Mountain Plains ATTC (HHS Region 8)

ATTC Addiction Technology Transfer Center Network

Funded by Substance Abuse and Mental Health Services Administration

Medication for Substance Use Disorders: Integration of an Already Effective Treatment

July 25, 2023

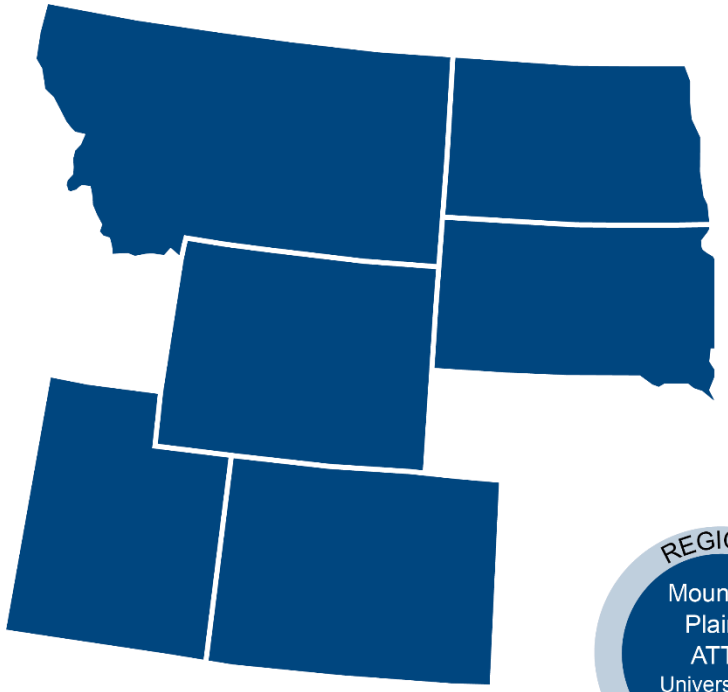
Ryan Jackman, MD

SAMHSA

Substance Abuse and Mental Health Services Administration

The Mountain Plains Addiction Technology Transfer Center

The Mountain Plains ATTC accelerates the adoption and implementation of evidence-based and promising addiction treatments and recovery-oriented practices and services; Heightens the awareness, knowledge, and skills of the workforce that addresses the needs of people with substance use or other behavioral health disorders; and fosters regional and national alliances among culturally diverse practitioners, researchers, policy makers, funders, and the recovery community



REGION 8
Mountain Plains ATTC
University of North Dakota

Housekeeping

- Please remember to MUTE yourself during our presentation.
- Questions can be asked in chat box.
- Today's session is being recorded and will be posted on the Mountain Plains ATTC website.
- Slides are available right now on the Mountain Plains ATTC website
- Instructions on how to obtain a Certificates of Attendance will be in an email following the training.
- After todays presentation we will be asking you to complete a survey

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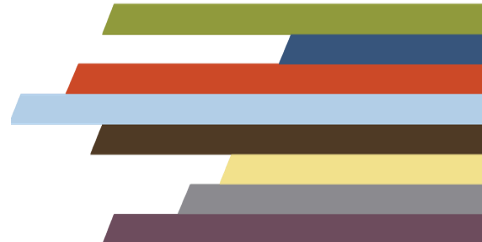
At the time of this presentation, Miriam E. Delphin-Rittmon, Ph.D, served as SAMHSA Assistant Secretary. The opinions expressed herein are the views of our presenter and do not reflect the official position of the Department of Health and Human Services (DHHS), SAMHSA. No official support or endorsement of DHHS, SAMHSA, for the opinions described in this document is intended or should be inferred.



Evaluation Information

The ATTC is funded through SAMHSA to provide this training. As part of receiving this funding we are required to submit data related to the quality of this event.

At the end of today's training please take a moment to complete a **brief** survey about today's training.

The use of affirming language inspires hope and advances recovery.

LANGUAGE MATTERS.

Words have power.

PEOPLE FIRST.

The ATTC Network uses affirming language to promote the promises of recovery by advancing evidence-based and culturally informed practices.

ATTC

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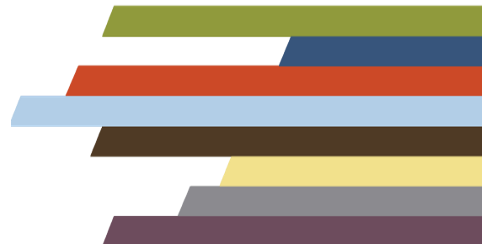
Conflicts

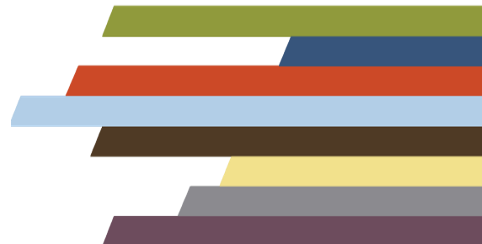
- I have no conflicts of interest to declare



