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Alcohol, Other Drugs, and Health: Current Evidence

JULY-AUGUST 2022

INTERVENTIONS & ASSESSMENTS

Is Mirtazapine a Treatment Option for Amphetamine and Methamphetamine Use Disorder?

There are currently no approved pharmacological treatments for amphetamine and methamphetamine use disorder (AMD). Emerging evidence suggests that mirtazapine may be an effective treatment option; this systematic review and meta-analysis summarized that evidence.

- Of the 206 studies screened, 2 parallel-arm randomized placebo-controlled trials were identified. These studies were conducted among cisgender men and transgender women (n=180), who received 30mg of mirtazapine (or placebo) per day.
- These studies found a non-significant reduction in methamphetamine use after 12 weeks among patients receiving mirtazapine compared with those receiving placebo. They found no improvement in treatment retention or depression symptom severity.

Comments: Mirtazapine may reduce methamphetamine use among people with AMD, but the current evidence is inconclusive. More studies are needed to determine whether what was identified in the current study was attributable to imprecision in the effect estimate and there is indeed an effect on methamphetamine use, or if there is no benefit.

Nicolas Bertholet, MD, MSc

Reference: Naji L, Dennis B, Rosic T, et al. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis. *Drug Alcohol Depend*. 2022;232:109295

HEALTH OUTCOMES

Alcohol Use Disorder Pharmacotherapy Associated with Improved Liver Disease Outcomes

Alcohol use disorder (AUD) pharmacotherapy is underutilized, despite evidence that it improves drinking outcomes. Evidence of the long-term health benefits of AUD pharmacotherapy has been lacking. This study leveraged a long-term cohort of patients with AUD to assess the association between receipt of AUD pharmacotherapy* and the risk of alcohol-associated liver disease (ALD).

- Of the 9635 patients with AUD (83% white) followed for a mean of 9.2 years, 1135 (12%) had diagnosis of ALD and 3906 (41%) were treated with AUD

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Alcohol Use Disorder Pharmacotherapy Associated with Improved Liver Disease Outcomes (continued from page 1)

pharmacotherapy for a mean of 4.1 years.

- In multivariable analyses, receipt of any AUD pharmacotherapy was associated with a decreased incidence of ALD (adjusted odds ratio [aOR], 0.37).
  - Associations were strongest for gabapentin, topiramate, baclofen and naltrexone; they were insignificant for disulfiram.
  - Acamprosate was associated with an increased risk of ALD (aOR, 2.59).
- The overall association of AUD pharmacotherapy and incident ALD was dose-dependent.
- Receipt of any AUD pharmacotherapy was associated with lower incidence of hepatic decompensation in patients with cirrhosis (aOR, 0.35). Associations were strongest for naltrexone, gabapentin, and topiramate; they were insignificant for baclofen, acamprosate, and disulfiram.

* Defined as ≥3 months of disulfiram, acamprosate, naltrexone, gabapentin, topiramate, or baclofen.

Comments: This single-site study provides novel observational evidence of the potential long-term medical benefits of AUD pharmacotherapy, including non-FDA approved medications (i.e., gabapentin, topiramate, and baclofen). The finding that acamprosate, which has no liver toxicity or metabolism, was associated with an increased risk of ALD likely results from higher-risk patients having been systematically chosen for acamprosate treatment. Comparative medication trials would be necessary to confirm the medical benefits and potential harms of specific AUD medications.

Joseph Merrill, MD, MPH

Reference: Vannier AGL, Shay JES, Fomin V, et al. Incidence and progression of alcohol-associated liver disease after medical therapy for alcohol use disorder. *JAMA Netw Open*. 2022;5(5):e2213014.

Mortality Risk is High in the First Year After Presenting to the Emergency Department With Alcohol Use Disorder

Alcohol-related morbidity and mortality have increased substantially over the last 20 years and particularly during the COVID-19 pandemic. Individuals with injuries or illness related to alcohol use are increasingly presenting to emergency departments (EDs). This retrospective cohort study examined mortality risk among individuals presenting to California EDs for an alcohol-related cause from 2009 to 2011.

- Over the study period, 437,855 individuals sought ED care for acute alcohol intoxication or alcohol use disorder (AUD), comprising 3% of all ED visits.
- Most individuals were male (68%) and non-Hispanic White (54%).
- The mortality rate was 609 per 100,000 in the year after the ED visit, a rate that is 8 times higher than that of demographically matched individuals.
- Most deaths occurred within 6 months of the ED visit.
- Most deaths were attributed to unintentional poisoning or suicide.

Comments: Great attention has been placed on the mortality risk associated with opioid use disorder after ED visits. This study shows that patients with AUD who are seen in the ED are also at increased risk of death. Evidence-based treatments and referrals are urgently needed for individuals with AUD who present for services.

