Case-Based Application: Treatment of Chronic Alcohol Use Disorder In Patients with Opioid Use Disorder

Clement Chen, PharmD, BCPS
Friday, August 13th, 2021

Credit: Chun Tong, MD
Rutgers NJMS Chief Psychiatry Resident

RUTGERS Robert Wood Johnson Medical School
Cooper University Health Care
DHS Department of Human Services
Cooper Medical School of Rowan University
RUTGERS New Jersey Medical School

Disclosures

No disclosures

Objectives

- State the prevalence of alcohol use disorder and treatment today compared with those of opioid use disorder
- Identify the treatment available for alcohol use disorder
- Examine the available literature on the chronic management of alcohol and opioid use disorder
- Formulate a strategy to manage a patient with both alcohol and opioid use disorders

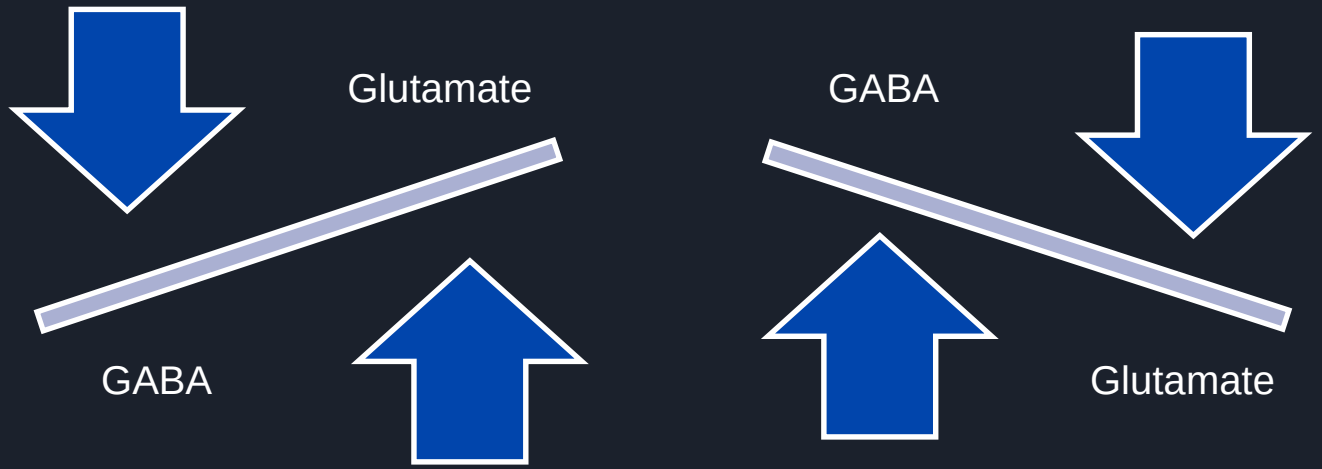
Background

Alcohol Use During COVID-19

- The average alcohol intake of social consumers **DECREASED** during the first few months of COVID-19 compared to the same time period in previous years
- The average alcohol intake from chronic/excessive drinkers **INCREASED** during COVID-19 compared to the same time period in previous years

Increased alcohol intake associated with and worsened amongst those already with alcohol misuse/alcohol use disorder

