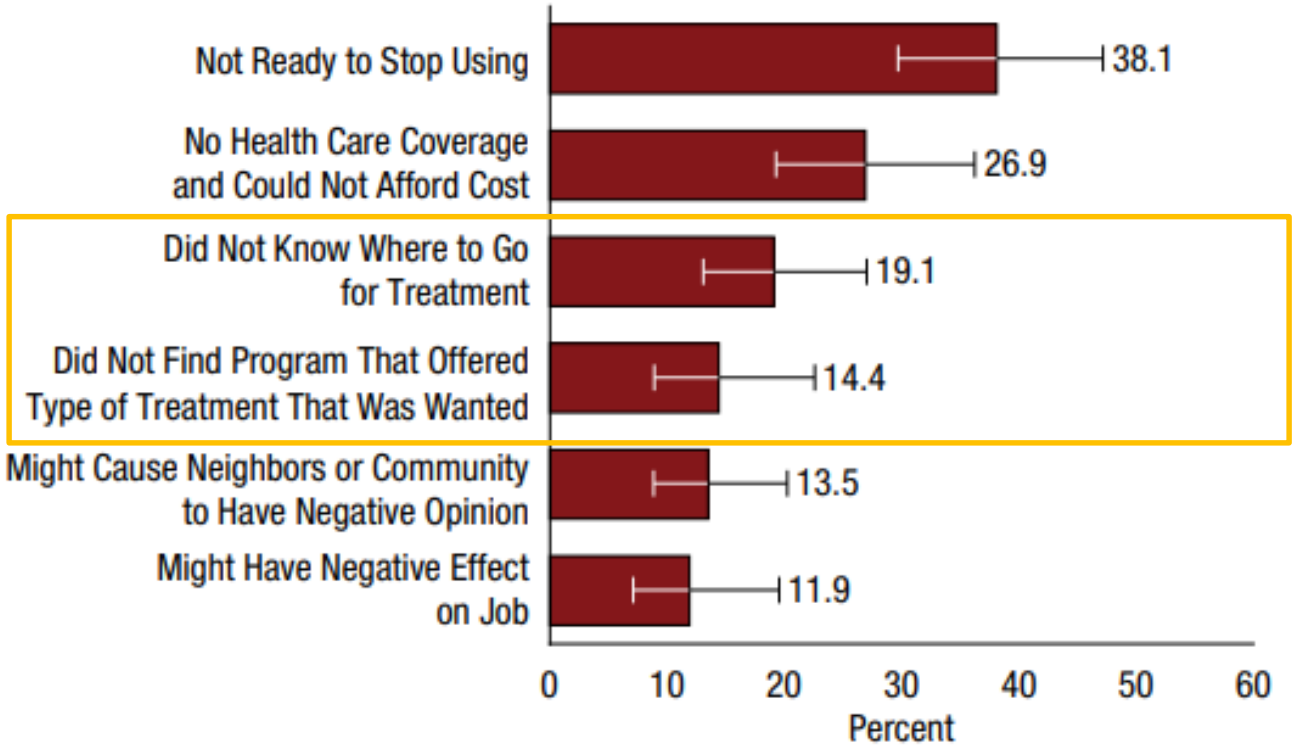
Figure 17. Reasons for Not Receiving Substance Use Treatment in the Past Year among Adults Aged 18 or Older Who Felt They Needed Treatment in the Past Year: Percentages, 2016



Note: Respondents could indicate multiple reasons for not receiving mental health services; thus, these response categories are not mutually exclusive.

Park-Lee, E., Lipari, R. N., Hedden, S. L., Kroutil, L. A., & Porter, J. D. (2017, September). *Receipt of services for substance use and mental health issues among adults: Results from the 2016 National Survey on Drug Use and Health.* NSDUH Data Review. Retrieved from https://www.samhsa.gov/data

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Some complications of opioid use disorder

- Overdose
- Increased mortality (6-20x higher than general population; Hser et al., 2015)
- Infections
  - Cellulitis/abscess
  - Osteomyelitis
  - Septic emboli
  - Endophthalmitis
  - Endocarditis
  - HIV
  - HCV
    - 32% become positive for HCV within 1 year of IDU
    - 53% positive within 5 years (Hagan et al., 2008)

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Pharmacotherapy for OUD

- One of many tools in the “recovery toolbox” we can offer to patients
- Reduce cravings which can help stabilize and strengthen coping capacity
- Allow patients to focus on behavioral therapies
- Increase periods of abstinence and instill a sense of self-efficacy to help sustain recovery
- Improve clinical outcomes for patients and reduce impact on families/loved ones

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Pharmacotherapy for OUD

- Evidence based treatments to
  - Decrease opioid and injection drug use
  - Reduce transmission of hepatitis C and HIV
  - Decrease criminal behavior
  - Retain people in treatment
  - Decrease overdose
  - Reduce sexual risk behaviors (e.g., trading sex for money/drugs)
  - Improve in physical and mental health and social functioning

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Medications for Opioid Use Disorder

- Full agonist
  - Methadone
- Partial agonist
  - Buprenorphine/naloxone
  - Buprenorphine
- Antagonist
  - Naltrexone
  - Naltrexone-XR

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METHADONE

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Methadone

- Methadone clinics started after Dole & Nyswander's study published in 1965
- Methadone, when used for treatment of OUD, is dosed at licensed opioid treatment programs (i.e., no Rx for tabs)
- Full mu-agonist
- Half-life of 24-36 hours
- Dosed once daily except for rapid metabolizers

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Methadone

- At least 1 year history of opioid use disorder (mod-severe)
  - Exceptions
    - Pregnant women
    - Released from correctional facility within last 6 mos
    - Previously treated patients up to 2 years after discharge
- Person under 18
  - Must have been detoxed twice or psychosocial treatment within 12 mos
  - Parents must consent in writing
  - In PA – more restrictive regulations for minors – only if pregnant

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Methadone

- Induction
  - Typically started on no higher than 30 mg on day 1 unless physician can document withdrawal, can give additional 10 mg
  - Risk of death from overdose is highest during induction
    - Increased risk with increased dose and sedative use (this includes alcohol)
  - Takes 3-7 days to reach steady state, so dose changes should reflect this time period
    - Dose change of no more than 5 mg every 5 days

Methadone Induction

- Greatest risk of overdose death during induction (Zador & Sunjic, 2000 & 2002)
  - 42% methadone clinic deaths occur during first 2 weeks
  - Of 9835 people started on methadone in 1996,
    - 7 died in the first week = overall mortality rate of 7.1 per 10,000 inductions

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Methadone

- Aims of treatment
  - Alleviate withdrawal symptoms
  - Block euphoric effects of self-administered opioids
  - Eliminate cravings for opioids
- Methadone doesn't treat other substance use
- Effective dose
  - Typically 80-120 mg daily
  - Should be able to function without impairment of physical or emotional responses
- Not much utility in checking serum methadone levels (unless checking peak/trough)

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Methadone Take-Home Criteria

- Absence of recent drug & alcohol abuse
- Regular attendance at clinic
- Absence of serious behavioral problems at clinic
- Absence of known recent criminal activity
- Stable home environment & relationships
- Acceptable time in maintenance tx
- Assurance of safe storage
- Rehabilitative benefit of take-homes outweighs risk of diversion

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Methadone

- Metabolized by the liver
- There are a number of medications that can interact with methadone, increasing or decreasing methadone level
  - Increased methadone level → may cause intoxication
  - Decreased methadone level → may cause withdrawal
- Boosting – clonazepam or diazepam is taken one hour after receiving methadone in order to get high from methadone (Stitzer et al., 1981)