Melissa B. Weimer, DO, MCR

Reference: Goldman-Mellor S, Olfson M, Schoenbaum M. Acute injury mortality and all-cause mortality following emergency department presentation for alcohol use disorder. *Drug Alcohol Depend*. 2022;236:109472.

Apparent Cardioprotective Effects of Moderate Alcohol Consumption Likely Explained by Other Lifestyle Factors

Some observational studies demonstrate a lower risk of cardiovascular disease (CVD) with light-moderate alcohol intake compared with abstinence or heavy consumption. However, confounding lifestyle factors may explain these patterns. Researchers explored the association between alcohol consumption and CVD using a large genetic databank with 371,463 participants that included blood samples and lifestyle information. They constructed a "genetic instrument" based on single nucleotide polymorphisms (SNPs) associated with an alcohol use disorder diagnosis and AUDIT-C answers, but independent of other lifestyle factors.* Researchers measured the association between these SNPs and adverse cardiovascular outcomes to minimize confounding and establish a causal relationship.

- For every 1 standard deviation increase in genetically predicted alcohol consumption, the risk of hypertension and coronary artery disease increased (odds ratios, 1.3 and 1.4, respectively).
- The risk for CVD with alcohol consumption increased exponentially, beginning at 7–14 drinks in a week. This pattern was also found for all-cause mortality.
- Similarly, there was a positive and quadratic association between alcohol consumption and systolic blood pressure, diastolic blood pressure, and LDL cholesterol level.

* Defined as: smoking, body mass index, physical activity, vegetable intake, red meat intake, overall health rating, C-reactive protein level, and total cholesterol level.

Comments: Using a novel method to reduce confounding, this study supports a causal and exponential association between alcohol intake and CVD, beginning at low levels of consumption. These findings suggest that the apparent cardioprotective effects of moderate alcohol consumption found in some observational studies are due to confounding lifestyle factors. Moreover, this study supports the theory that no amount of alcohol is protective against CVD.

Lea Selitsky, MD, MPH** and Darius A. Rastegar, MD

** Contributing editorial intern and Addiction Medicine Fellow, Johns Hopkins University.

Reference: Biddinger KJ, Emdin CA, Haas ME, et al. Association of habitual alcohol intake with risk of cardiovascular disease. *JAMA Netw Open*. 2022;5(3):e223849.

Assessing the Role of Benzodiazepines in US Fatal Overdoses

The epidemiology of fatal overdoses involving benzodiazepines has received less attention than those involving opioids. This cross-sectional study used death record data from the US National Vital Statistics System to examine benzodiazepine-involved overdoses between 2000 and 2019 with attention to time trends, race/ethnicity, other substances used concomitantly with benzodiazepines, and suicide intentionality.

- From 2000 to 2019, 118,208 overdose deaths involved benzodiazepines; 84% of these also involved an opioid.
- 10,677 (9%) of benzodiazepine-involved overdose deaths did not involve an opioid, cocaine, other psychostimulant, barbiturate, or alcohol.
- Most overdose deaths were accidental, but 9% of benzodiazepine plus opioid-involved cases and 36% of cases without an opioid were intentional (i.e., suicides).
- In 2019, there were 9731 benzodiazepine-involved cases, which was an almost 20% reduction from 2017.
- After large increases from 2000 to 2017, benzodiazepine-involved overdose death rates (with and without an opioid) decreased between 2017 and 2019, but these reductions were mostly in non-Hispanic White individuals.

Comments: These data reinforce known risks of concomitant benzodiazepine and opioid use, but, strikingly, they also highlight the role of benzodiazepines in intentional overdose or suicide. Standard reporting on cause of death is unlikely to fully capture suicidal intent, which implies that these numbers are underestimates. This study did not include prescribing data, but based on accrued knowledge, clinicians should avoid co-prescribing benzodiazepine and opioid medications when possible, prescribe naloxone when patients are taking benzodiazepines and opioids, and better screen for and address suicidality.

Aaron D. Fox, MD

Reference: Kleinman RA, Weiss RD. Benzodiazepine-involved overdose deaths in the USA: 2000-2019. *J Gen Intern Med*. 2022;37 (8):2103–2109.

Menthol Bans Reduce the Proportion of Youth Who Use Menthol Flavored Tobacco Product

This study analyzed data from the International Tobacco Control Youth Tobacco and Vaping Surveys to compare rates of menthol tobacco product use among 7067 people aged 16–19 years with current smoking. Participants were from: Canada, where menthol is banned; the United Kingdom (UK), where a menthol ban was implemented during the observation window; and the United States (US), where menthol products are available.

- Menthol smoking was more prevalent among youth in the US than the UK (adjusted odds ratio [aOR], 5.58).
- The proportion of youth with menthol cigarette use in Canada (3% in 2018 to 2% in 2020) and the US (34% in 2018 and 2020) were stable throughout the observation period.
- The proportion of youth who used menthol cigarettes in the UK decreased from 9–12% before the ban to 3% after the ban.