Balance of GABA and Glutamate – The Neurobiology of Alcohol Use Disorder



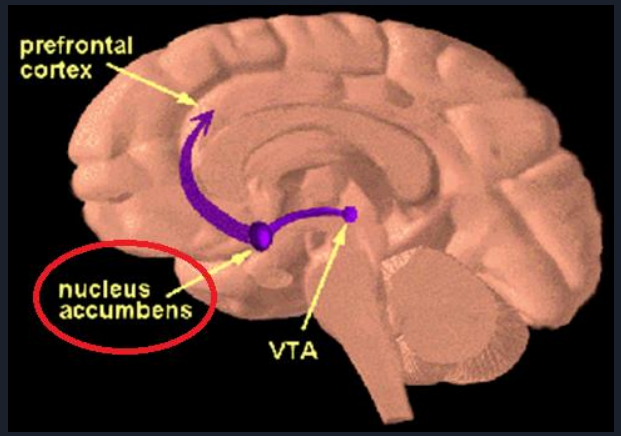
Acute

Chronic

Effects on Dopamine– The Neurobiology of Alcohol Use Disorder

Executive function disorder
FRONTAL CORTEX

Craving and Negative Affect



Neuroadaptations

Reward deficit disorder
REWARD PATHWAY

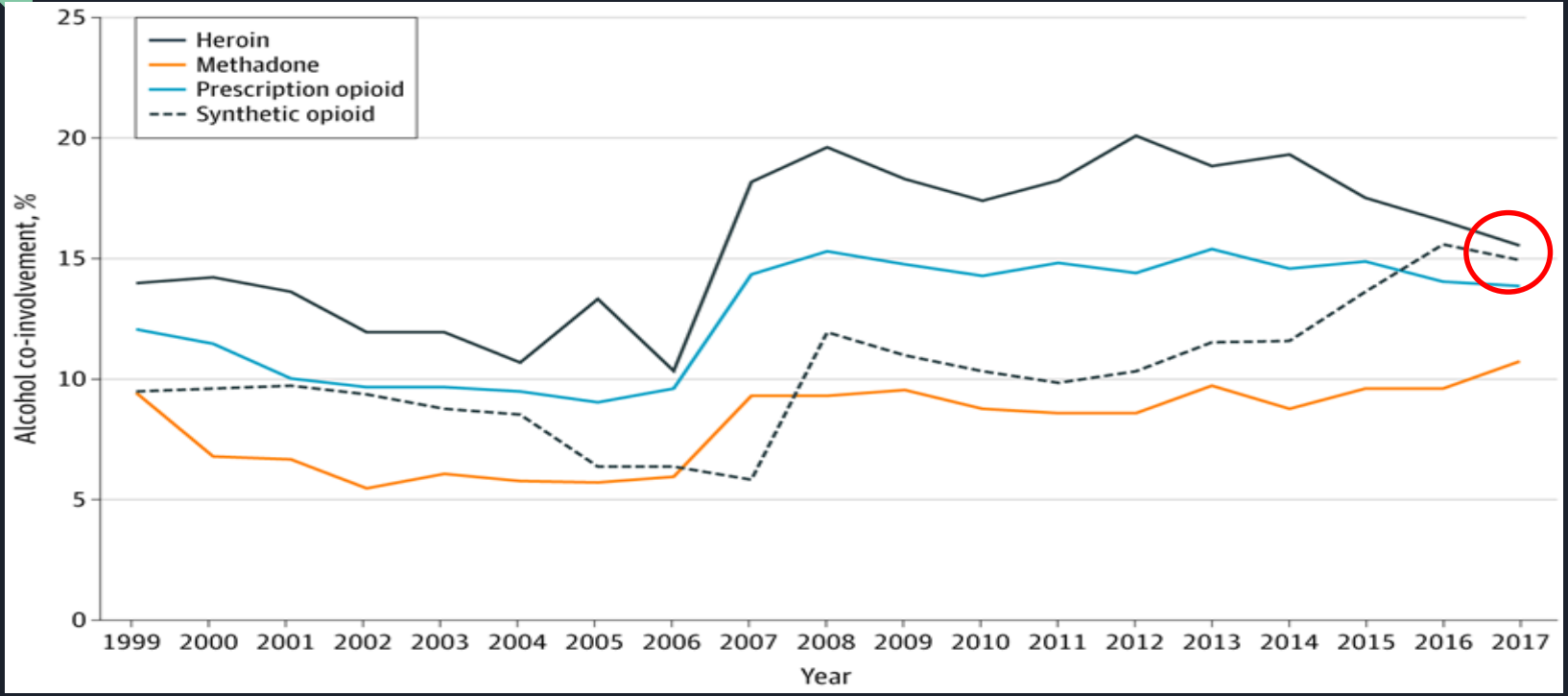
Drug-Liking

Withdrawal and Negative Affect

Stress-Surfeit Disorder
ANTI-REWARD PATHWAY

Kakko J, et al. *Front Psychiatry.* 2019 Aug 30:10:592.