Objectives

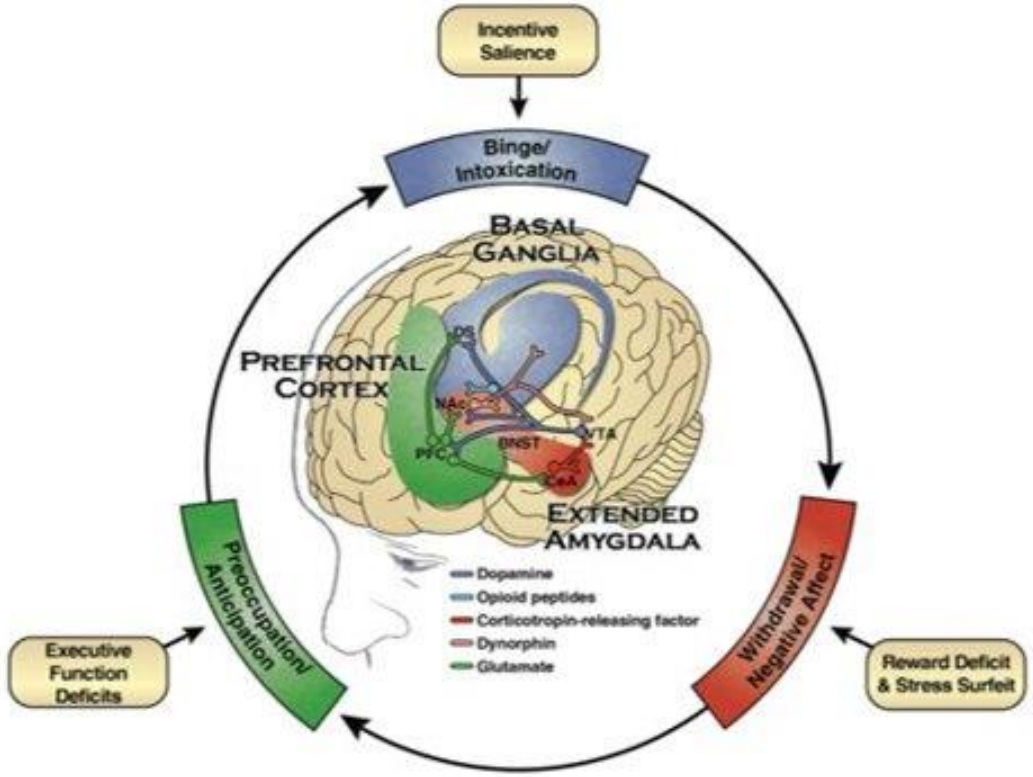
By the end of this session, participants will be able to:

1. Identify medications approved for the treatment of substance use disorders
2. Recognize the distinct stages of the addiction cycle and how medications are able to pharmacologically disrupt this cycle.
3. Discuss with a patient/client the benefits, risks, and limitations of various medications.



Substance use disorder symptomatology

- Loss of control
  - Using more than intended or longer than intended
  - Not able to cut down
  - Continued use despite physical or psychological syptoms
- Neurologic changes
  - Cravings
  - Tolerance → Withdrawal
- Consequences
  - Failure to fulfill obligations
  - Effects on relationships, hobbies, and safety



What if we treated SUD like we did Hypertension?

	Hypertension	Substance Use Disorder
Screening	Every appointment with vitals Normalized, limited to no stigma Action recommended if abnormal	Universal screening for SUD annually Screening every appointment if concern Remove Stigma Action recommended if abnormal
Team Involvement	All staff are involved in workflows	All staff involved in workflows
Interventions	Behavioral changes reviewed and medication prescribed at the same visit Regular rechecks with labs if medications are started	Plan and prescription for MAT at the same appointment BH interventions as supported by evidence Regular appointments with labs, UDT
Why we intervene	HTN is directly correlated with increased risk of morbidity and mortality	SUD is directly correlated with increased risk of morbidity and mortality

Medication isn’t the only intervention, but it is a lifesaving intervention

“This would have been very tragic had they gone over the dam,” Austin Police Department Assistant Chief Scott Perry said in a Friday news conference. “It’s a very high dam and there would have been probably severe injuries if not loss of life due to that.”

The group was distracted and didn’t notice the boat had passed two marked buoys notifying them to turn around, officer Bradley Smith, with the police department’s lake patrol unit, said during the news conference. “By the time they realized they were almost at the dam, they tried to turn around to avoid it but the suction was too powerful and pulled them against the dam,” Smith said…“

It was very nerve wracking, because approaching the boat, you have to make sure you don't wake it so it doesn't fall over the edge, but you still have to get there quick enough before it actually does fall off the edge," Smith said. "So it's a balancing act on our part.“