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Methadone

Potential Adverse Effects from Methadone

Low energy	**QT prolongation**	Cough
Back pain	Abnormal dreams	Rhinitis
Swelling	Anxiety	Yawning
Chills	Decreased libido	Postural hypotension
Hot flashes	Depression	Bradycardia
Malaise	Euphoria	Hyperprolactinemia
Weight gain	Headache	Amenorrhea
Constipation	Insomnia	**Sweating**
Dry Mouth	Somnolence	Rash
Blurred vision	Sexual dysfunction	Urinary retention

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Methadone

- Urine drug testing
  - Federal regulations state must be done at least 8 times per year
  - Must screen for presence of methadone and metabolite
    - Methadone is synthetic so you must test for it specifically (won't be +opiates)
  - Should also screen for oxycodone (won't be +opiates)
  - Must also test for other drugs prevalent in the area

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Methadone in Hospital

- When patient is admitted to hospital on methadone always
  - Get a release signed and call their OTP to verify
    - 1. Methadone dose
    - 2. Date of last dose (if patient hasn't dosed in >3 days, dose is typically dropped to 30 mg or less)
  - This ensures you will not dose a patient with methadone who is not enrolled in a clinic
  - This will decrease the chance that you will overdose the patient on methadone
- On discharge patient is not discharged with methadone tablets under any circumstance

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In General

- It is high risk to prescribe benzodiazepines to patients on methadone
  - Clinics have policies against benzodiazepines due to the high abuse of these medications in conjunction with methadone
  - Similarly, benzodiazepine receptor agonists and barbiturates should not be prescribed with methadone
- If a patient is on methadone and has pain, he/she can be prescribed short-courses of opioids; care should be coordinated with the clinic

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Methadone

- Take-home points:
  - Have to have at least 1 year history of OUD to start methadone
  - Induction and stabilization can take weeks to months due to pharmacokinetics of methadone
  - It can take weeks to months for patients to get on a stable dose of methadone, during this time, substance use is common
  - Methadone treats OUD
  - Patients have to be stable to get take-home doses
  - An understanding of urine toxicology is required if making decisions based on results

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BUPRENORPHINE

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Buprenorphine

- In 2000, DATA was passed which allowed physicians to treat patients with opioid dependence and withdrawal with schedule III-V drugs which are specifically indicated by the FDA for this purpose
- In 2002, FDA approved buprenorphine and buprenorphine/naloxone for treatment of opioid dependence

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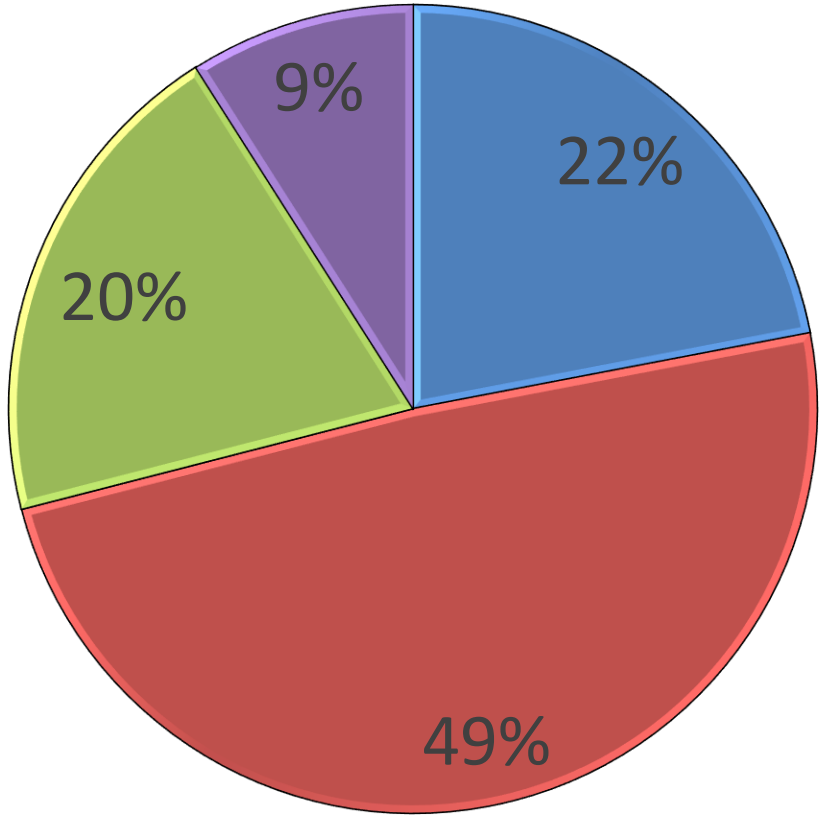
Physician Monthly Census for Buprenorphine



Stein BD, Sorbero M, Dick AW, Pacula RL, Burns RM, Gordon AJ. Physician Capacity to Treat Opioid Use Disorder With Buprenorphine-Assisted Treatment. JAMA. 2016 Sep 20;316(11):1211-1212. PubMed PMID: 27654608.

CARA Allows Additional Prescribers

- Qualifying APRNs and PA-Cs given ability to prescribe buprenorphine for OUD until 10/1/21
- Have to complete 24 hours of training to be eligible for a waiver
  - 8 of the hours can be the course that physicians have traditionally taken
- Follow the 30 and 100 patient limits
- Works with, or is supervised by, a qualifying physician if required by state law

Public Law 114-198. https://www.congress.gov/114/plaws/publ198/PLAW-114publ198.pdf. Accessed Sept 2, 2017.

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Buprenorphine

- Product has to be labeled to opioid use disorder (withdrawal or maintenance)
- Buprenorphine (“Subutex,” Probuphine subdermal, Sublocade)
- Buprenorphine/naloxone (Suboxone Film, bup/nx film, bup/nx tabs, Zubsolv, Bunavail)
- The following cannot be used
  - Buprenex (IV, IM – pain med)
  - Butrans (transdermal - pain med)
  - Belbuca (buccal strip – pain med)

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Formulations

	SL tab	SL film	Buccal film	Implant	Long-acting SC injectable
buprenorphine (generic)	x				
bup/nx (generic)	x	x			
Suboxone		x	x		
Zubsolv	x				
Bunavail			x		
Cassipa			x		
Probuphine				x	
Sublocade					x

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Dose equivalents of transmucosal formulations

	Equivalent Buprenorphine Dose (Naloxone Dose Noted if Included in Formulation)					
	1 mg	2 mg	4 mg	8 mg	12 mg	16 mg
buprenorphine tabs		2		8		
bup/nx (tabs & film)		2/0.5	4/1 film	8/2	12/3 film	
Suboxone (bup/nx)		2/0.5	4/1	8/2	12/3	
Zubsolv (bup/nx)	0.7/0.18	1.4/0.36	2.9/0.71	5.7/1.4	8.6/2.1	11.4/2.9
Bunavail (bup/nx)			2.1/0.3	4.2/0.7	6.3/1	
Cassipa (bup/nx)						16/4

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Buprenorphine/Naloxone

- Buprenorphine – partial mu-opioid agonist which partially binds to the opioid receptor
  - Has very high affinity for mu receptor
  - Has slow dissociation from mu receptor
- Because it is a partial mu agonist it has a ceiling effect, which means larger doses do not result in larger effects, so safer in overdose (with some exceptions)
- Naloxone – opioid antagonist which is not active if the medication is taken as directed
  - Naloxone 2-10% bioavailable