Co-Involvement of Alcohol in Opioid Overdose Deaths



Tori ME, et al. *JAMA Netw Open.* 2020 Apr 1;3(4):e202361.

Alcohol Use- And Opioid Use Disorders Today

Alcohol Use Disorder	Opioid Use Disorder
Affects 15 million	Affects 2 million
Only 7% received treatment	Only 21% received treatment

1/3 with OUD have current alcohol misuse → 23% with OUD also had AUD

Opioid misuse is significantly associated with poorer AUD treatment outcomes

Dydyk AM, Jain NK, Gupta M. Opioid Use Disorder. [Updated 2021 Jul 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553166/

Patient-Centered Opioid Treatment. Accessed on: 8/2/21. Accessed from: https://www.asam.org/advocacy/federal-advocacy/ensure-equitable-access-and-coverage-for-comprehensive-high-quality-addiction-care/p-coat-apm

NIH: Alcohol Use in the United States. Accessed on: 8/2/21. Accessed from: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics

Witkiewitz, et al. *Alcohol Clin Exp Res.* 2018 Jul;42(&):1249-59.

Prevalence of Documented Alcohol and OUD Diagnoses and Treatment in a Regional Primary Care Network

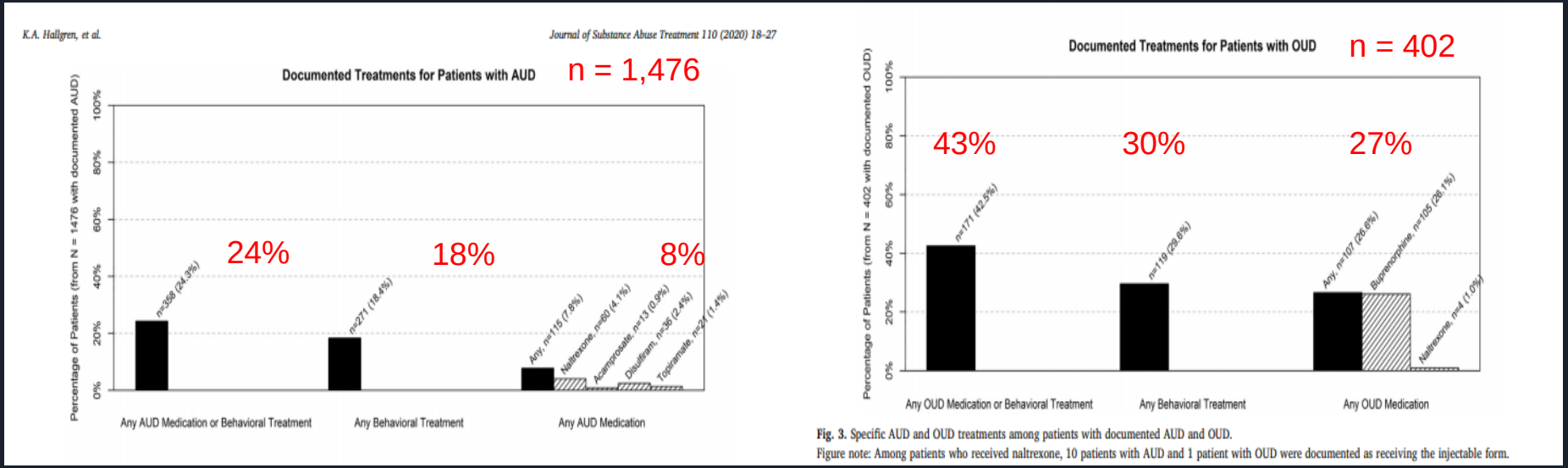


Fig. 3. Specific AUD and OUD treatments among patients with documented AUD and OUD.
Figure note: Among patients who received naltrexone, 10 patients with AUD and 1 patient with OUD were documented as receiving the injectable form.

Hallgren KA, et al. *J Subst Abuse Treat.* 2020 Mar;110:18-27.

