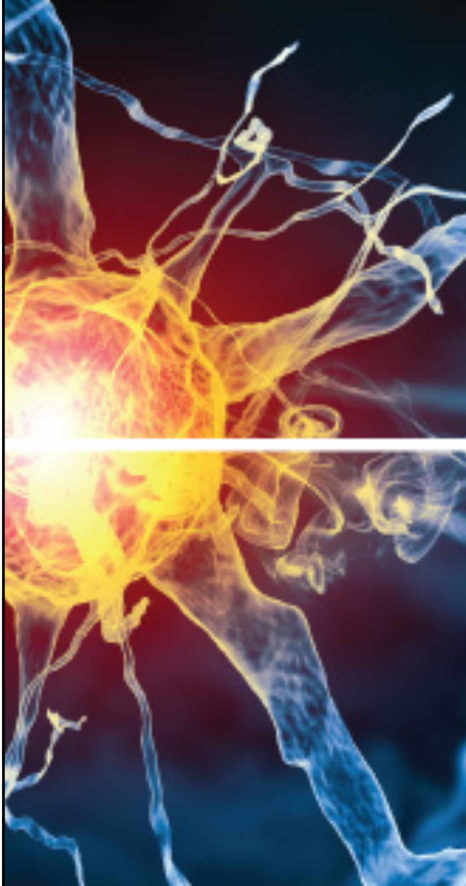
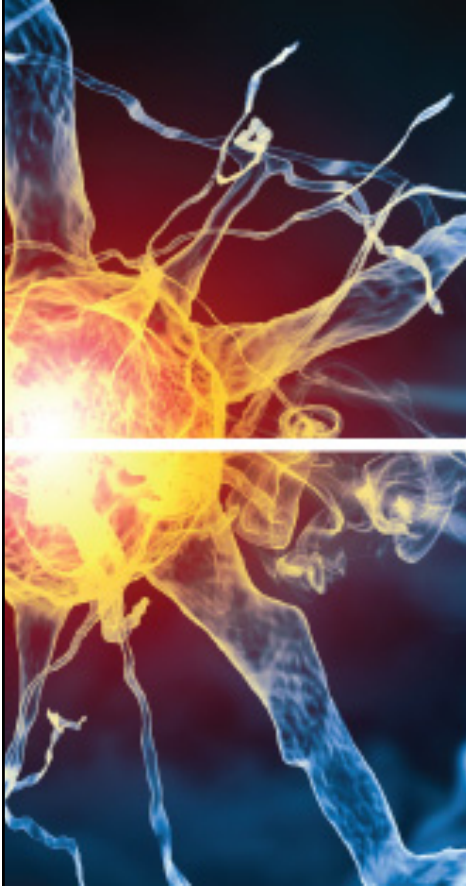


Addressing the Opioid Epidemic: Biological Mechanisms and Novel Treatments:

How to Reduce Non-Adherence,
Predict Relapse, and Prevent Overdose



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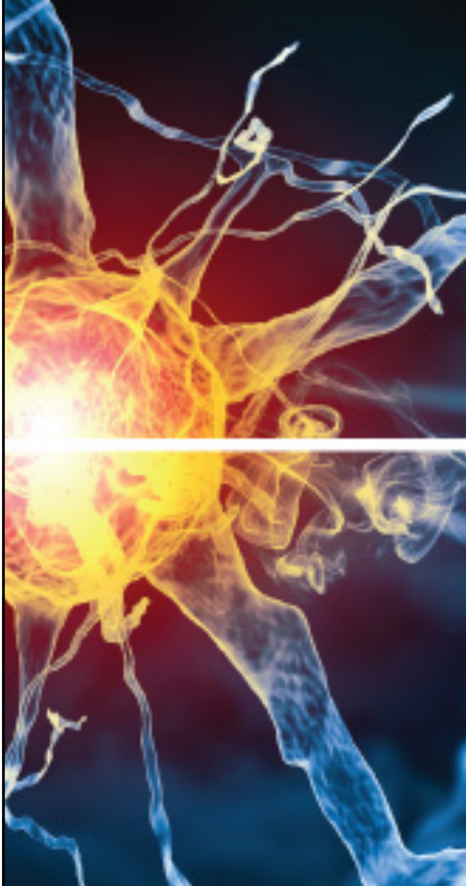
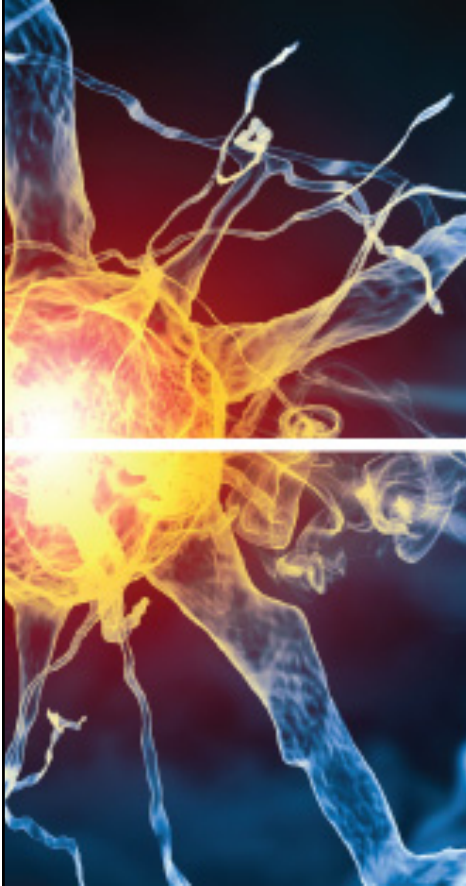


