Alcohol, Other Drugs, and Health: Current Evidence

MARCH-APRIL 2024

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BEHIND THE EVIDENCE

***Hosted by* Honora L. Englander & Marc R. Larochelle**

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INTERVENTIONS & ASSESSMENTS

Acamprosate and Oral Naltrexone Are Effective—but Underutilized—Medications for Alcohol Use Disorder

Alcohol use disorder (AUD) is one of the most prevalent substance use disorders in the US. Effective medications for AUD (MAUD) have been available for over 40 years; however, less than 1 percent of individuals with AUD receive them. A recent systematic review of studies lasting ≥12 weeks described the effects on alcohol consumption of FDA-approved MAUD (i.e., acamprosate, disulfiram, and naltrexone), and those that are prescribed off-label for AUD (i.e., baclofen, gabapentin, varenicline, topiramate, prazosin, and ondansetron).

- Of the 118 clinical trials that were included, 100 combined MAUD and non-medication treatments (e.g., counseling).
- There was moderate strength of evidence for the use of acamprosate and oral naltrexone (50mg/day) for reducing return to any drinking and percentage of drinking days (numbers needed to treat [NNT] to prevent one person from returning to any drinking = 11 for acamprosate and 18 for oral naltrexone).
- Oral naltrexone (50mg/day) had moderate strength of evidence for reduction of return to heavy drinking (NNT = 11, compared with placebo).
- Studies involving disulfiram were limited. Studies of baclofen and gabapentin had low strength of evidence. Topiramate had moderate strength of evidence for reduction in drinking days, but had more adverse effects.
- Health outcomes like motor vehicle crashes, injuries, quality of life, function, and mortality were infrequently reported.
- Overall adverse effects were low across studies.

Comments: In this systematic review and meta-analysis, the evidence was strongest for the benefit of naltrexone and acamprosate, which appear to have approximately equal efficacy for treating AUD. The well-established benefits of MAUD suggest that, in the absence of clinical contraindications, all patients who have AUD should be offered one of these two medications. Given the prevalence of AUD in the US and worldwide, inclusive studies exploring all treatment options in all populations—including minoritized and older populations, and individuals with comorbidities such as liver disease—are greatly needed.

Melissa B. Weimer, DO, MCR

Reference: McPheeters M, O'Connor EA, Riley S, et al. Pharmacotherapy for alcohol use disorder: a systematic review and meta-analysis. *JAMA*. 2023;330(17):1653–1665.

***Alcohol, Other Drugs, and Health: Current Evidence* is a project of the Grayken Center for Addiction at Boston Medical Center, produced in cooperation with Boston University. Initially supported by a grant from the National Institute on Alcohol Abuse and Alcoholism, the newsletter was supported by grant no. R25-DA013582 (PI: Jeffrey Samet) from the National Institute on Drug Abuse (NIDA) until July 2022. The content is solely the responsibility of the authors and does not necessarily represent the official views of Boston Medical Center, NIDA, or the National Institutes of Health.**

State of the Evidence for Psychosocial Interventions Among People With Alcohol Use Disorder and Liver Disease

Researchers summarized the current evidence for the efficacy of psychosocial interventions to reduce alcohol use among people with alcohol use disorder (AUD) and alcohol -related liver disease. The authors conducted a systematic review of randomized trials of interventions with the primary outcome of reduced alcohol consumption or abstinence at the longest available follow-up.

- Ten trials were included, with a total of 1519 participants. The studies were conducted between 1990 and 2020; eight were in the US, one in Australia, and one in China. Follow-up varied between eight and 24 months. Reduction in alcohol consumption was the primary outcome in four trials; abstinence was the primary outcome in six.
- The interventions studied were cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), motivational interviewing (MI), brief intervention/brief advice (BI/BA), and peer support. Four studies combined more than one intervention (BI and MI, MI and MET, or CBT and MET). The number of sessions varied from one to 36.
- Five studies reported on reductions in alcohol consumption. The interventions were: MET, MET/MI, and MI/BI. A significant effect was observed in one study (one of the two studies that assessed MET efficacy).
- Abstinence was reported in six studies. A significant effect was shown in three studies (MET, peer support [Alcoholics Anonymous], and MET/CBT).
- The overall level of certainty of evidence was assessed as moderate, with some studies presenting a high risk of bias and methodological limitations.