https://www.cnn.com/2021/06/11/us/texas-longhorn-dam-rescue/index.html

Role of medication

Restore Executive Control Over Drug Use

Buprenorphine

Methadone

Naltrexone

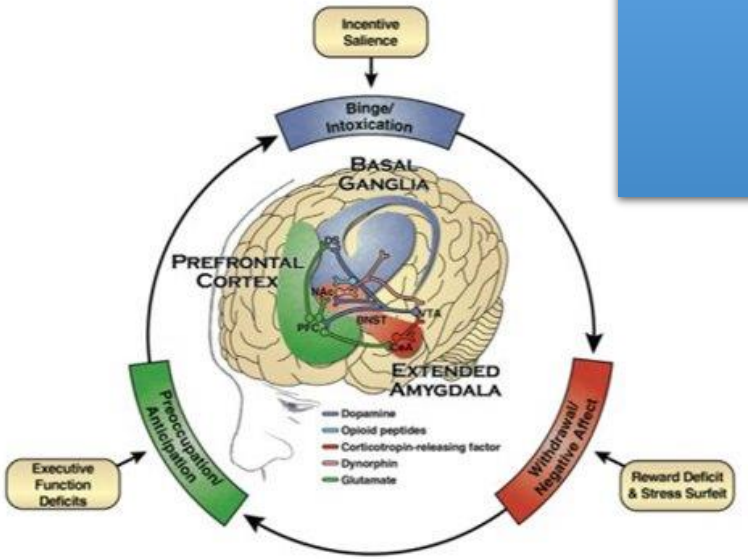
Acamprosate

Nicotine Replacement

Chantix

N-Acetylcysteine*

Mirtazapine*



Restore Response to Natural Rewards and Inhibit Drug Reward

Buprenorphine

Methadone

Acamprosate

Chantix

Gabapentin*

Topiramate*

Buproprion*

Manage Withdrawal and Restore Balance to Stress Response

Buprenorphine

Methadone

Nicotine Replacement

Gabapentin*

Buproprion*

N-Acetylcysteine*

Medications for Substance Use Disorder

Most effective
Greatest evidence

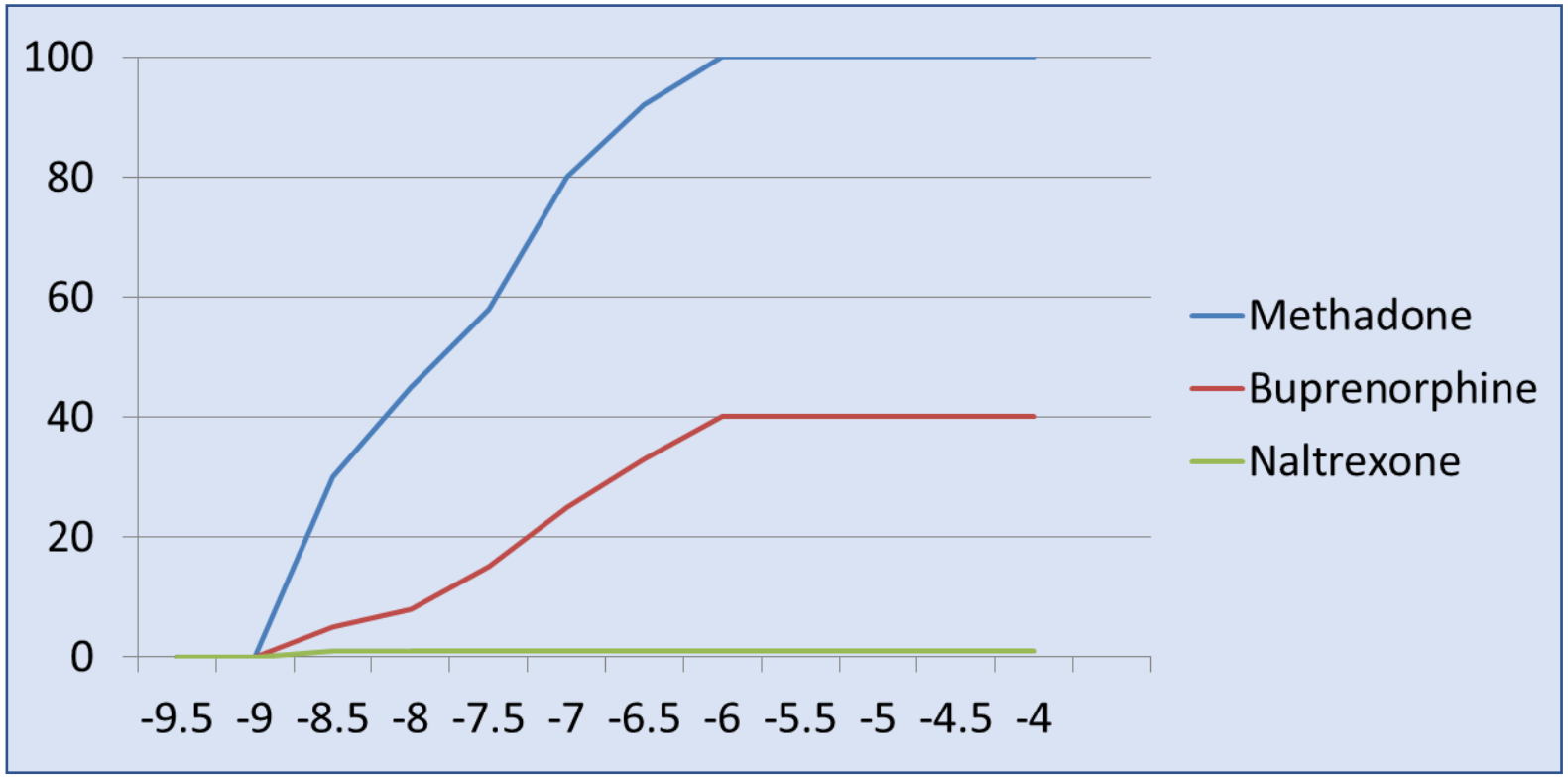
Least effective
Least evidence

Opioid Use Disorder	Nicotine Use Disorder	Alcohol Use Disorder	Stimulant Use Disorder
FDA Approved Buprenorphine Buprenorphine/Naloxone Methadone Naltrexone (injection only) **Off Label Use** None	**FDA Approved** Chantix Nicotine replacement **Off Label Use** None	**FDA Approved** Naltrexone (oral, injection) Acamprosate Disulfiram **Off Label Use** Gabapentin Topiramate Baclofen	**FDA Approved** None **Off Label Use** Naltrexone Buproprion Mirtazapine