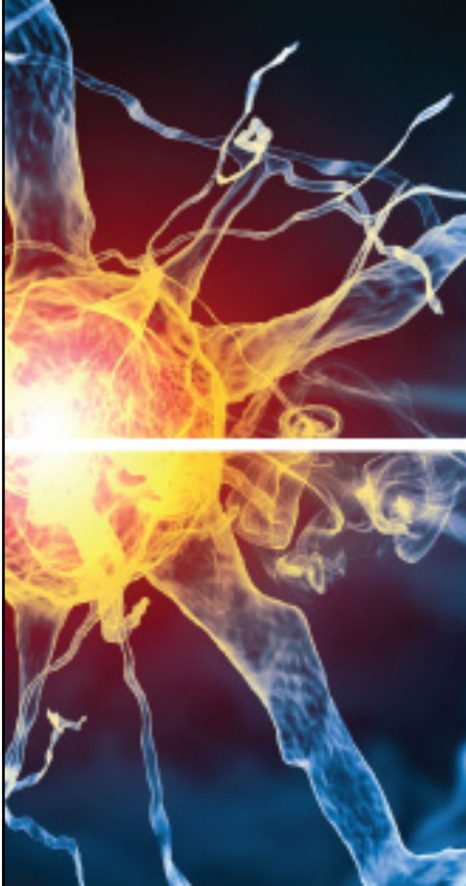
1 Learning Objective

Recognize opioid use disorder to optimize patient outcomes.



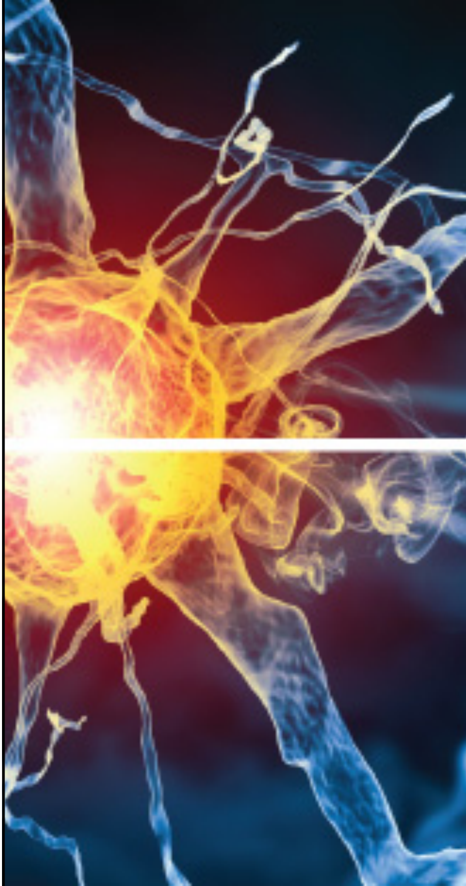
2 Learning Objective

Select appropriate treatment selection based on the mechanism of action (MOA) of agents in opiate use disorder.



3 Learning Objective

Incorporate into practice tools and strategies for the management of opioid use.