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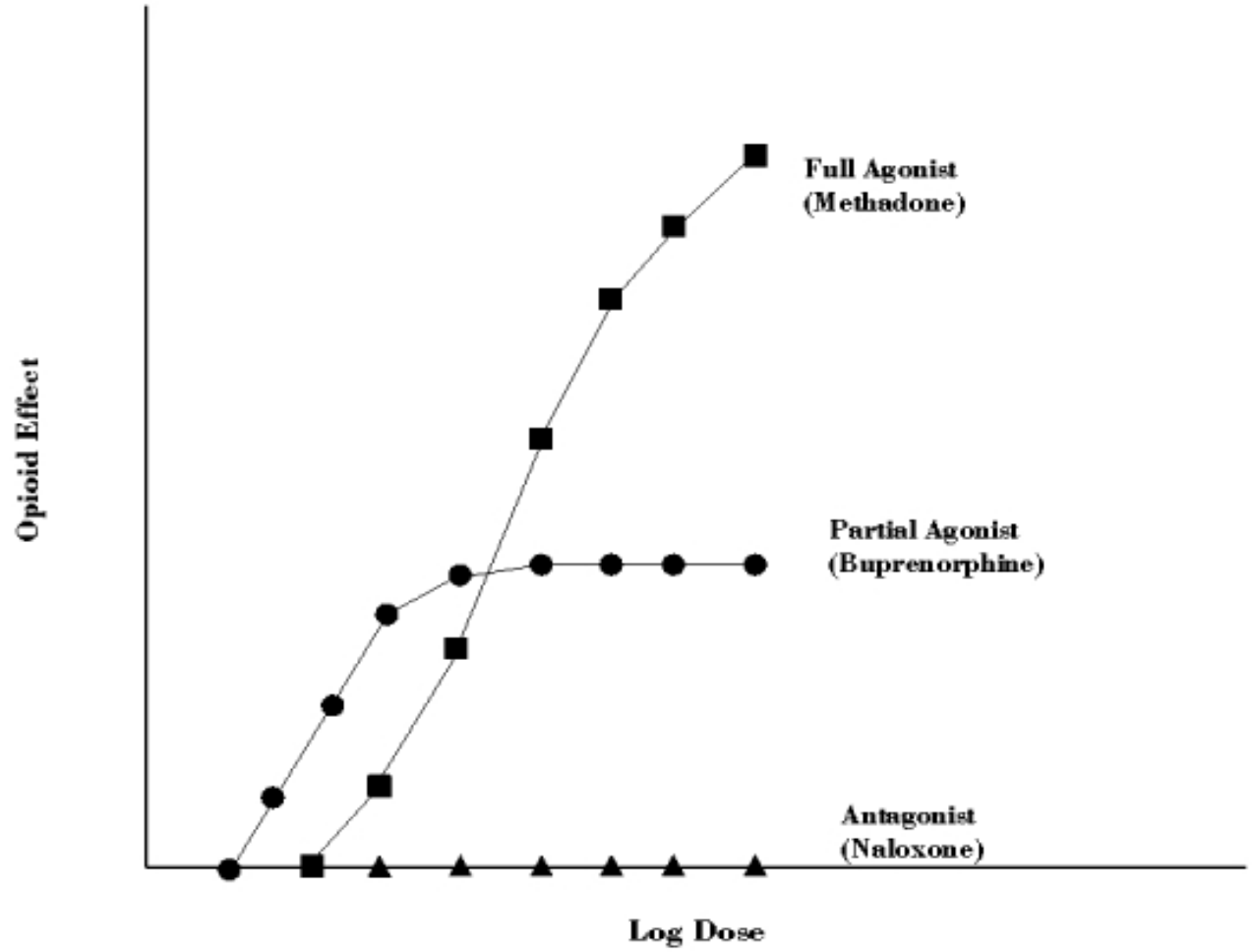
Buprenorphine vs. Methadone



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Buprenorphine Induction

- To start on buprenorphine, patients need to be in visible opioid withdrawal otherwise risk precipitated withdrawal (COWS=12)
- Patients converting from methadone to buprenorphine need
  - Methadone dose of 30 mg or lower
  - No methadone for at least 36 hours prior to starting buprenorphine
- Induction is typically 4-8 mg of buprenorphine
- Induction is usually accomplished in a matter of a few days

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Buprenorphine

- Patients come to office weekly to start
- Get 1-week supply of medication
- Give urine specimen each visit
- Need to do some form of psychosocial treatment (typically an insurance requirement)
- When stable, advance treatment as physician feels comfortable, that is, giving 2-week supply of medication
- If there is a lapse, then resume weekly visits

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Buprenorphine Maintenance

- Maintenance doses on average are 12-20 mg
- Patients are being successfully maintained at lower doses
- Medicaid typically pays for no more than 16 mg daily
- Take daily but could take every other day ($T_{1/2}$=36 hrs)
- Concerns for risk of diversion at higher doses
- PET study by Greenwald et al. (2003) showed
  - 78.9-91.5% of mu receptors were occupied at 16 mg
  - 84.1-98.4% of mu receptors were occupied at 32 mg

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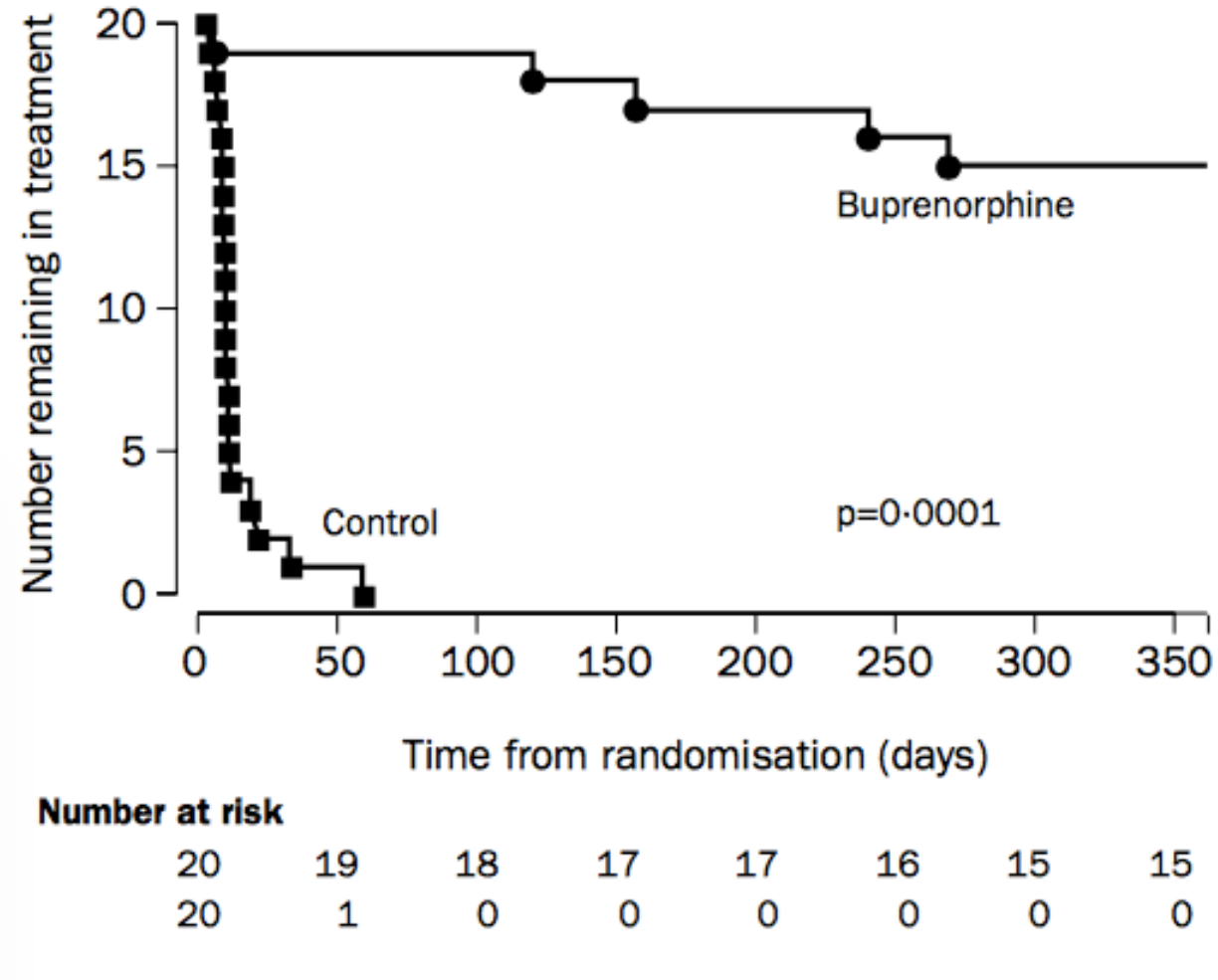
Kakko et al., 2003