Association Between OUD and AUD

- Opioid misuse predicted a 38% greater odds of heavy drinking during treatment (OR=1.38; p=0.001)
- Opioid misuse significantly associated with time to first heavy drinking and in heavier and more frequent drinking profile (OR=2.90; p=0.003)
- Alcohol misuse shown to be a risk factor for non-adherence to pharmacotherapy
- OUD has higher prevalence of hepatitis C, and chronic alcohol use can speed up the progression to cirrhosis
- Alcohol misuse can worsen psychiatric comorbidities, including anxiety, depression, and suicidality

Hallgren KA, et al. *J Subst Abuse Treat.* 2020 Mar;110:18-27.
Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17.

Health Effects of Chronic Opioid and Alcohol Use Disorder

Opioid Use Disorder	Alcohol Use Disorder
Respiratory Depression → overdose death!	Respiratory Depression and overdose death → in combination with opioids
Increased risk of Hepatitis A/B/C/HIV	Liver/pancreatic disease → cirrhosis, alcoholic fatty liver disease, pancreatitis, cancers
Worsens management of other chronic health conditions	Heart disease → arrhythmias, heart failure
	Neurological conditions → Wernicke-Korsakoff Syndrome/encephalopathy
	Hematologic conditions → anemia
Worsen underlying psychiatric conditions	

Treatment of Alcohol Use Disorder: A Comparison with Opioid Use Disorder

Summary of Screening and Diagnosis of Alcohol Use Disorder

- USPSTF recommends routine screening for risky alcohol use and alcohol use disorder in those 18 years of age or older
  - AUDIT-C for Alcohol Use
  - CAGE Questionnaire
- American Psychiatric Association recommends screening for co-morbid conditions for those diagnosed with AUD
  - Major depressive disorder, suicidal ideation, and hepatic disease
- Withdrawal can be fatal
  - Evaluate with PAWSS (Prediction of Alcohol Withdrawal Severity Scale) to determine risk for alcohol withdrawal syndrome
- Diagnosis based on DSM-5 criteria for alcohol use disorder
- Assess withdrawal with CIWA-Ar to determine severity

Clinical Resource, Outpatient Alcohol Detox and Relapse Prevention. Pharmacist's letter/Prescriber's Letter. February 2019.
USPSTF Unhealth Alcohol Use in Adolescents and Adults: Available from: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/unhealthy-alcohol-use-in-adolescents-and-adults-screening-and-behavioral-counseling-interventions
Reus VI, et al. *Am J Psychiatry* 2018;86:86-89.
Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17

High-Risk Concerns with Alcohol Use Disorder

- Patients with severe symptoms
- Serious or unstable psychiatric or medical comorbidities
- Pregnancy
- History of delirium or seizures
- Withdrawal symptoms despite a blood alcohol level over 1g/dL
- Heart rate > 120 beats per minute
- Serious infection

Clinical Resource, Outpatient Alcohol Detox and Relapse Prevention. Pharmacist's letter/Prescriber's Letter. February 2019.

Treatment Options for Chronic Management of AUD Compared with OUD

- Pharmacotherapy **recommended** for moderate-severe alcohol use disorder
  - MAUD + CBT associated with reduced alcohol consumption compared to MAUD alone
  - Possible to go with abstinent therapy but should ensure behavioral interventions
- Pharmacotherapy **ALWAYS** recommended for opioid use disorder
  - NNT = 2 for retention in treatment with buprenorphine
  - Mortality benefit
  - ? Psychosocial interventions

Medications for Alcohol Use Disorder	Medications for Opioid use Disorder
Oral or XR-Naltrexone	XR-Naltrexone Only
Acamprosate	Buprenorphine
Disulfiram	Methadone

Ray LA, et al. *JAMA Netw Open.* 2020 Jun 1;3(6):e208279.
Larochelle MR, et al. *Ann Intern Med.* 2018 Aug 7;169(3):137-45.
Mattick RP, et al. *Cochrane Database Syst Rev.* 2014;(2):CD00207

What Options for AUD Should be Chosen?