MAT for opioid use disorder

Medication	Dosing	Contraindications	Comments
First Line			
Buprenorphine Buprenorphine /Naloxone	Sublingual 4-32mg/day SubQ (100-300mg/month)	Acute hepatitis or liver failure may necessitate a lower dose Overdose risk present with alcohol use and benzodiazepine/sedative use	• Can precipitate withdrawal, initiation timing important • Reduces cravings and withdrawal • Overdose risk higher if using CNS depressants intermittently and in high doses • Buprenorphine/Naloxone is preferred formulation • Will address chronic pain if dose is divided, though lower concentration formulations are approved for this (weekly patch, buccal films) • Safe in pregnancy and with breastfeeding
Methadone	60mg or more per day. Patient dependent	History of cardiac arrhythmia (QTc > 500) Acute hepatitis or liver failure may necessitate a lower dose Overdose risk present with alcohol use and benzodiazepine/sedative use	• Requires daily dosing through a DEA licensed methadone maintenance treatment program • Split dosing is heavily restricted, so treating pain through a methadone maintenance program often results in higher doses • Full-agonist opioid so does not precipitate withdrawal • Reduces cravings and withdrawal • Overdose risk higher when using CNS depressants intermittently and in high doses or with rapid escalation of medication • Safe in pregnancy and with breastfeeding
Naltrexone IM injection	380mg IM every 4 weeks	Acute hepatitis or liver failure may necessitate a lower dose	• Will precipitate withdrawal. Administer 7 or more days after last opioid for dependent patients • Reduces appetite for opioids. No effect on withdrawal. • Can be used for multiple substance use disorders • Side effect of flu like symptoms in < 20% of patients. Lasts days to two weeks. Improves with future injections

Mu opioid receptor activity



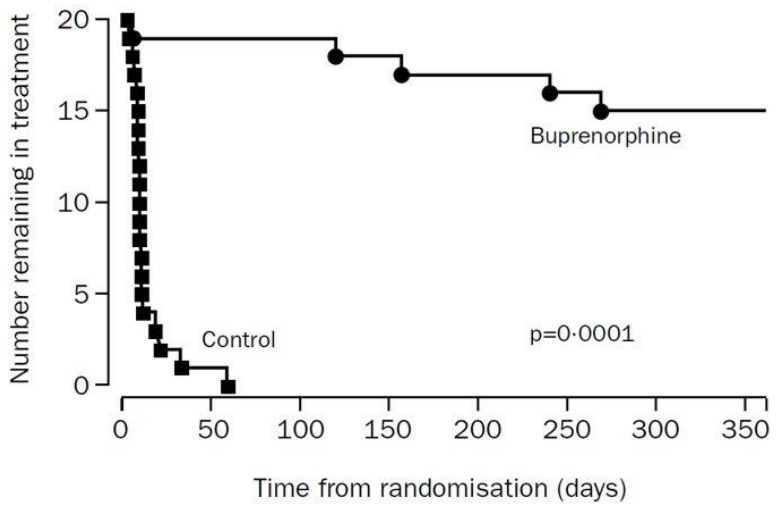
Buprenorphine

- Partial mu-opioid agonist
- Long half-life: mean elimination half-life = 37 hrs
- Metabolized by liver to norbuprenorphine
- High receptor affinity

- 80-90% relapse to drug use without it
- Increased treatment retention
- 80% decreases in drug use, crime
- 70% decrease all cause death rate

Why You Should Prescribe: Effective

"Why wouldn't you prescribe medications for opioid use disorder? It's like playing on easy mode." - Corey Davis, JD, MSPH



Results

Completion 52 wk trial:

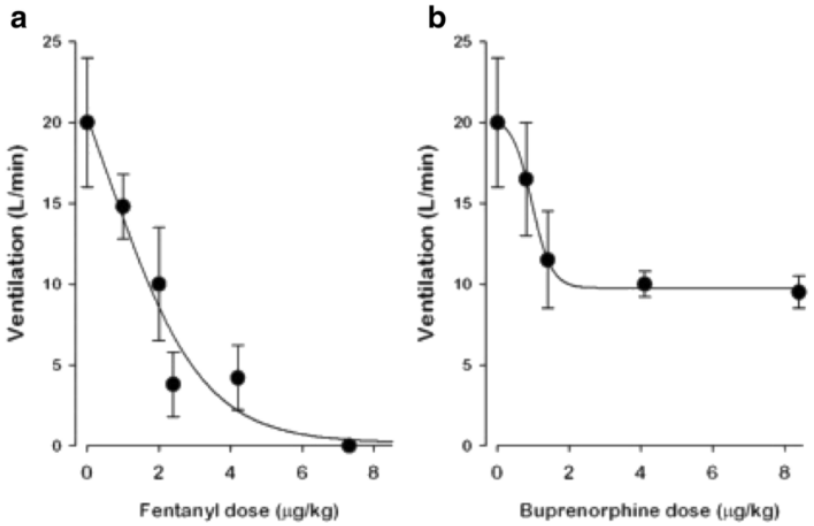
taper = 0%

- maintenance = 75%

Mortality

- taper = 20%

Kakko J et al. *Lancet.* 2003.