4 Learning Objective

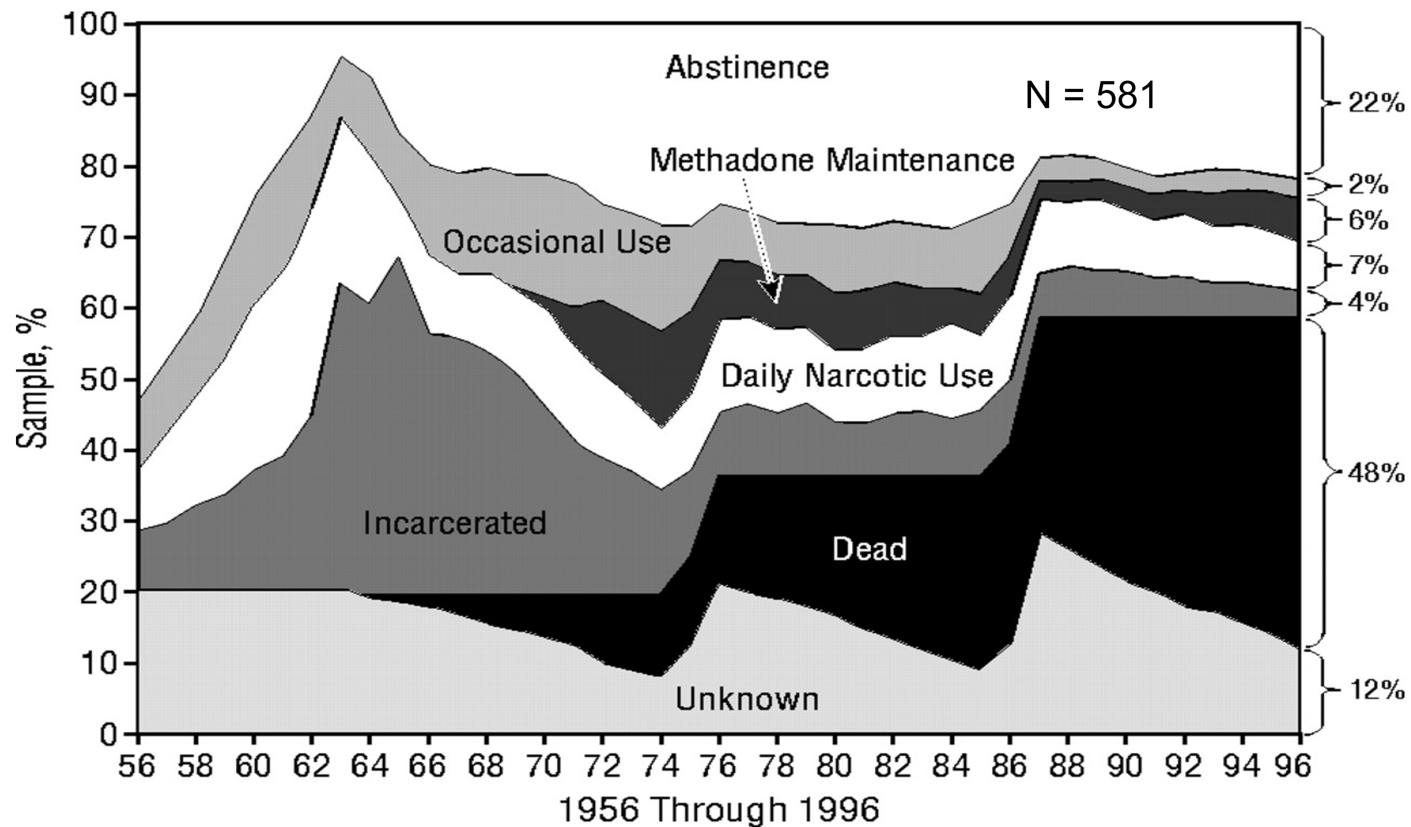
Evaluate overdose risk in opioid use.

Opioid Use Disorder

- Heroin, prescription opioids
- Super potent synthetic opioids
  - Fentanyl, carfentanyl
- Chronic, relapsing disorder
- High mortality rate: > 1% per year
  - Overdose death due to respiratory arrest
  - Now leading cause of accidental death in U.S.

Webster L, et al. *Pain Med.* 2011;(12):S26–S35.

Heroin Addiction: Lifetime History over 40 Year Follow-up



Hser Y-I, et al. *Arch Gen Psychiatry*. 2001;58(5):503-508.