Comments: Manufacturers add menthol to tobacco products to make their taste more appealing, making smoking and vaping easier for people who are new to it. According to the US Centers for Disease Control, youth are more likely to try a menthol cigarette as their first cigarette, and those who first start with a menthol cigarette are more likely to continue smoking. Public health decisions require balancing the rights of adults to access addictive products with the potential harms to youth. This study sheds light on that balance.

Sharon Levy, MD

Reference: East KA, Reid JL, Burkhalter R, et al. Evaluating the outcomes of the menthol cigarette ban in England by comparing menthol cigarette smoking among youth in England, Canada, and the US, 2018–2020. *JAMA Netw Open*. 2022;5 (5):e2210029.

HIV AND HCV

Hepatitis C Treatment at a Syringe Service Program Associated With a Higher Probability of Cure Than Facilitated Referral to Off-site Treatment

Two-thirds of new hepatitis C virus (HCV) infections occur in people who inject drugs (PWID). Despite high rates of HCV cure among PWID, treatment initiation remains low due to restrictive policies, stigma, and inflexible care in traditional healthcare settings. This single-site, randomized controlled trial evaluated the effect of an HCV treatment model co-located at a syringe service program (SSP)—including flexible appointments, drop-ins, and proactive outreach for missed visits—compared with facilitated referral by an on-site coordinator to off-site HCV care. The outcome was the probability of HCV cure (sustained virologic response) 12 months after study enrollment.

- Patients receiving HCV care at an SSP had a higher probability of HCV cure (55 of 82 patients; 67%), compared with those receiving off-site HCV care (19 of 83 patients; 23%).
- Differences in HCV cure probabilities were driven by higher rates of referral to and attendance at HCV clinician visits (attendance among those referred: 87% co-located care versus 37% off-site care). Among those in both groups who initiated medication, the probabilities of cure were similar (~85%).

Comments: Co-located HCV care in an SSP resulted in a probability of cure that was 3 times higher than a facilitated referral to off-site care model, largely driven by increased treatment initiation. Notably, many study participants were successful in the co-located program despite not being direct clients of the SSP, suggesting that providing care in a de-stigmatized harm reduction setting provides a substantial engagement advantage over traditional medical care settings.

Paul J. Christine, MD, PhD* & Alexander Y. Walley, MD, MSc

* Contributing editorial intern and Addiction Medicine Fellow, Boston Medical Center

Reference: Eckhardt B, Mateu-Gelabert P, Aponte-Melendez Y, et al. Accessible hepatitis C care for people who inject drugs: a randomized clinical trial. *JAMA Intern Med*. 2022;182(5):494–502.

PRESCRIPTION DRUGS & PAIN

Prescribed Opioid Medication Discontinuation or Rapid Dose Decrease Associated With Subsequent Overdose

The increase in opioid prescribing for chronic pain that started in the early 1990s led to an increase in overdose and opioid use disorder (OUD). In response to this, there have been efforts to decrease initial opioid prescribing, as well as decreasing or discontinuing opioid medications among patients receiving them for chronic pain. This study used data from a US private health insurer to identify individuals who received high-dose, long-term opioid therapy (HDLTOT, defined as ≥90 morphine milligram equivalents/day for ≥90% of 90 consecutive days), and to investigate the association between rapid discontinuation (defined as >10% dose reduction within a week or 34% within a month) and subsequent overdose or diagnosis of OUD.

- There were 19,443 enrollees who received HDLTOT. During a follow-up period of up to 4 years, there were 59 fatal opioid overdoses, 215 nonfatal overdoses, and 2796 incident OUD diagnoses.
- Rapid reduction or discontinuation of opioid medication was associated with an increased risk of fatal and nonfatal overdoses compared with dose maintenance or gradual reduction (year 1 weighted hazard ratio (HR) was 1.43 and year 2–4 was 1.95).
- Rapid reduction was not associated with an incident diagnosis of OUD in the first 2 years (HR, 1.01), but was 25–48 months afterwards (HR, 1.28).

Comments: This study suggests that rapid dose decreases or discontinuation of opioid medications among people who are prescribed them may lead to harms. We do not know the reasons behind the rapid dose reductions in this cohort; the observed association may be at least partly due to clinicians being more likely to do this with higher-risk patients. In any case, we should continue to avoid initiating opioids for chronic pain and to treat those who are already taking opioid medications in a patient-centered manner that avoids drastic and arbitrary changes.

Darius A. Rastegar, MD

Reference: DiPrete BL, Ranapurwala SI, Maierhofer CN, et al. Association of opioid dose reduction with opioid overdose and opioid use disorder among patients receiving high-dose, long-term opioid therapy in North Carolina. *JAMA Netw Open*. 2022;5(4):e229191.

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