Comments: The current evidence for effective interventions for alcohol reduction or cessation among people with AUD and liver disease is limited. These results indicate that MET and integrated interventions have potential. Future research is needed to refine which treatment modalities are most appropriate to address alcohol consumption in people with AUD and liver disease, especially since these patients are often excluded from clinical trials of interventions due to comorbidities and/or their pharmacological profiles.

Nicolas Bertholet, MD, MSc

Reference: Hemrage S, Brobbin E, Deluca P, Drummond C. Efficacy of psychosocial interventions to reduce alcohol use in comorbid alcohol use disorder and alcohol-related liver disease: a systematic review of randomized controlled trials. *Alcohol Alcohol*. 2023;58(5):478–484.

Real-world Administration of Extended-release Buprenorphine Suggests That Deviation From Standard Dosing is Common

The recommended administration of extended-release buprenorphine (BUP-ER) to treat opioid use disorder is 300 mg/month for two months followed by 100 mg/month after stabilization on transmucosal buprenorphine for ≥7 days. However, little is known about real-world use. Researchers performed a population-based cohort study characterizing BUP-ER administration among 2366 adults residing in Ontario, Canada who had outpatient BUP-ER initiations between 2020 and 2022. Patients were considered to have continuous treatment if BUP-ER was refilled within 56 days and were censored if they switched to a different opioid agonist treatment, died, or reached the maximum follow-up date.

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Real-world Administration of Extended-release Buprenorphine Suggests That Deviation From Standard Dosing is Common *(continued from page 2)*

- The median time to BUP-ER discontinuation was 183 days, with 30 percent retention at 365 days.
- Over half (52 percent) of the cohort received 300 mg for ≥3 injections, and 19 percent only received 300 mg injections.
- Among those who did reduce to 100 mg, 29 percent of the cohort had a subsequent increase back to 300 mg.
- Over half (52 percent) of the cohort continued transmucosal buprenorphine-naloxone after BUP-ER initiation.

Comments: This study provides evidence that real-world administration of BUP-ER often deviates from the manufacturer's recommendations, suggesting possible inadequacy of the standard protocol for many patients. Despite adjustments, >70 percent of patients who initiated BUP-ER discontinued it within the year, although one-third subsequently re-initiated. It is not clear how provider practices (e.g., lack of dose adjustments or transmucosal supplementation), patient characteristics (e.g., fentanyl exposure), or other factors influence discontinuation or deviation from the standard protocol.

Brigid Adviento, MD, MPH* & Darius A. Rastegar, MD

* 2023–24 Rich Saitz Editorial Intern & Addiction Medicine Fellow, University of Iowa Hospitals and Clinics

Reference: Iacono A, Wang T, Tadrous M, et al. Characteristics, treatment patterns and retention with extended-release subcutaneous buprenorphine for opioid use disorder: A population-based cohort study in Ontario, Canada. *Drug Alcohol Depend*. 2024;254:111032.

Bupropion Modestly Effective for Amphetamine-type Stimulant Use Disorder

Amphetamine-type stimulant use disorder (ATSUD) is a growing problem with limited effective treatment options. The antidepressant medication bupropion has some stimulant-like effects that may be useful for the treatment of ATSUD. This systematic review and meta-analysis included randomized placebo-controlled trials of bupropion for ATSUD.

- The meta-analysis included eight trials with 1239 participants.
- The number of ATS-positive urine drug tests was significantly lower among patients receiving bupropion (relative risk [RR], 0.90); the effect was larger among patients who remained in treatment for 12 weeks (RR, 0.85).
- End-of-treatment ATS craving was significantly lower among patients receiving bupropion.
- Receipt of bupropion was not associated with improved treatment retention or adherence, or decreased symptom severity for substance use disorder or depression.