Opioid Use Disorder: Comorbidity

- Co-occurring psychiatric disorders
  - Major depression, post traumatic stress disorder (PTSD)
  - Attention deficit disorder (ADHD)
  - “Externalizing” features (impulsivity, irritability, aggression)
- Co-occurring medical disorders
  - HIV
  - Hepatitis C
  - Pain

Nunes EV, et al. *Arch Gen Psychiatry.* 1998;55(2):153-160.

Opioid Use Disorder

- Effective medications:
  - Methadone, buprenorphine, naltrexone
  - Eliminate or reduce opioid use and protect against overdose
  - High rates of dropout from treatment undermine effectiveness
  - ~50% of patients drop out by 3 to 6 months

Sharma, A. et al. *Curr Psychiatry Rep.* (2017);19:35.

Opioid and Overdose Epidemic

- Liberal narcotic analgesic prescribing beginning in 1990s
- Expansion of heroin availability in 2000s
- Drug overdose now the leading cause of accidental death in many parts of the U.S.
  - Heroin mixed with fentanyl and carfentanyl

Kerensky T, et al. *Addict Sci Clin Pract.* 2017;(12):4.

Comparison between Opioid Use Disorder Epidemic and HIV epidemic

- Chronic disorders with high mortality
- Stigma
- Effective treatments, variable adherence

Williams J ,et al, *NEJM. 2016;(*375):813-815.

Opioid Overdose

- Opioid agonists suppress respiration[1]
- Tolerance[1]
  - Chronic exposure to opioids induces tolerance
  - Tolerance is protective against overdose
  - Loss (or lack) of tolerance increases overdose risk
  - The highest risk of overdose is after release from jail, or release from “detoxification” or residential treatment, or discontinuation of medication treatment[2]
- Fentanyl and carfentanyl[3]
- Individual differences in risk for overdose?

[1]Morgan MM, et al. *Br J Pharmacol* 2011;164(4):1322-1334.

[2]Binswanger IA, et al. *Ann Intern Med.* 2013;159(9):592-600.

[3]Boyer EW. *NEJM.* 2012;367(2):146-155.

Opioid Overdose

- Prevention with Naloxone rescue kits
- Short-acting opioid antagonist
  - Intramuscular (IM) or intransal (IN)
  - Reverses overdose including restoring breath
  - If the overdose is witnessed
- Distribution to patients, friends, family, police, paramedics and other first responders

Kerensky T, et al. *Addict Sci Clin Pract.* 2017;12:4.

Treatments

- Improving adherence
- Predicting dropout and relapse

Methadone Maintenance

- Full opioid agonist with slow (oral) absorption and slow elimination (long half life)[1]
- Titrated to effective dose range (80 mg/day) it induces tolerance in opioid system, resulting in blockade of effects of illicit opioids[1]
  - 70% retained in treatment, 50% sustained abstinence[2]
  - Protects against overdose and death[2]
  - Adequate dose (approximately 80 mg/day) is important[1]
- Limitations[2]:
  - Opioid side effects
  - Availability limited, acceptability

[1][Package Insert]. Drugs@FDA Website.

[2]Bart G. *J Addict Dis.* 2012;31(3): 207–225.

Buprenorphine Maintenance

- High affinity partial agonist
  - Less opioid-like effects, less side effects
  - Long acting
  - Ceiling on agonist effects
  - Little respiratory depression, greater safety
  - Blocks the effects of illicit opioids
  - Convenient: can be prescribed out of any office or medical setting
  - Dose range 8 mg/day to 32 mg/day
  - Adequate dosage important to effectiveness
- Limitations
  - Adherence to daily sublingual pill or strips is less favorable than methadone
  - > 50% drop out by 3 to 6 months