Naltrexone

- Reduces positive reinforcement (reward craving)
- **Reduces the euphorogenic/reinforcing effect of alcohol**
- Prevents a slip from becoming a full-blown relapse
- Generally 50mg daily ORAL / 380mg IM monthly
- Cannot be used with opioids including methadone and buprenorphine

Acamprosate

- Reduces negative reinforcement (abstinence craving)
- Acts to block the glutamatergic system that is upregulated in chronic alcoholism by resting the neuroadaptive changes
- Generally 666mg **three times a day**; dose adjusted for renal impairment

Disulfiram

- Irreversibly binds to acetaldehyde dehydrogenase by inhibiting the metabolism of acetaldehyde to acetate
- Acetaldehyde builds up leading to a violent reaction (nausea, vomiting, flushing)
- 250-500mg daily
- Adverse events: Liver toxicity / suicidal thoughts

Fairbanks, et al. *Mayo Clin Proc.* 2020 Sep;95(9):1964-77.

Clinical Pearls

Naltrexone

- **Associated with a small but significant reduction in return to any drinking and return to heavy drinking**
  - Heavy drinking NNT=12; daily drinking NNT=25; abstinence NNT=20
- Larger effect on heavy drinking and alcohol cravings than acamprosate
- Can give with AST/ALT up to 5 times the ULN
- Oral doses can start at 25mg/day given possible GI side-effects
- First-line option

Acamprosate

- Minimal effect on dopamine concentrations so greatest effect on **promoting initial abstinence** than alcohol cravings
- Associated with small, but significant return to alcohol consumption and percent days of drinking
  - Return to any drinking NNT=12; Reduced drinking NNT=9
  - Help with negative emotional-state based craving
- Good first-line alternative to naltrexone

Disulfiram

- Can have serious adverse events that include acute cardiovascular disease (MI) and psychosis
- Only for sustaining complete alcohol abstinence
- No significant effect on return to drinking, heavy drinking, quality of life or function, or mortality
- Must be adherent to therapy
- Third-line after naltrexone and acamprosate

Fairbanks, et al. *Mayo Clin Proc.* 2020 Sep;95(9):1964-77.

Other Agents for Chronic Alcohol Use Disorder?

- Gabapentin – may improve abstinence
- Topiramate – may reduce binge drinking and improve abstinence
- Baclofen – for those already abstinent and have high alcohol use
- Prazosin – may reduce heavy drinking and number of drinks/week

Clinical Resource, Outpatient Alcohol Detox and Relapse Prevention. Pharmacist's letter/Prescriber's Letter. February 2019.

Opportunity for Collaborative Care for Opioid and Alcohol Use Disorders in Primary Care

- Randomized clinical trial of 377 primary care patient in a FQHC
- 1:1 randomization to collaborative care vs. usual care
  - Population-based management approach vs. vs. receiving a number for appointment scheduling and list of community referrals
- **Primary Outcome:** Use of evidence-based treatment for alcohol and OUD and self-reported abstinence from opioids or alcohol at 6 months

FQHC = Federally Qualified Health Center

Watkins KE, et al. *JAMA Intern Med.* 2017 Oct 1;177(10):1480-88.

Opportunity for Collaborative Care for Opioid and Alcohol Use Disorders in Primary Care

	Collaborative Care	Usual Care	P-Value
Proportion of Patients Receiving Any Treatment	73 (39%)	32 (17%)	P<0.001
Proportion Reporting Abstinence at 6 months	33%	22%	P=0.03
Proportion Reporting Abstinence from Opioids, Any Alcohol, Cocaine, Methamphetamines, and Marijuana, past 30 days	26%	16%	P=0.01

Watkins KE, et al. *JAMA Intern Med.* 2017 Oct 1;177(10):1480-88.

Co-Management

We know how alcohol and opioid interact when present in the body, but *we don't have as much information on:*

1) How alcohol use affect MOUD
2) MOUD effects alcohol use
3) More broadly, using MAUD in those with OUD

Nolan, S. et al. 2016 - Alcohol use in opioid agonist treatment

Findings

- In rats, we know alcohol increase methadone peak concentration, and acute methadone use increase alcohol level/chronic use reduce alcohol level suggest both substances share a similar metabolic pathway.
- MOUD seems to not have a significant effect on alcohol use: 3 studies indicating an increase in alcohol consumption during treatment, 3 studies indicating a decrease in alcohol consumption and 9 studies reporting no change
- Patients discharged from methadone clinics have shown an increased risk of overdose and increased mortality from excessive alcohol use, e.g. suicide attempts, unintentional overdoses involving various substances including benzodiazepines, illicit opioids and etc. Patient initiating on methadone also known to be at high risk given respiratory suppressive effect of combining methadone and alcohol use.