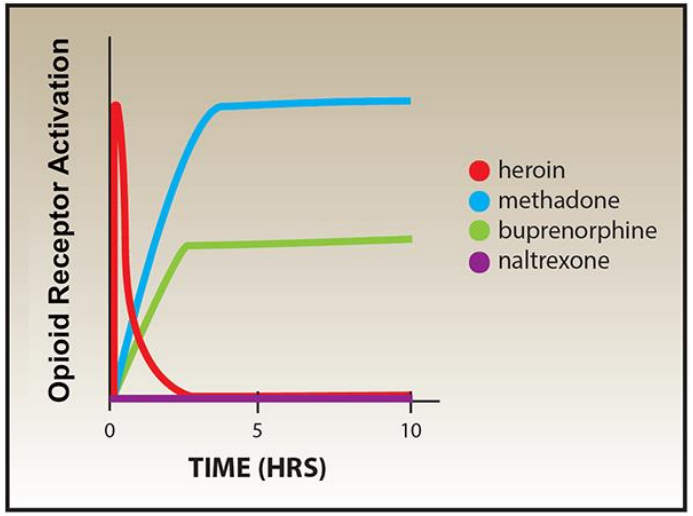


Why You Should Prescribe: Safe

- Highly safe medication - for both acute and chronic dosing
- Primary side effects: nausea and constipation - like other mu agonist opioids, but may be less severe and more self-limiting
- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance
- No evidence of organ damage with chronic dosing of Buprenorphine “mono” or “combo” formulations
- Side effects are similar to other opioids: constipation itching, and hormone suppression. More dry mouth. Less depression.

Buprenorphine Abuse Profile

- Euphoria in non-opioid dependent individuals
- Abuse potential less than full opioid agonists
- Abuse among opioid-dependent individuals is relatively low
- Naloxone (combo product) has limited bio-availability orally or sublingually, but is active if crushed, dissolved, and injected which will cause initial withdrawal resulting in less likability and less diversion.
- Most illicit use is to prevent or treat withdrawal and cravings



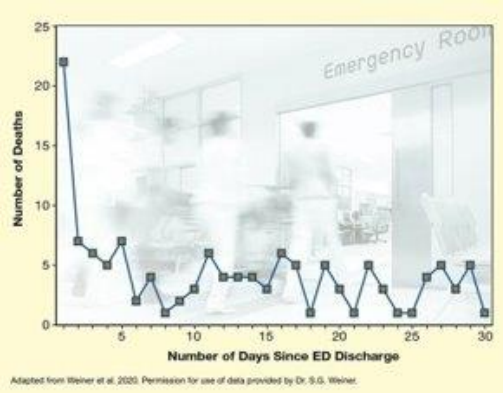
Yokel MA et al. *Curr Drug Abuse Rev.* 2011.

Lofwall MR, Walsh SL. *J Addic Med.* 2014.

Published in final edited form as:
Ann Emerg Med. 2020 January ; 75(1): 13–17. doi:10.1016/j.annemergmed.2019.04.020.

One Year Mortality of Patients after Emergency Department Treatment for Nonfatal Opioid Overdose

Scott G. Weiner, MD, MPH,
Brigham and Women's Hospital, Boston, MA



Of 11,557 included in the study, 635 (5.5%) died within one year and of those 130 (20.5%) died within one month

Alzuhairi *et al. BMC Cardiovascular Disorders* (2017) 17:279
DOI 10.1186/s12872-017-0710-3

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Long-term prognosis of patients with non-ST-segment elevation myocardial infarction according to coronary arteries atherosclerosis extent on coronary angiography: a historical cohort study

Karam Sadoon Alzuhairi[1*], Peter Søgaard[1,2], Jan Ravkilde[1], Aziza Azimi[3], Michael Mæng[4], Lisette Okkels Jensen[5] and Christian Torp-Pedersen[3]

One-year mortality for NSTEMI patients with 0VD was 3.7%, DA 5.7%, 1VD 2.5%, 2VD 4.8%, and 3VD 11. 5%

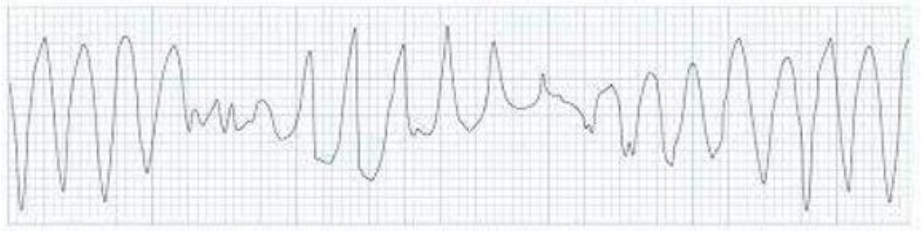
Why You Should Prescribe: Lifesaving

Methadone

- ***Full Agonist* at mu receptor**
- ***Long acting (***Half-life ~ 15-60 Hours)
  - Metabolized to EDDP
- ***Weak affinity*** for mu receptor
- *Can be displaced by partial agonists (e,g. burprenorphine) and antagonists (e.g.naloxone, naltrexone)*, which can both precipitate withdrawal