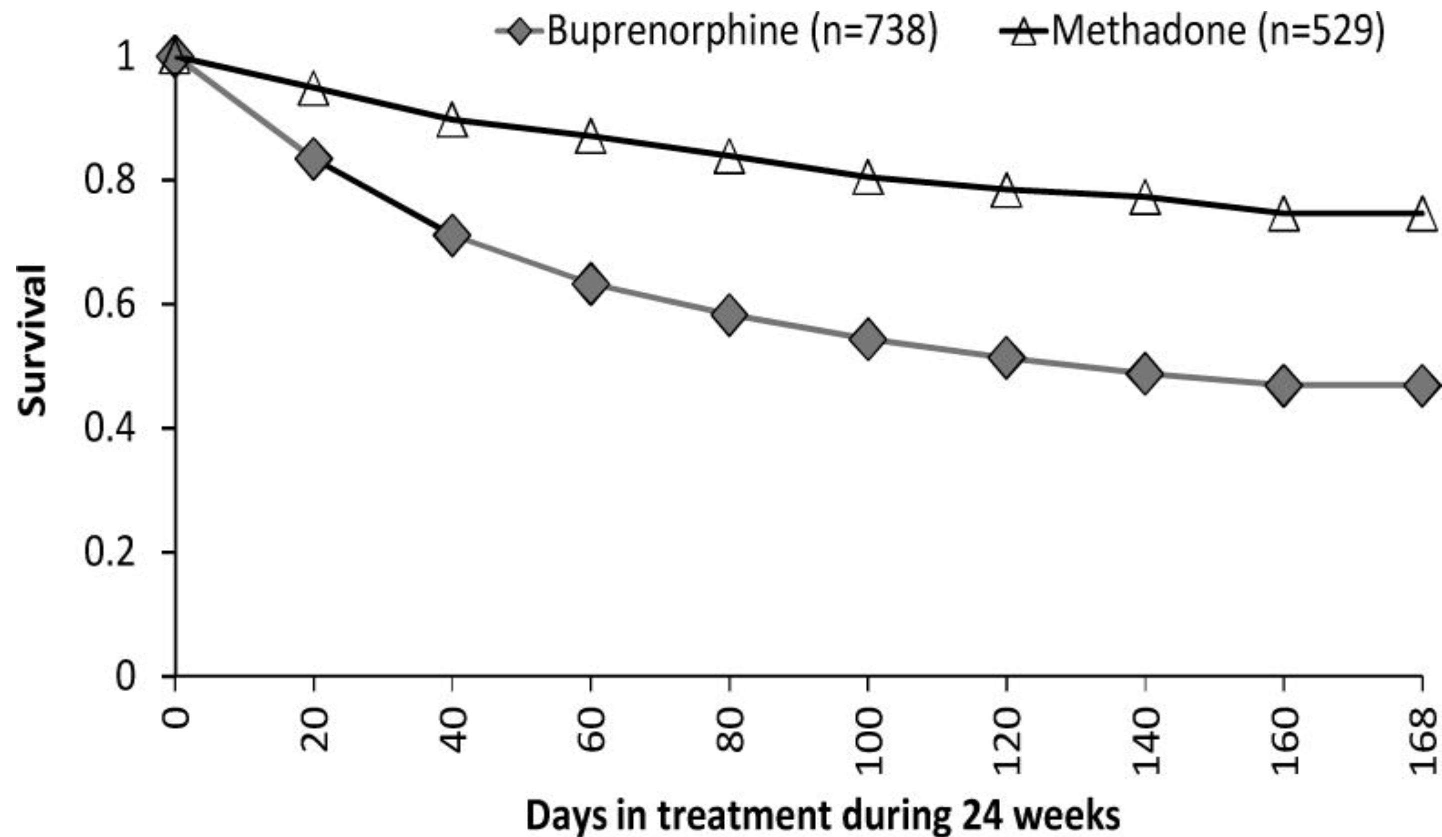
Sittambalam CD, et al. *J Community Hosp Intern Med Perspect*. 2014;4(2):10.3402.

Cochrane Meta-analysis of Buprenorphine vs Methadone

- 31 randomized clinical trials
  - N = 5430 total patients
- Buprenorphine improves retention in treatment at low doses
- Buprenorphine improves abstinence from opioids at high doses
- Some evidence that methadone more effective overall

Mattick RP, et el. *Cochrane Database Sys Rev*. 2014;6(2):CD002207.

Attrition from Methadone vs Buprenorphine Retention in Treatment over 6 Months in CTN-0027



Hser Y-I, et al. *Addiction*. 2014;109(1):79-87.

Methadone and Buprenorphine: What happens over the long term/treatment discontinued?

- Long term follow up study of CTN-0027
- Located close to 90% of sample at 4 year follow up
- 4 outcome trajectories (growth mixture modeling), predictors

Hser Y-I, et al. *Addiction*. 2016;111(4):695-705.

Predictors of Long Term Outcome in CTN-0027

- Strongest Predictor:
  - Staying in treatment with methadone or buprenorphine
- Other predictors of worse opioid outcome:
  - Severity indicators
    - cocaine use
    - IV use
    - psychiatric symptoms
  - Younger age
  - Buprenorphine

Hser Y-I, et al. *Addiction*. 2016;111(4):695-705.