OAT = opioid agonist therapy

Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17

Nolan, S. et al. 2016 - Alcohol use in opioid agonist treatment

Findings

- Alcohol misuse during MOUD is associated with poor adherence to treatment leading to negative outcomes, hepatitis, liver cirrhosis, worsening psychiatric symptoms including anxiety, depression, and suicidality.
- However, places that offer treatment of AUD may not offer MOUD (can be due to concern of mixing MOUD, benzo, and risk of overdose), despite evidence suggest treating AUD improve outcome of patient on MOUD.
- Overall there's not as much attention in the scientific community looking at treating AUD + OUD

Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17

Nolan, S. et al. 2016 - Alcohol use in opioid agonist treatment

Management

- Guidelines are lacking
  - High prevalence of alcohol misuse
  - Lower threshold for determining risky alcohol use
- Screening: recommend Alcohol Use Disorder Identification Test (AUDIT, or AUDIT-C for the short version for initial screening)
- Brief Intervention

Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17

Alcohol Use Disorder Identification Test-C:

In men, a score of 4 or more is considered positive;
in women, a score of 3 or more is considered positive.

Q1: How often did you have a drink containing alcohol in the past year?

- ❑ Never - 0
- ❑ Monthly or less - 1
- ❑ Two to four times a month - 2
- ❑ Two to three times a week - 3
- ❑ Four or more times a week - 4

Q2: How many drinks did you have on a typical day when you were drinking in the past year? None, I do not drink 0

- ❑ 1 or 2 - 0
- ❑ 3 or 4 - 1
- ❑ 5 or 6 - 2
- ❑ 7 to 9 - 3
- ❑ 10 or more - 4

Q3: How often did you have six or more drinks on one occasion in the past year?

- ❑ Never - 0
- ❑ Less than monthly - 1
- ❑ Monthly - 2
- ❑ Weekly - 3
- ❑ Daily or almost daily - 4

Nolan, S. et al. 2016 - Alcohol use in opioid agonist treatment

Lab

- CMP w. LFT, CBC w. diff (MCV), BAC (acute) or
- Biomarkers
  - **Carbohydrate-deficient transferrin** (CDT, correlate well with an individual's drinking pattern, especially during the preceding 30 days),
  - **Gamma-Glutamyl Transferase** (GGT, 2-3 weeks, nonspecific, affected by age and other medical condition e.g. obesity, diabetes), and
  - **Phosphatidylethanol** (PEth, detect longer term exposure (2-3 weeks).

Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17

Nolan, S. et al. 2016 - Alcohol use in opioid agonist treatment

Treatment:

- Cannot use naltrexone (if on OAT)
- Data is lacking for use of Acamprosate and disulfiram (support by 2 meta analyses but 1 study excluded methadone)
- Extended-release naltrexone (XR-NTX) have shown promise for the treatment of both alcohol misuse and opioid dependence

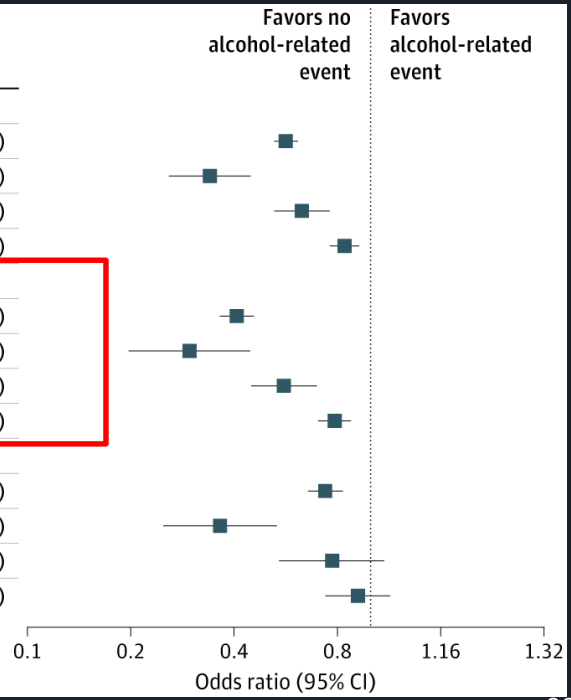
Nolan S, et al. *Addict Sci Clin Pract.* 2016;11:17