Controls – 6 day bup taper, daily dosing of placebo + relapse prevention
Buprenorphine – 16 mg bup + relapse prevention

Buprenorphine

- Typical adverse effects
  - Diaphoresis
  - Constipation
  - Headache
  - Insomnia
  - Nausea, vomiting
  - Hypotension
  - Sexual dysfunction
  - Seizures
  - Hepatitis, hepatoxicity

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Implantable buprenorphine (Probuphine)

- 4 rods implanted in arm, 74.2 mg each (equivalent to 80 mg of buprenorphine HCl)
- Patients stable on 8 mg of buprenorphine or less
- Implanted and removed by someone who can perform minor surgical procedures
- Removed after 6 months, new rods can be implanted in the other arm

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Long-acting injectable buprenorphine (Sublocade)

- 7 days with transmucosal buprenorphine (8-24 mg)
- 300 mg SC x2 months
- 100 mg SC monthly thereafter for maintenance
  - May increase to 300 mg monthly if suboptimal response to 100 mg (+UDS, self-reported use)
- Minimum time between doses = 26 days
- Steady state in 4-6 months
- If missed dose, give as soon as possible
  - Noted that occasional delays up to 2 weeks may not have clinically significant impact
- After steady state is achieved, patients stopping injections may have buprenorphine detectable in plasma for up to 12 months
- Correlation between plasma and urine concentrations not studied

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Buprenorphine

- Urine drug testing
  - Must test for presence of buprenorphine and metabolite (norbuprenorphine)
  - Buprenorphine is synthetic so you must test for it specifically (won't be +opiates)
  - Should also screen for oxycodone (won't be +opiates)
  - Must also test for other drugs prevalent in the area

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Buprenorphine in Hospital

- When patient is admitted to hospital who takes buprenorphine,
  - Get a release signed and call their doctor or pharmacy to verify
    - 1. Buprenorphine/naloxone dose
    - 2. That they are still in treatment
  - Check the PDMP
  - Check for buprenorphine in urine tox
- On discharge, you probably aren't writing for buprenorphine, they will return to their doctor

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In General

- Risk of harm is increased when patients taking buprenorphine are prescribed benzodiazepines
  - Some clinics and/or doctors have policies against benzodiazepines due to concerns about safety and misuse
  - Similarly, benzodiazepine receptor agonists and barbiturates may increase harm
- If a patient is on buprenorphine and has pain, he/she may be prescribed short-courses of opioids; care should be coordinated with the clinic/doctor prescribing buprenorphine

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Methadone vs. Buprenorphine

- Methadone
  - Needs high level of monitoring
  - Uses several classes of substances (may need more monitoring)
  - History of selling/diverting
  - No insurance or limited means
  - Poor response to buprenorphine or prior treatment of high dose methadone
- Buprenorphine
  - Can be trusted with one-week supply of medication
  - Perceived low risk of diverting
  - Has insurance or means to pay for treatment
  - Has history of prolonged QT interval or taking meds that prolong QT interval

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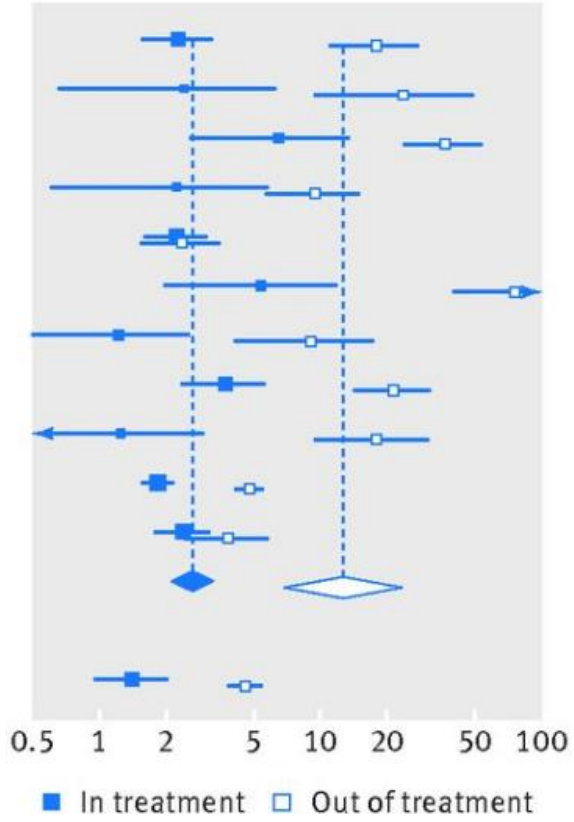
Overdose mortality rates in and out of opioid maintenance treatment and pooled overdose mortality rates, 1974-2016.

	No of deaths/ person years		Overdose mortality rate/ 1000 person years (95% CI)	Overdose mortality rate/ 1000 person years (95% CI)	
	In treatment	Out of treatment		In treatment	Out of treatment
Methadone					
Gearing et al 1974	33/14 474	21/1170		2.3 (1.6 to 3.2)	17.9 (11.1 to 27.4)
Cushman 1977	4/1655	7/297		2.4 (0.7 to 6.2)	23.6 (9.5 to 48.6)
Grönbladh et al 1990	7/1085	27/740		6.4 (2.6 to 13.3)	36.5 (24.0 to 53.1)
Caplehorn et al 1996	4/1792	19/2004		2.2 (0.6 to 5.7)	9.5 (5.7 to 14.8)
Buster et al 2002	42/18 747	26/10 983		2.2 (1.6 to 3.0)	2.4 (1.6 to 3.5)
Scherbaum et al 2002	6/1114	13/172		5.4 (2.0 to 11.7)	75.6 (40.2 to 129.2)
Davoli et al 2007	7/5751	9/998		1.2 (0.5 to 2.5)	9.0 (4.1 to 17.1)
Clausen et al 2008	24/6450	28/1303		3.7 (2.4 to 5.5)	21.5 (14.3 to 31.1)
Peles et al 2010	5/3985	13/727		1.2 (0.4 to 2.9)	17.9 (9.5 to 30.6)
Kimber et al 2015	169/91 792	216/45 265		1.8 (1.6 to 2.1)	4.8 (4.2 to 5.4)
Cousins et al 2016	54/22 648	24/6247		2.4 (1.8 to 3.1)	3.8 (2.5 to 5.7)
Overall				2.6 (2.1 to 3.3)	12.7 (6.9 to 23.4)
Buprenorphine					
Kimber et al 2015	31/21 936	143/31 239		1.4 (1.0 to 2.0)	4.6 (3.9 to 5.4)



Sordo et al., 2017

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Massachusetts Medicaid Patients with OUD 2004-2010