Buprenorphine Treatment of Prescription Opioid Dependence (CTN-0030) N = 653

- Sequential design:
  - 12 week stabilization/taper for non responders, 3-year follow up
  - Response = sustained abstinence
- Findings 12 week trial:
  - Almost no responders to 3 week buprenorphine (7%)
  - 49% response to 12 week buprenorphine
  - > 90% relapse after buprenorphine discontinuation
  - Predictors of buprenorphine treatment outcome
    - Worse outcome: Younger age, ever IN or IV use, > 1 past treatment episode
    - Better outcome: History of Major Depression
    - Better outcome: Initial treatment response (abstinent in first 2 weeks)
- Long term follow up: Predictors of abstinence:
    - On agonist treatment (buprenorphine or methadone)
    - Never used heroin

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

Summary: Methadone and Buprenorphine

- Both medications are effective
- Substantial dropout, especially from buprenorphine
  - > 50 % by 3 to 6 months
- Predictors:
  - Better outcome: stay on medication
  - Worse outcome:
    - Poor initial response
    - Not on medication
    - Younger age
    - Severity (heroin use, IV use, other drug use (cocaine)

Can Behavioral Treatments Reduce Dropout and Improve Abstinence?

- McLellan et al., JAMA 1993[1]
  - Regular counseling (weekly) superior to minimal counseling
  - Intensive psychosocial support yielded a small added benefit
- Weiss et al., CTN-0030[2]
  - Weekly Drug Counseling had no advantage over Medical Management alone

[1]McLellan AT, et al. *J Am Med Assoc*. 1993;269(15):1953-9.

[2]Weiss RD, et al. *Arch Gen Psychiatry*. 2011;68(12)1238-1246.

Naltrexone

- High affinity opioid receptor antagonist[1]
- Blocks the effects of other opioids without producing any opioid-like effects[1]
- Patients maintained on naltrexone generally feel well (few side effects) and do not use opioids[1]
- Induction hurdle[1]
  - Patients need to be either fully detoxified (no opioids left on receptors)2
  - Or, induced with ascending doses of naltrexone + clonidine and other non opioid meds that attenuate withdrawal[3]
- Poor adherence to oral naltrexone[1,4]

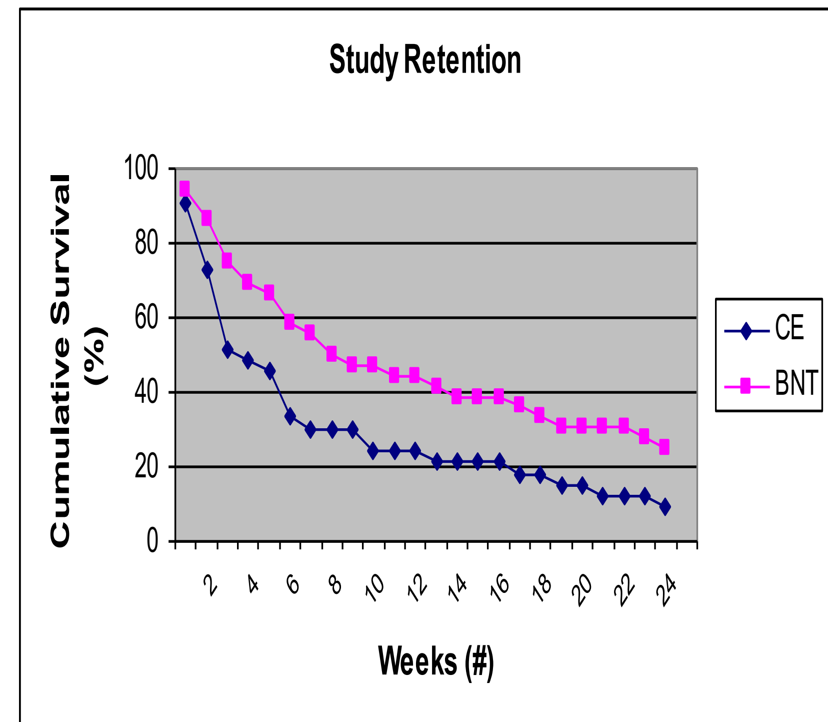
[1]Helm S. *Pain. Psychician.* 2008;11(2):225-235.
[2]Kosten TR, et al. *Sci Pract Perspect*. 2002;1(1):13-20.
[3]Sigmon SC, et al. *Am J Drug Alcohol Abuse.* 2012;38(3):187-199.
[4]Sullivan MA, et al. *Drug Alcohol Depend.* 2015;147:122-129.