Association of Opioid Use Disorder Treatment and Alcohol-Related Acute Event

n = 13,335

- Methadone had greatest overall reduction
- Buprenorphine had greater reduction in participants with a recent AUD claim
- Naltrexone use greatest among those with AUD claim

Group	Odds ratio (95% CI)
All participants	
Buprenorphine	0.57 (0.52-0.61)
Methadone	0.34 (0.26-0.45)
Naltrexone extended release	0.63 (0.52-0.76)
Naltrexone oral	0.84 (0.76-0.93)
Participants with recent AUD claim	
Buprenorphine	0.41 (0.36-0.46)
Methadone	0.30 (0.20-0.45)
Naltrexone extended release	0.56 (0.45-0.70)
Naltrexone oral	0.79 (0.70-0.88)
Participants without recent AUD claim	
Buprenorphine	0.74 (0.66-0.83)
Methadone	0.36 (0.25-0.53)
Naltrexone extended release	0.77 (0.54-1.10)
Naltrexone oral	0.92 (0.74-1.14)



Xu KY, et al. *JAMA Netw Open*. 2021;4(2):e210061.

Strategies to Manage Alcohol and Opioid Use Disorders

- Treat opioid use disorder with evidence-based MOUD!
  - Mortality vs. abstinence data
  - Reduction in alcohol-related acute events
- Provide pharmacotherapy for moderate-severe alcohol use disorder
  - Acamprosate may be the best FDA-approved option as naltrexone is contraindicated in those on opioid agonist MOUD
  - Other therapies?
  - At the very least, psychosocial therapy should be provided
- Properly educate the patient about the risks of morbidity/mortality to ensure that patients make better informed decisions
  - Respiratory depression
- Use of medications for alcohol use disorder **may** be more beneficial in those after period of detoxification (acamprosate) and longer abstinence (acamprosate and naltrexone)

Conclusions

- Co-morbid alcohol and opioid use disorder carry significant morbidity/mortality than either disorder alone
- There is a strong association with alcohol misuse in those with opioid use disorder
- Ensure appropriate screening and interventions for treatment
- Utilize a multidisciplinary approach to improve patient outcomes

Case Presentation

Patrick McFadden, MD
Addiction Medicine Fellow
Rutgers NJMS

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

The patient is a **65-year-old African-American/Black male** with a past medical history of recurrent acute **pancreatitis,** questionable chronic pancreatitis, hypertension, seizure disorder, peptic ulcer disease, history of cholangitis s/p ERCP and biliary stent placement (subsequently removed), asymmetric gynecomastia R>>L (malignancy to be r/o), COPD, alcohol use disorder, heroin use disorder (on methadone but actively using) who presents for abdominal pain x 1 day. The patient is admitted to observation for alcoholic pancreatitis vs. gastritis, and an addiction medicine consultation service was called upon for management of the patient's alcohol use disorder and opioid use disorder.

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

Chart review:

- The patient's chart is significant for frequent Emergency Department visit (8 on records since the beginning of 2021) due to various complaints including abdominal pain, seizure, anemia.
- The patient has in the past use methadone for opioid use disorder, however, he continues to experience relapses to heroin use while on methadone.
- The patient is still actively using alcohol. He also reported multiple episodes of seizure this month.