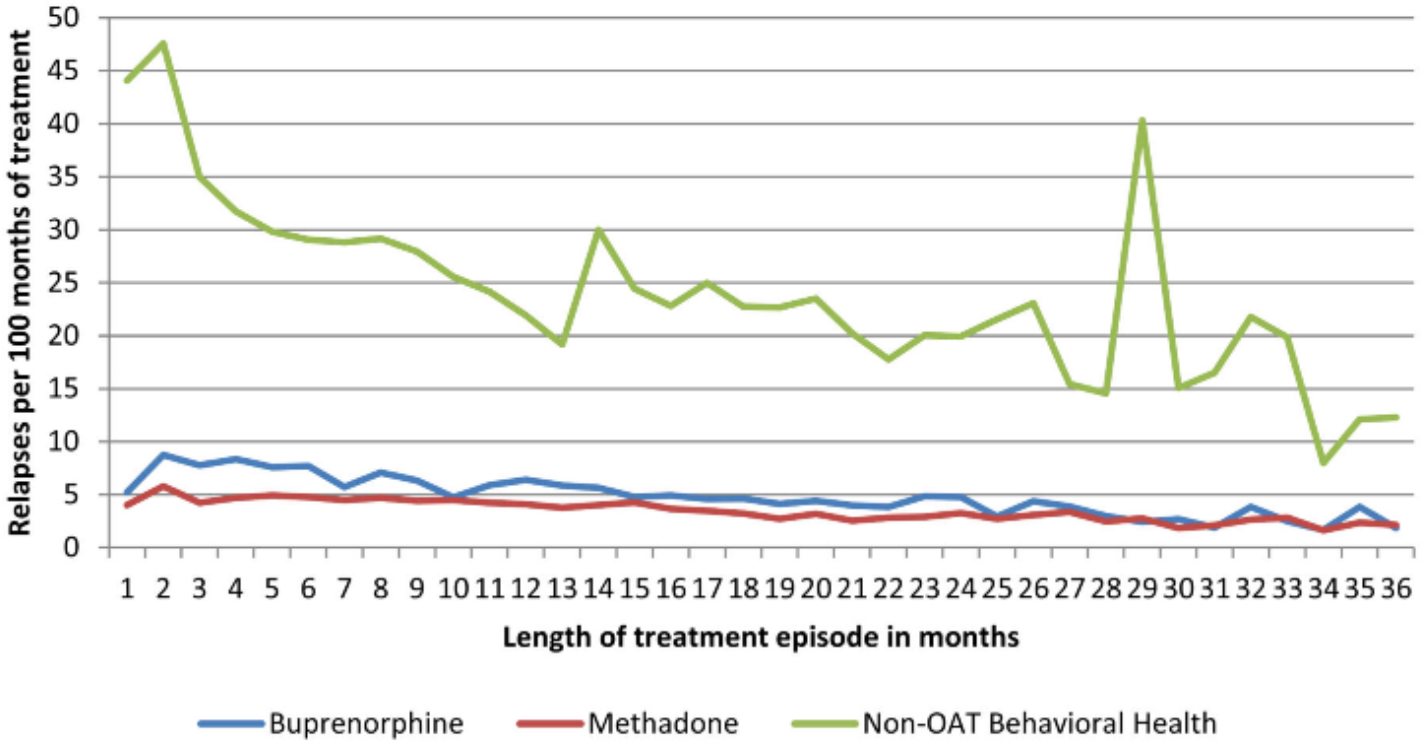

Figure 1. Relapses during treatment among MassHealth members who received treatment for opioid addiction between 2003 – 2010[1]

[1]N = 18,866 episodes of buprenorphine treatment, 24,309 episodes of methadone treatment and 31,220 episodes of non-OAT behavioral health treatment in month 1. 33% of buprenorphine episodes, 52% of methadone episodes, and 12% of non-OAT treatment episodes lasted 12 months or more. 13% of buprenorphine treatment episodes, 27% of methadone episodes, and 1% of non-OAT treatment episodes lasted 24 months or longer.

Clark et al., 2015

Pregnancy

- There is 30+ years of research on methadone for pregnant women with opioid use disorder
- Buprenorphine shown to be acceptable treatment as well, more and more evidence of less neonatal abstinence syndrome (NAS)
- Opioids are not teratogenic*
- Intoxication and withdrawal are harmful for the embryo/fetus so it is better to have constant level of opioid
- Babies born on methadone or buprenorphine need to be monitored for NAS

*Some evidence that codeine may cause fetal heart defects

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NALTREXONE

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Naltrexone

- Tablets approved for opioid dependence in 1984
- Naltrexone-XR (Vivitrol) approved for opioid dependence in 2010
- Opioid antagonist
- High affinity for mu-opioid receptor
- Will displace bound mu-agonist
- Blocks opioids from binding to mu receptors, thereby preventing euphoria from illicit opioid use

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Naltrexone

- Naltrexone tablets usually prescribed 50-100 mg daily
- Naltrexone-XR prescribed 380 mg IM monthly
- This drug defies criticism of “replacing one drug for another”
- Patients may be less willing to take an antagonist than agonist, however
- Good medication for health care professionals, those in the criminal justice system, and patients with comorbid benzodiazepine or alcohol dependence

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Naltrexone

- Metabolized by the liver
- Check liver function prior to starting and periodically during treatment
- Adverse effects include: nausea, vomiting, diarrhea, constipation, headache, dizziness, fatigue, muscle cramps, rash, diaphoresis, delayed ejaculation, precipitated withdrawal, hepatitis, liver failure

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Naltrexone

- Cochrane review (Minozzi et al., 2011): Review of 13 studies which included 1158 participants concluded
  - There hasn't been an adequate evaluation of oral naltrexone treatment for opioid use disorder to say whether it is an effective treatment

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Naltrexone-XR

- In a double-blind, placebo controlled study of naltrexone-XR patients were randomized to placebo, 192 mg of naltrexone, or 384 mg of naltrexone
  - Subjects in 384 mg naltrexone group were retained in treatment longer
  - If assumed missing UDS were +, naltrexone groups had fewer +UDS

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Krupitsky et al., 2011

- Double blind, placebo controlled, multi-center RCT of naltrexone-XR in Russia

	XR-NTX (n=126)	Placebo (n=124)
Age (years)	29·4 (4·8)	29·7 (3·6)
Men	113 (90%)	107 (86%)
White	124 (98%)	124 (100%)
Duration of opioid dependence (years)	9·1 (4·5)	10·0 (3·9)
Days of pre-study inpatient detoxification	18 (9)	18 (7)
Opioid craving scale	18 (23)	22 (24)
HIV serology positive	51 (40%)	52 (42%)
Hepatitis C positive	111 (88%)	117 (94%)

Data are mean (SD) or number (%). XR-NTX=extended-release naltrexone.