How to Improve the Adherence and Effectiveness of Naltrexone?

- Behavioral therapy
- Long acting injection or implant

Behavioral Therapy Improves Adherence to Oral Naltrexone

- 5 published studies, N = 69
- Therapy components
  - Contingency Management
  - Motivational Interviewing
  - CBT
  - Involving family to monitor adherence
- Adherence improves
  - Dropout still high overall
  - Risk of overdose after stopping oral naltrexone



Nunes EV, et al. *Am J Drug Alc Abuse*. 2006;32(4):503-517.

Predictors of Better Adherence to Oral Naltrexone

- Severity[1]
  - Prescription opioids, lower level heroin use
- Cannabis use during treatment[2,3]
  - Replicated across 3 trials

[1]Church SH, et al. *Am J Drug Alcohol Abuse*. 2001;27(3):441-452.

[2]Raby WN, et al. *Am J Addict.* 2009;18(4):301-308.

[3]Bisaga A, et al. *Drug Alcohol Depend.* 2015;154:38-45.

Long-acting Naltrexone Injection or Implant

- Addresses compliance issue by circumventing need for daily pill-taking[1]
- Naltrexone formulated into poly-(lactide-co-glycolide)[2]
  - 1 month duration
- Naltrexone implant – approved in Russia[3]
  - 2 to 3 month duration
- Australian implant[4]
  - 6 month duration

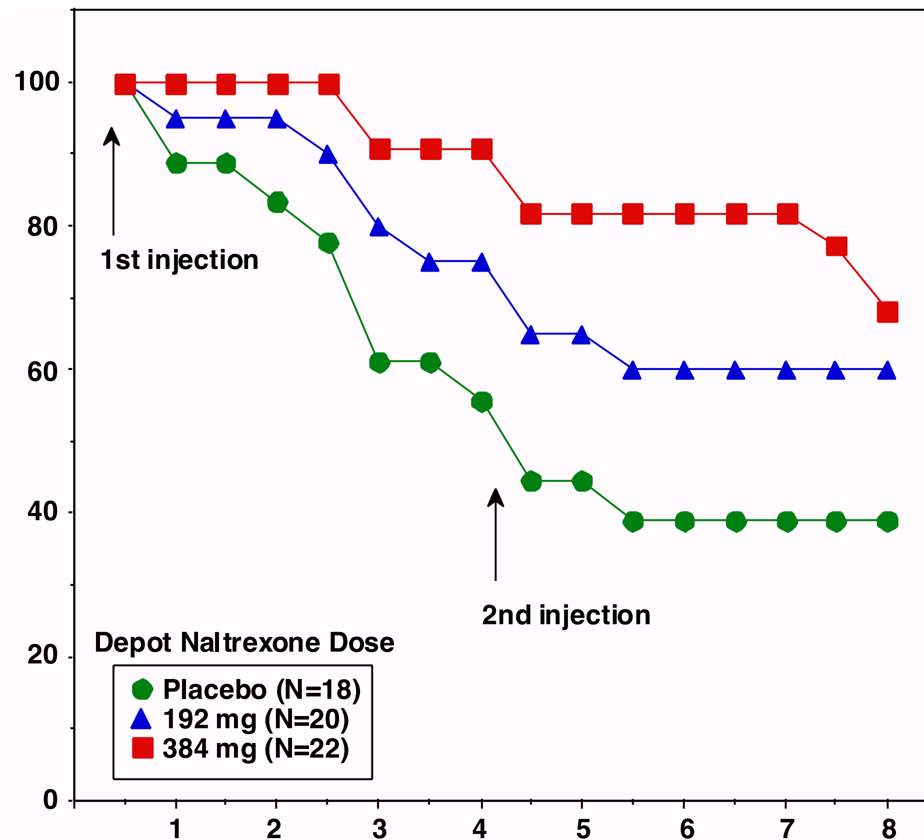
[1]Johnson BA. *Ther Clin Risk Manag*. 2007;3(5):741-749.

[2]Lobmaier PP, et al. *CNS Neurosci Ther.* 2011 Dec;17(6):629-36.

[3]Krupitsky E, et al. *Am J Drug Alcohol Abuse.* 2016;42(5):614-620.

[4]Hulse GK, et al. *Aust N Z J Obstet Gynaecol.* 2002;42(1):93-4.