Monitoring

- Significant respiratory suppression and potential respiratory arrest in overdose
- QTc prolongation



Naltrexone

- ***Full Antagonist*** at mu receptor, Competitive binding at mu receptor
- ***Long acting***
  - Half-life:
    - Oral ~ 4 Hours
    - IM ~ 5-10 days
- ***High affinity*** for mu receptor
- *Blocks* other opioids
- *Displaces* other opioids
  - Can precipitate withdrawal
- ***Formulations***
- *Tablets: Revia®: FDA approved in 1984*
- *Extended-Release intramuscular injection: Vivitrol®: FDA approved in 2010*

THE LANCET

Volume 391, Issue 10118, 27 January–2 February 2018, Pages 309-318

Articles

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Dr Joshua D Lee MD [a], Edward V Nunes Jr MD [c], Patricia Novo MPH [b], Ken Bachrach PhD [d], Genie L Bailey MD [e f], Snehal Bhatt MD [g], Sarah Farkas MA [b], Marc Fishman MD [h i], Phoebe Gauthier MPH [b], Candace C Hodgkins PhD [j], Jacquie King MS [k], Robert Lindblad MD [k], David Liu MD [l], Abigail G Matthews PhD [k], Jeanine May PhD [k], K Michelle Peavy PhD [m], Stephen Ross MD [b], Dagmar Salazar MS [k], Paul Schkolnik PhD [n], Dikla Shmueli-Blumberg PhD [k]... John Rotrosen MD [b]

- 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287)
- The primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use.
- 24-week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287; hazard ratio [HR] 1·36, 95% CI 1·10–1·68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures.
- Opioid-negative urine samples (p<0·0001) and opioid-abstinent days (p<0·0001) favored BUP-NX compared with XR-NTX among the intention-to-treat population, but were similar across study groups among the per-protocol population.
- Self-reported opioid craving was initially less with XR-NTX than with BUP-NX (p=0·0012), then converged by week 24 (p=0·20).
- Treatment-emergent adverse events including overdose did not differ between treatment groups.

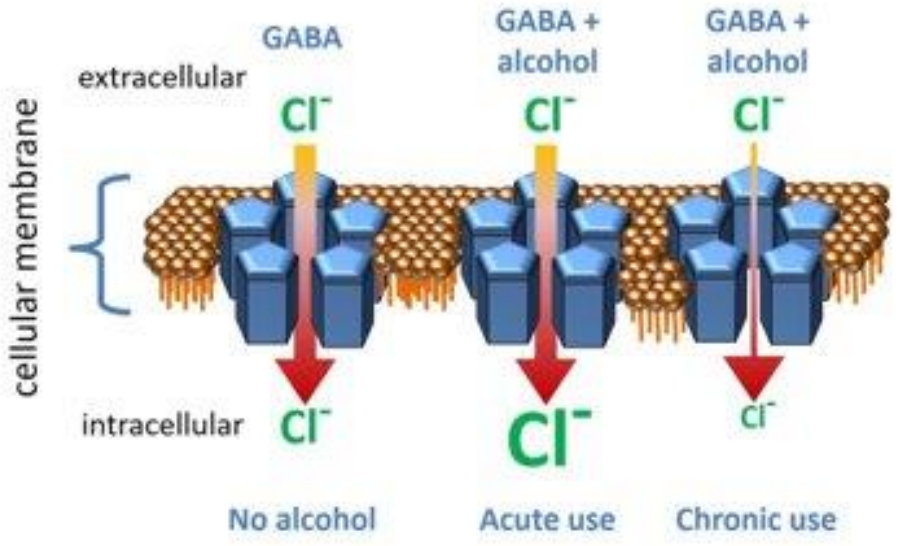
BOTTOM LINE: In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective.