Table 1: **Demographics and baseline clinical characteristics**

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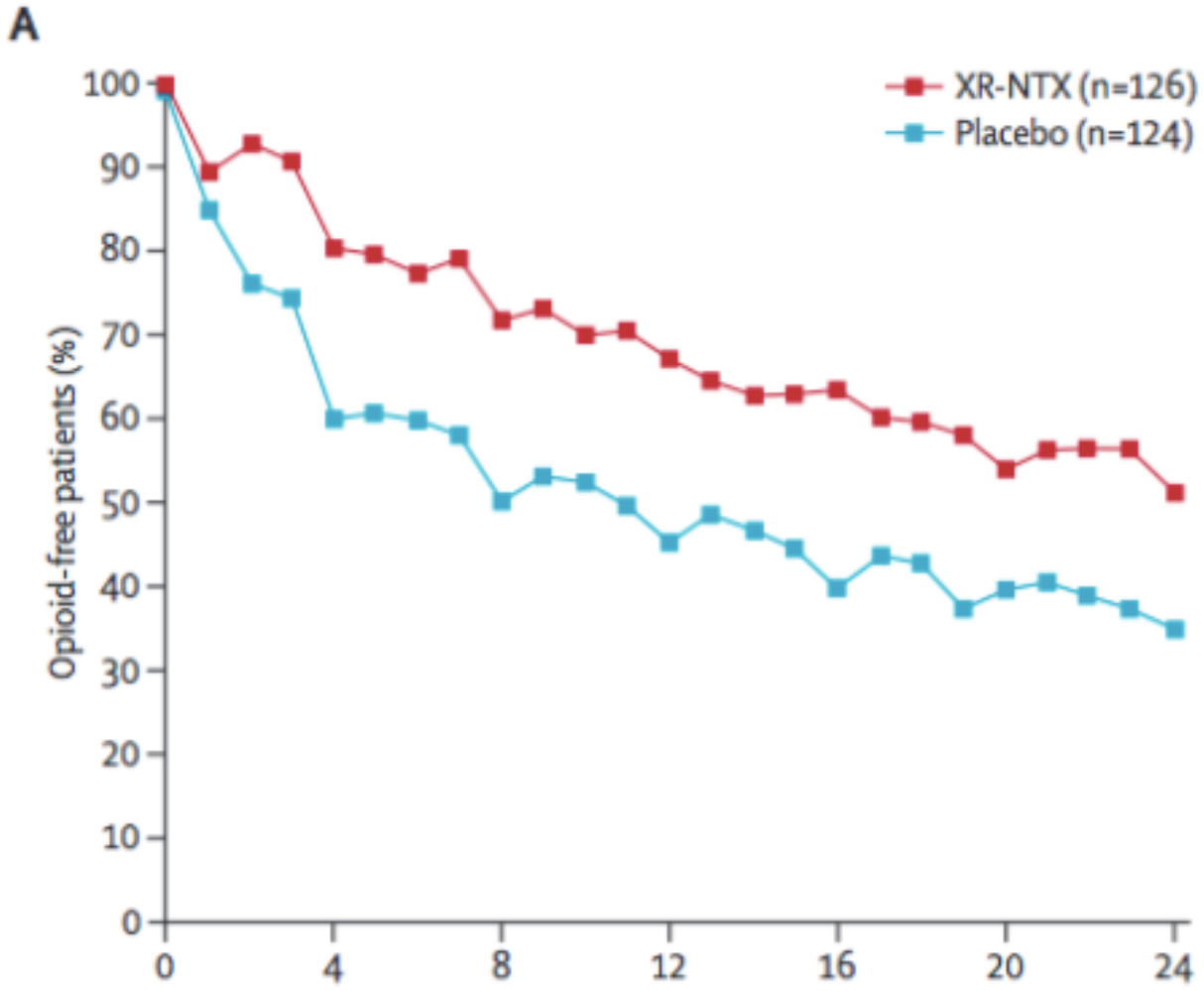
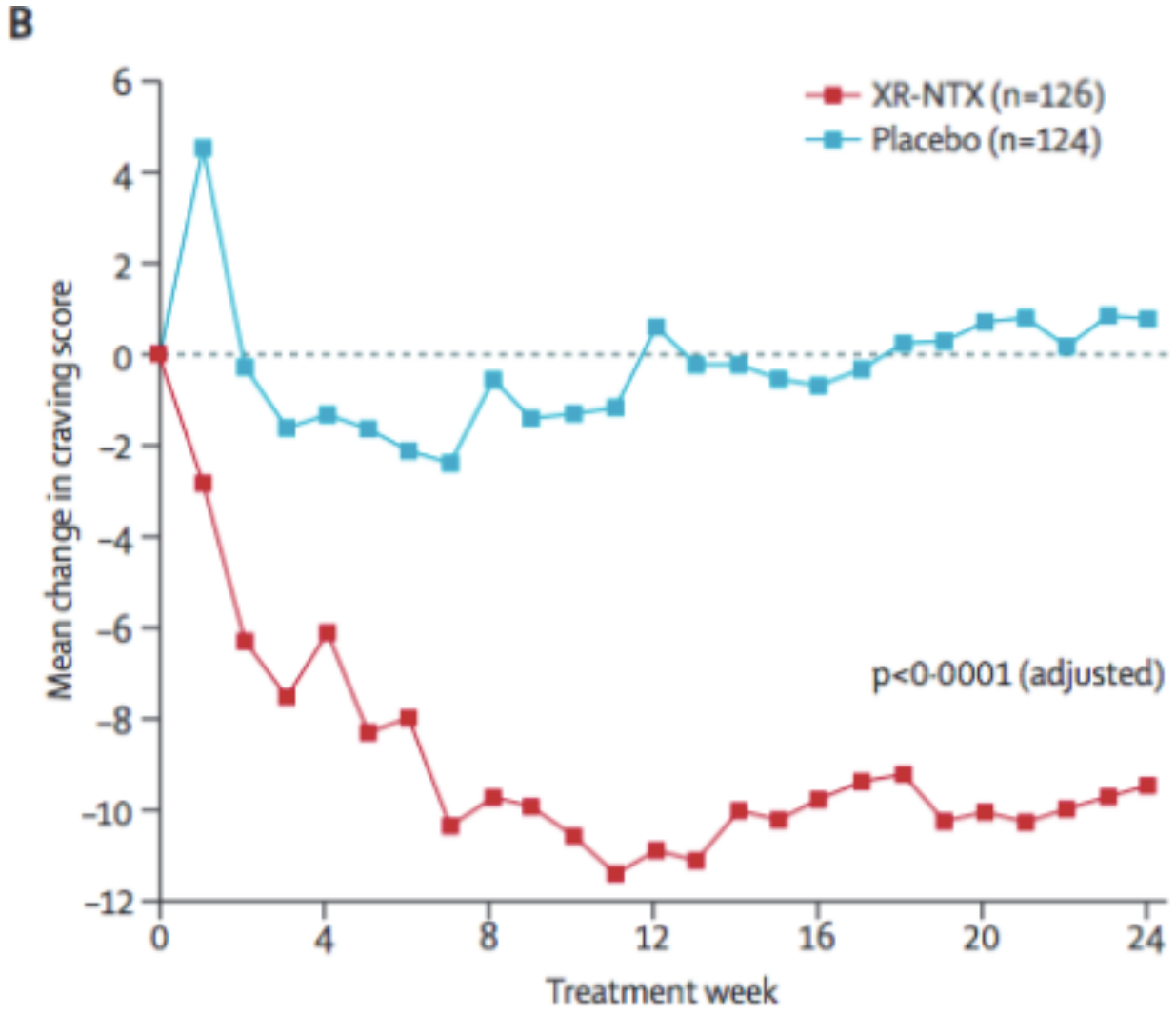
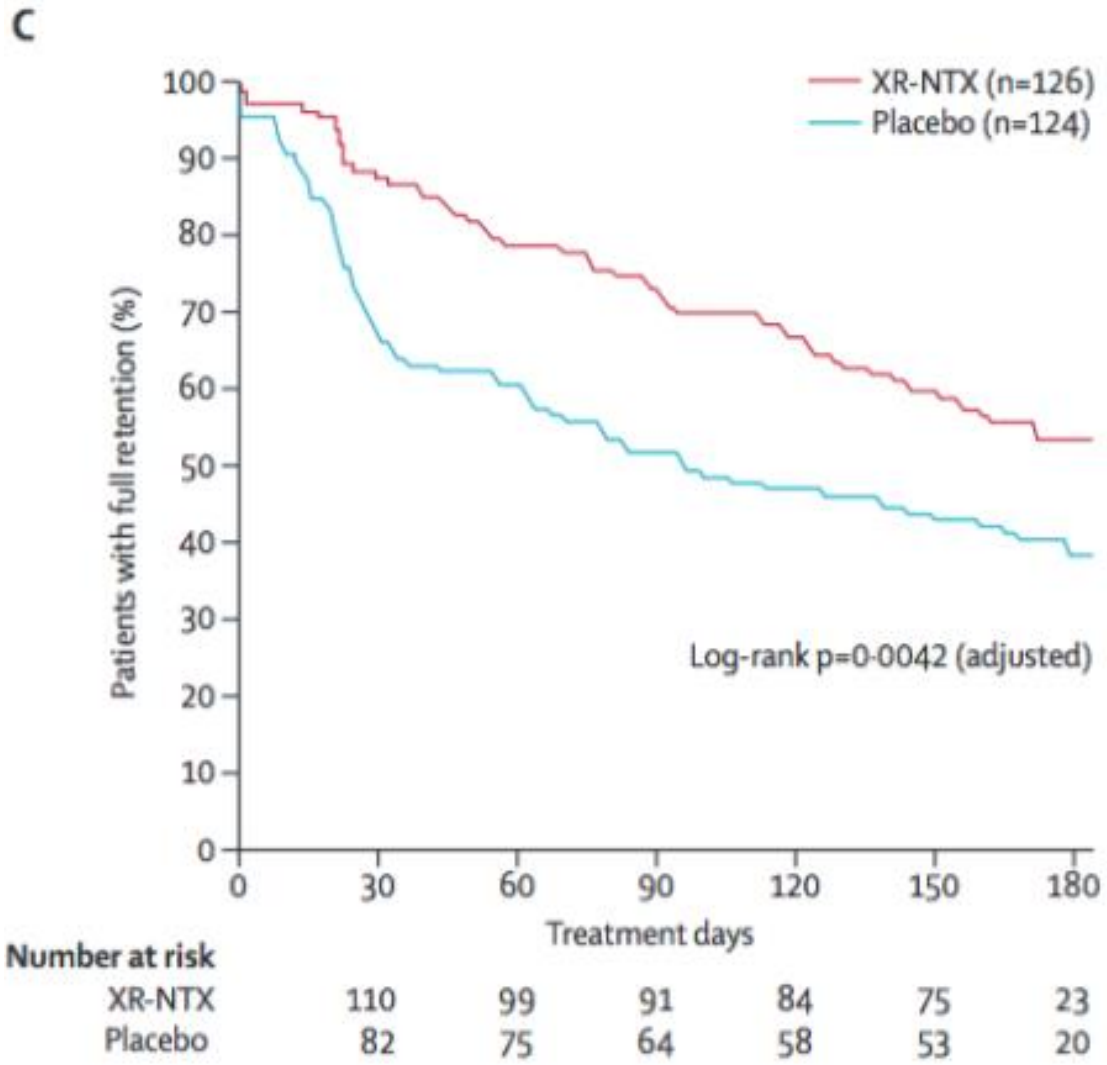
Krupitsky et al., 2011