Injectable Naltrexone Improves Retention for Opioid Dependence Treatment



Comer SD, et al. *Arch Gen Psychiatry*. 2006;63(2):210-218.

Two Effectiveness Trials of Injection Naltrexone

- Krupitsky E, et al.[1]
  - Naltrexone injection was superior to placebo on retention (P = .0042) and abstinence (p = .0002)[1]
- Lee JD, et al.[2]
  - Naltrexone injection was superior to Treatment as Usual in preventing relapse ($p < .001$)
  - 7 overdoses, all in Treatment as Usual group

[1]Krupitsky E, et al. *Lancet*. 2011;377(9776):1506-1513.

[2]Lee JD, et al. *N Engl J Med*. 2016;374(13):1232-1242.

Summary: Naltrexone

- Long-acting injection naltrexone is effective[1]
  - Induction hurdle (detox and naltrexone initiation)[2]
  - ~50% retained to 6 months, similar to buprenorphine[2]
  - As long as patients stay on naltrexone little opioid use[2]
- Behavioral therapy improved oral naltrexone outcome, should be tested with injection naltrexone[3]
- Stopping naltrexone associated with relapse[3]

[1][Package insert]. Drugs@FDA website.

[2]Schuckit M. *N Engl J Med*. 2016; 375:357-368.

[3]Brooks AC, et al. *J Clin Psychiatry*. 2010;71(10):1371-1378.

Long-Acting Buprenorphine Injection and Implants

- Buprenorphine implant[1]
  - 6 month duration of action
  - Modest blood levels
  - FDA approved for maintenance treatment of patients stable of low doses of sublingual buprenorphine
- Two long-acting (1 week to 1 month) injections likely to be available soon[2]
  - Subcutanous injection
  - Doses equivalent to 8 mg, 16 mg, or 24 mg sublingual
  - 1 week and 1 month durations

[1][Package insert]. Drugs@FDA website.

[2]Barnwal P, et al. *Ther Adv Psychopharmacol*. 2017;7(3):119-134.

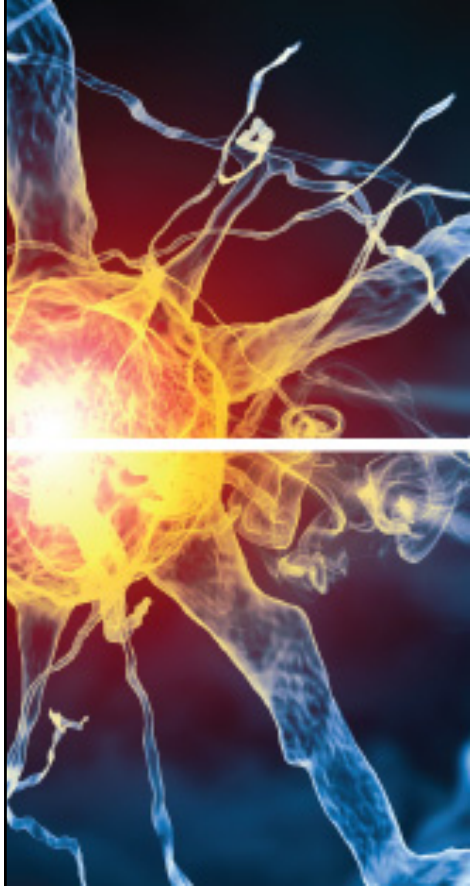
- Three very efficacious medications for opioid use disorder
- The major barrier to their effectiveness in practice is discontinuation of medication
  - Discontinuation predicts relapse
  - Relapse is associated with overdose and death
- Strategies to improve adherence
  - Behavioral therapies
  - Long-acting injections and implants
- Predicting prognosis and need to continue medication
  - Modest associations: severity, age, initial treatment response

Future Directions

- How to improve adherence, particularly to buprenorphine and injection naltrexone?
  - Behavioral therapies show promise
  - Further development of injections and implants
  - Adjunctive medications? Cannabinoids?
- How to make naltrexone initiation easier?
- How to improve prediction of prognosis and of need to stay on medication?
- How to predict risk of overdose?

Future Directions: Implementation

- How to attract more patients with opioid use disorder into effective medication treatment
- How to make treatment more available
  - Recruit more physicians to provide medication treatments
  - Nurse practitioners, physician assistants, pharmacists
  - Recruit health systems to provide medication treatments
  - Implementation models
    - Hub and spoke
    - Integrated care



Questions & Answers