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

Chart review:

Patient is in treatment for substance use disorders with a physician at the University Hospital IM clinic, with last follow-up note dated 4/15/2021. At the time, the outpatient doctor noted the patient "continues to report insomnia...think he is anxious and restless", "Still has not initiated suboxone, using 6-7 bags of heroin daily", and that patient never used suboxone for more than 3 days consecutively. The patient also smokes "a couple puff of cigarette every few days", and "drinking 3 large beers and 5-6 nips per day" which is an increase. "Wife with him is pushing for inpatient substance rehab- he is hesitant, very worried about losing his job, though he has been furloughed over a year now. He is considering returning to methadone clinic."

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

On evaluation by addiction medicine fellow:

- Started Methadone 90 mg from American Habitat started about 1 mo. ago. Continues to report craving, snort 4-5 bag heroin/day. Declined buprenorphine.
- Wife also uses heroin
- Smoke 1/2 ppd for 32 yr --> titrate to "few drags from time to time, declined NRT.
- Drinks 16 oz wine x 4 glasses + 4 shots of brandy a day on average, start around midday. Denies withdrawal symptoms ever (likelihood??)

Social hx: Patient lives with wife who also uses Current Employment: Works as laborer in a vinegar and cooking wine plant. Financially supported by self Currently insured.

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

Recommendation:

OUD

- Continue methadone at 20 mg tomorrow. May titrate to cravings.
- Replete lytes and repeat ECG
- ECG 24 hour after each increased in methadone
- Pt to follow with american Habitare
- Pt will need RX for NARCAN at dc

AUD

- Initiate UH withdrawal protocol
- Will discuss further acamprosate
- Discussed risk of combining EtOH with methadone and heroin

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

Hospital Med List:
OUD: Methadone 90 mg PO QDay, held due to prolong QTc. Patient is also on Roxicodone 20 mg PO Q6 PRN
AUD: Has Valium 10 mg PO QDay, Ativan 2 mg PO Q6 PRN for anxiety/agitation, Remeron 15 mg PO QHS (home med)

ED lab:
K2.3, Cl 89, Ca 8.1
Bil direct 0.4/Bil Tot 1.3
AST 32/ALT 19

WBC 19.1 --> 4.8 / Hgb 12.2 --> 9.7 the next day + hydration, BCx pending
MCV 97.0
uTox was not completed (unfortunately), historically positive for opiates and cannabinoids (2/18/21)

Other: Sed rate 60, C-reactive protein 52, Lactate 1.7

ECG: significantly prolonged QTc of 551 at HR 58.

ED CT shows:
1. There are findings consistent with acute on chronic pancreatitis.
2. There is extrahepatic and intrahepatic biliary ductal dilation. No choledocholithiasis is seen.

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

- Omeprazole (PRILOSEC) 40 MG Capsule Take 20 mg by mouth 2 (two) times daily.
- mirtazapine (REMERON) 15 MG Tablet Take 1 Tablet (15 mg total) by mouth At Bedtime.
- atorvastatin (LIPITOR) 10 MG Tablet Take 1 Tablet (10 mg total) by mouth At Bedtime.
- levETIRAcetam (KEPPRA) 750 MG Tablet Take 750 mg by mouth 2 times a day.
- chlorthalidone (HYGROTON) 25 MG Tablet Take 1 Tablet (25 mg total) by mouth
- amlodipine (NORVASC) 10 MG Tablet Take 1 Tablet (10 mg total) by mouth Daily.
- propranolol (INDERAL) 40 MG Tablet Take 1 Tablet (40 mg total) by mouth 3 times a day.
- polyethylene glycol (MIRALAX) 17 g 17 g packet Take 17 g by mouth Daily.
- albuterol (PROVENTIL-HFA) 108 (90 Base) MCG/ACT metered dose inhaler 2 Puffs by Inhalation route Every 4 hours as needed
- aspirin chewable 81 MG tablet Take 1 Tab (81 mg total) by mouth Daily.

Treatment of Chronic Alcohol Use disorder In Patients with Opioid Use Disorder - A case review.

Questions/Concerns for the SUD/MAT ECHO Panel

1. How do you manage the risk of inducing methadone for a patient who is still actively using opiate and alcohol?

2. What other pharmacological intervention/behavioral intervention/social intervention can you do to help this patient?

3. Can we hospitalized this patient? What care escalation options can we consider?

Thank You!