Krupitsky et al., 2011



Krupitsky et al., 2011



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Bup/nx vs. naltrexone-XR (Tanum et al., 2017)

- Norwegian randomized clinical trial lasting 12 weeks
- 159 patients randomized to
  - injections of naltrexone-XR 380 mg every fourth week
  - buprenorphine-naloxone 4-24 mg SL administered daily
- Attended standard drug counseling

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Bup/nx vs. naltrexone-XR (Tanum et al., 2017)

- Primary outcome variables
  - Retention in the study
  - Proportion of total number of UDTs without illicit opioids
  - Number of days of use of heroin and other illicit opioids

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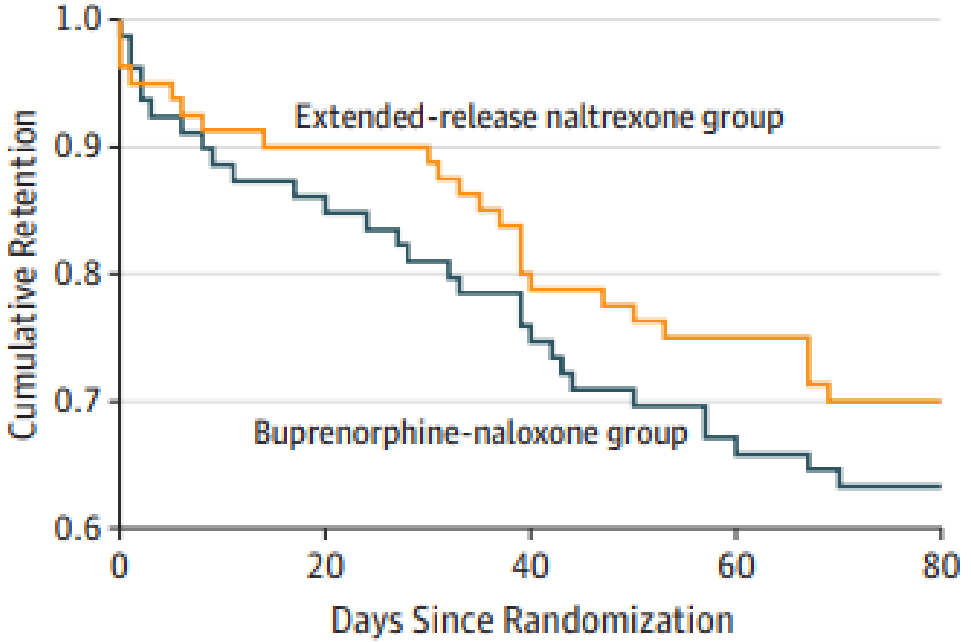
Bup/nx vs. naltrexone-XR (Tanum et al., 2017)



No. at risk					
Buprenorphine-naloxone group	78	67	59	52	50
Extended-release naltrexone group	78	73	64	60	56

Not statistically different;
No deaths in either group

Bup/nx vs. naltrexone-XR (Tanum et al., 2017)

Table 2. Days of Use of Heroin and Other Illegal Substances Assessed at Weeks 4, 8, and 12[a]

	Extended-Release Naltrexone		Buprenorphine-Naloxone		Extended-Release Naltrexone vs Buprenorphine-Naloxone	
Time Point	No. of Participants	Mean (SD)[b]	No. of Participants	Mean (SD)[b]	Mean Difference (95% CI)[c]	*P* Value[c]
Heroin Use						
Week 4	63	0.8 (1.5)	65	3.7 (7.4)	−3.0 (−4.9 to −1.2)	.001
Week 8	59	0.8 (1.9)	55	4.4 (9.1)	−3.3 (−5.1 to −1.5)	<.001
Week 12	57	1.1 (2.3)	50	4.1 (8.4)	−3.6 (−6.0 to −1.2)	.003
Other Illicit Opioids Use						
Week 4	63	1.2 (2.2)	65	4.2 (7.9)	−2.9 (−4.8 to −0.9)	.004
Week 8	59	1.8 (4.7)	55	4.0 (8.5)	−2.6 (−4.6 to −0.7)	.007
Week 12	57	2.0 (5.0)	50	4.4 (8.7)	−2.4 (−4.9 to 0.1)	.06

No significant differences between the treatment groups in the proportion of negative UDTs (P = .18).