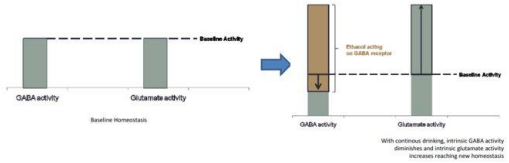
MAT for alcohol use disorder

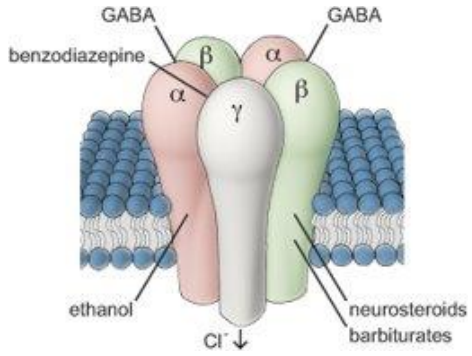
MEDICATION	DOSING	CONTRAINDICATIONS	COMMENTS
First Line			
Naltrexone	50 mg daily	Opioid use (patient should carry an alert for emergency personnel); acute hepatitis or liver failure	• May be started while patient is still drinking • Cannot be used with opioids • Reduces cravings; helps prevent relapse to heavy drinking • Can be combined with acamprosate once abstinence is achieved • IM formulation available (380 mg IM q4 weeks)
Acamprosate	666 mg TID 333 mg TID (CrCl 30-50 ml/min)	Severe renal impairment (CrCl < 30 ml/min)	• For patients who are abstinent • May be better than naltrexone for maintaining abstinence • Helps prevent relapse to heavy drinking
Second Line			
Disulfiram	Initial: 500 mg daily x 1-2 weeks Maintenance: 250 mg daily	Use of alcohol or ethanol-containing medications, metronidazole, severe myocardial disease/coronary occlusion, psychosis	• For patient who are abstinent (minimum 12 hours since last drink) • Does not reduce cravings • Requires a motivated patient • Poorly tolerated
Topiramate	Initial: 25-50 mg daily with slow titration up to 150 mg BID Taper when discontinued		• Reduces heavy drinking days • Poorly tolerated • Trials comparing naltrexone to topiramate found little difference in outcomes
Baclofen	Initial: 5 mg TID x 3 days, then 10 mg TID Taper when discontinued		• Mixed results in studies, may improve chance of abstinence

Acamprosate

- Mechanism not fully defined.
- Similar in structure to GABA and increases the activity of the GABA-ergic system while also decreasing the activity of glutamate in the CNS on NMDA receptors
- Need to monitor renal activity



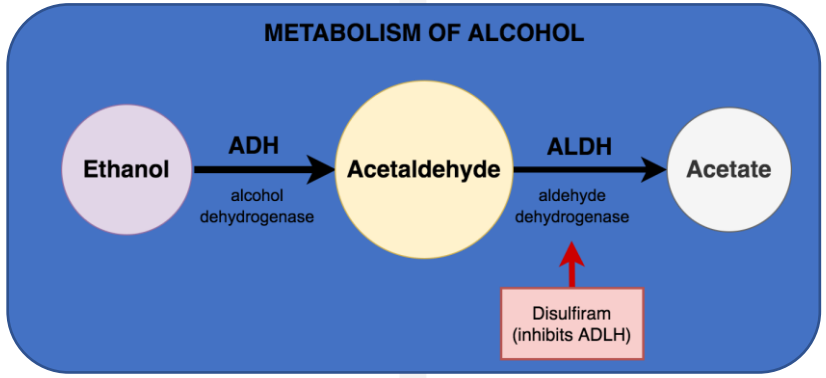




Disulfiram

- Blocks the oxidation of alcohol at the acetaldehyde stage.
- Increased acetaldehyde cause flushing, headache, nausea, vomiting, diaphoresis, palpitations/tachycardia, syncope
- Rarely can cause liver failure

	Reinforcement (Increase / maintain behavior)	Punishment (Decrease behavior)
Positive (add stimulus)	Add pleasant stimulus *to* **Increase / maintain** behavior	Add aversive stimulus *to* **Decrease** behavior
Negative (remove stimulus)	Remove aversive stimulus *to* **Increase / maintain** behavior	Remove pleasant stimulus *to* **Decrease** behavior



MAT for Methamphetamine Use Disorder

Substance	Goal	Outcome
Stimulants	Eliminate cravings and withdrawal	No significant improvement in negative UDT or 3 weeks sustained abstinence relative to placebo per systematic review of 11 clinical trials and 791 patients.
NTX + NAC	Decrease appetite and cravings	NTX performed better alone than with NAC in decreasing MA use. In RCT of NAC only (+Matrix model) in which there was a 30% drop out rate, NAC resulted in significant decrease in Cocaine Craving Questionnaire
Baclofen Gabapentin	Increases GABA activity to decrease negative reinforcement	Baclofen 20mg TID or Gabapentin 800mg TID was no different in MA use compared to placebo. Only one subgroup with high adherence noted a difference, though not reproduced
Others w/o effect	TCAs (imipramine, desipramine), SSRIs (fluoexteine, sertraline, paroxetine), ondasetron, topiramate, and CCB (amlodipine)	

Buproprion

- Mechanism is not fully understood. Weak reuptake inhibitor of dopamine and norepinephrine.
- Lowers the seizure threshold above 450mg (studies limited to immediate release tablets)
- Often used due to "stimulating effect" which may offset craving for stimulants minimally