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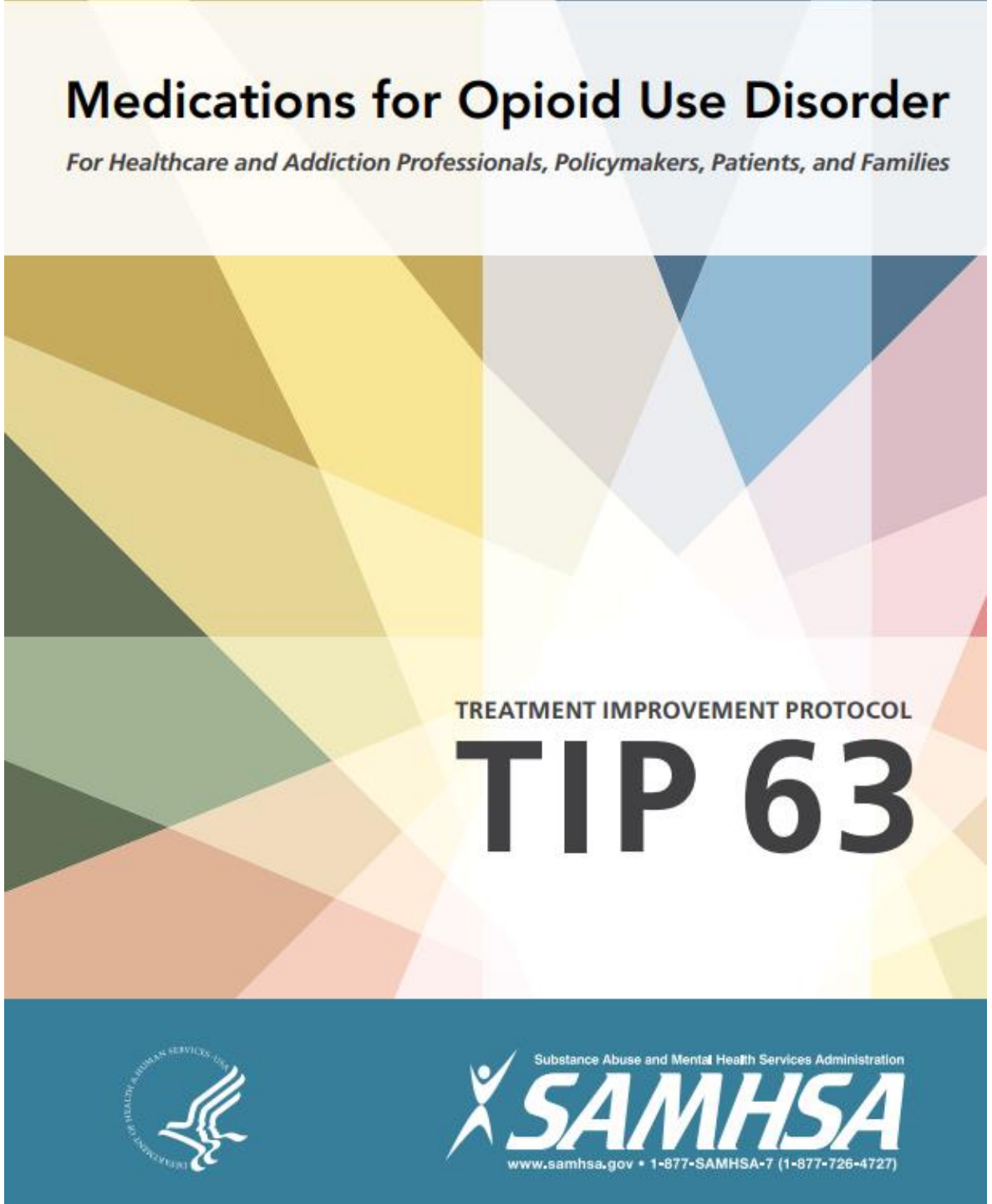

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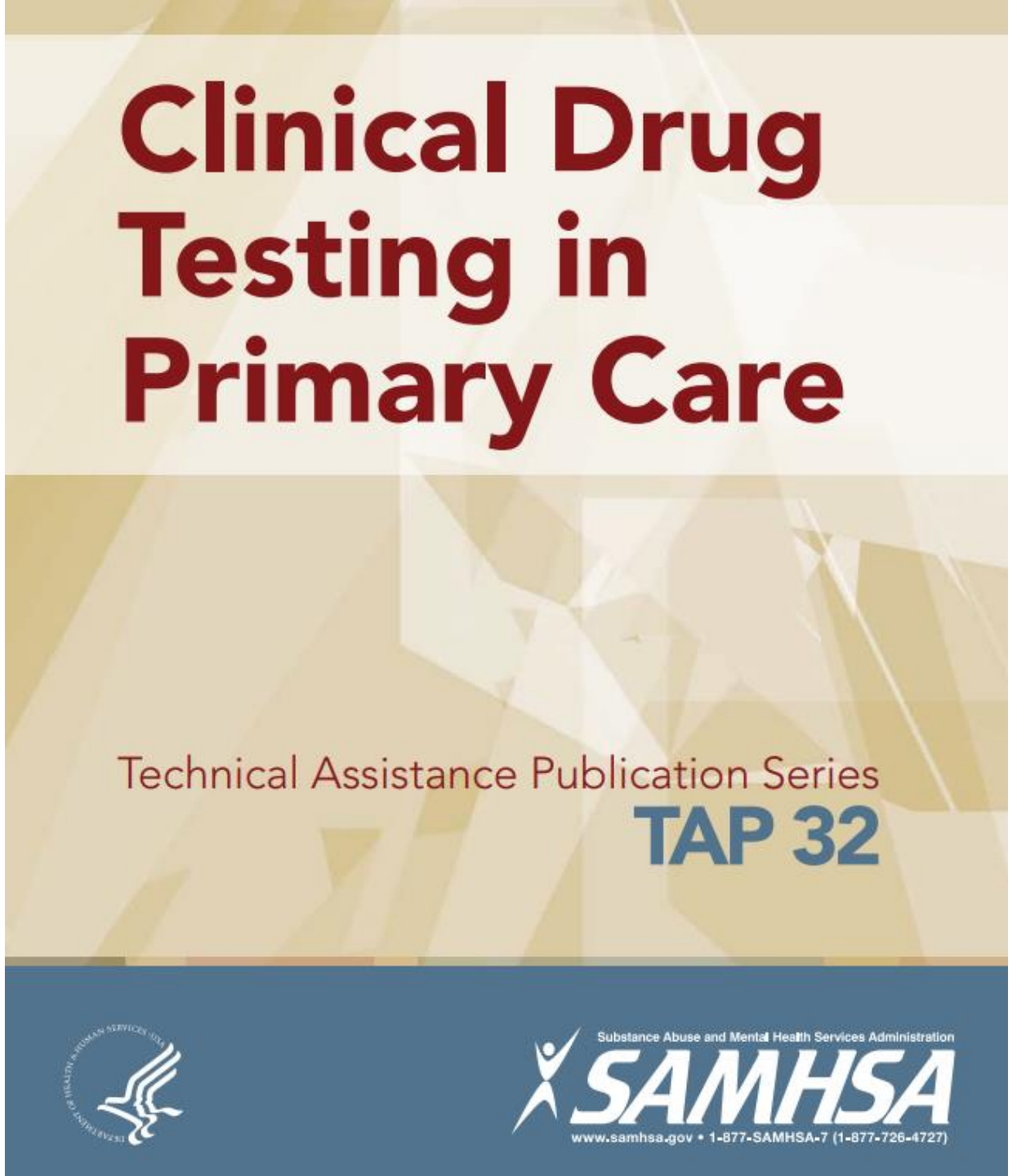

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Additional Resources

- www.PCSS-now.org (Prescribers Clinical Support System)
  - Webinars (upcoming and archived)
    - Buprenorphine waiver training (online or live)
  - Clinical coaching (one:one coaching, small group discussions)
  - Resources (e.g., clinical tools)
- www.getSTR-TA.org (Opioid Response Network)
  - Provider or clinic can put in request for education and training resources. The Opioid Response Network utilizes local experts in prevention, treatment, and recovery who are collaborating to facilitate access to evidence-based resources

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QUESTIONS/DISCUSSION

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