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

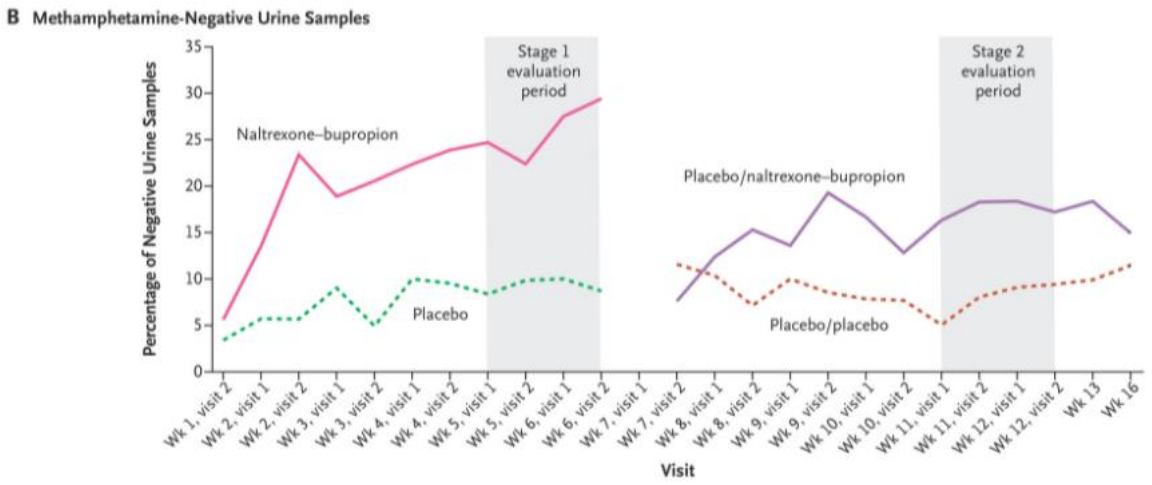
Madhukar H. Trivedi, M.D., Robrina Walker, Ph.D., Walter Ling, M.D., Adriane dela Cruz, M.D., Ph.D., Gaurav Sharma, Ph.D., Thomas Carmody, Ph.D., Udi E. Ghitza, Ph.D., Aimee Wahle, M.S., Mora Kim, M.P.H., Kathy Shores-Wilson, Ph.D., Steven Sparenborg, Ph.D., Phillip Coffin, M.D., M.I.A., et al.

January 14, 2021
N Engl J Med 2021; 384:140-153
DOI: 10.1056/NEJMoa2020214

29 References 7 Citing Articles

Results

- Of 668 enrolled participants there was a 13.6% response rate to the intervention (75% of urine drug samples at the end of each stage were negative) compared to 2.5% to placebo when the average was weighted across both stages



Study strengths

- Multisite, double-blind, 2 stage RCT
- low attrition, high adherence

Mirtazapine

- Alpha2 adrenergic antagonist which causes an increase in release of norepinephrine and serotonin.
- It is also a serotonin and histamine receptor antagonist
- It does not act as a reuptake inhibitor of these chemicals
- Effectiveness is in improving sleep and decreasing impulsivity or higher risk behaviors.

ORIGINAL ARTICLE

Mirtazapine to Reduce Methamphetamine Use

A Randomized Controlled Trial

Grant N. Colfax, MD; Glenn-Milo Santos, MPH; Moupali Das, MD, MPH; Deirdre McDermott Santos, MSN, FNP; Tim Matheson, PhD; James Gasper, PharmD; Steve Shoptaw, PhD; Eric Vittinghoff, PhD

Arch Gen Psychiatry Nov 2011

- Double-blind RCT (12 week trial), 60 participants (All MSM)
- Mirtazapine 30mg daily vs placebo
- In treatment arm urine drug test positivity decreased from 73% to 44%. NNT for negative weekly urine test was 3.1.
- Associated with decrease in sexual risk behaviors
- Limited adherence

Medication Summary

Restore Executive Control Over Drug Use

Buprenorphine

Methadone

Naltrexone

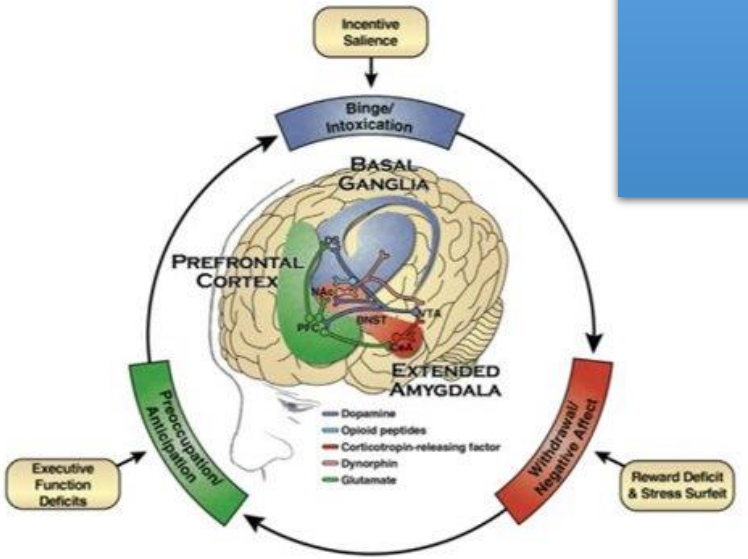
Acamprosate

Nicotine Replacement

Chantix

N-Acetylcysteine*

Mirtazapine*



Restore Response to Natural Rewards and Inhibit Drug Reward

Buprenorphine

Methadone

Acamprosate

Chantix

Gabapentin*

Topiramate*

Buproprion*

Manage Withdrawal and Restore Balance to Stress Response

Buprenorphine

Methadone

Nicotine Replacement

Gabapentin*

Buproprion*

N-Acetylcysteine*

QUESTIONS