Comments: This study shows that bupropion has a modest effect on unhealthy amphetamine use and craving, suggesting its utility in a multimodal treatment approach for individuals with ATSUD. Of note, these studies excluded individuals with severe depression; bupropion may be a reasonable choice for people with co-occurring major depression and ATSUD.

Darius A. Rastegar, MD

Reference: Bakouni H, Sharafi H, Bahremand A, et al. Bupropion for the treatment of amphetamine-type stimulant use disorder: a systematic review of placebo-controlled randomized clinical trials. *Drug Alcohol Depend*. 2023;253:111018.

HEALTH OUTCOMES

Buprenorphine Interrupted or Discontinued Among a Majority of Inpatients in Veterans Administration Hospitals

In this longitudinal cohort study, investigators tracked inpatient buprenorphine administration and subsequent post-discharge outpatient buprenorphine prescriptions among all patients with active buprenorphine prescriptions at the time of medical or surgical admission to a US Veterans Association hospital between October 2018 and March 2020. The primary outcome was receipt of an outpatient buprenorphine prescription between one day prior, to 60 days following discharge.

Patients receiving sublingual buprenorphine (likely for opioid use disorder) were analyzed separately from those receiving buccal or transdermal formulations (likely for chronic pain).

- Only 44 percent of patients (N=830) were administered any buprenorphine during their hospital admission.
- More patients receiving sublingual buprenorphine (61 percent, or 243/401) were administered buprenorphine during admission

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Buprenorphine Interrupted or Discontinued Among a Majority of Inpatients in Veterans Administration Hospitals

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than those receiving buccal (51 percent, or 26/51) or transdermal (25 percent, or 95/378) formulations.
- Of 273 patients who received full opioid agonist medications in the first 36 hours of admission, only 18 percent received buprenorphine concomitantly.
- Of 216 patients who were hospitalized for >72 hours and discontinued buprenorphine during admission, only 16 percent restarted buprenorphine in the 36 hours before discharge.
- Of 766 patients who were discharged from medical or surgical units, 74 percent received an outpatient buprenorphine prescription, which was significantly higher among those administered buprenorphine 36 hours before discharge (94 percent or 251/267), compared with those who were not (64 percent, or 318/499).

Comments: Buprenorphine was discontinued during hospitalization for more than half of patients in this cohort, and a substantial fraction did not appear to restart treatment post-discharge. The Society of Hospital Medicine recommends* continuing buprenorphine during hospitalization, including in the setting of acute pain or perioperatively. US regulations allow all DEA-licensed providers to prescribe buprenorphine, and opioid or non-opioid analgesics can be safely administered to patients continuing buprenorphine during hospitalization.

Aaron D. Fox, MD

References: Mosher HJ, Hadlandsmyth K, Alexander B, Lund BC. Continuation of buprenorphine during hospitalization and subsequent retention in therapy: an observational study in Veterans Administration hospitals. *J Gen Intern Med*. 2024;39 (2):207-213.
*Calcaterra SL, Martin M, Bottner R, et al. Management of opioid use disorder and associated conditions among hospitalized adults: A Consensus Statement from the Society of Hospital Medicine. *J Hosp Med*. 2022;17(9):744-756.

Establishment of an Overdose Prevention Site Was Not Associated With an Increase in Visible Signs of Substance Use and Homelessness

Overdose prevention site (OPS) services—also referred to as safe consumption sites—are intended to prevent overdose and other harms associated with substance use, and to provide support and linkage to other services. Critics argue that these sites may encourage substance use, and have negative effects on nearby neighborhoods. In 2022, researchers in San Francisco, California conducted systematic street observations of 10 indicators of substance and homelessness-related "social nuisance"* in a 500-meter radius around an OPS, and a comparison point in the same city, with two prior observations in both locations in 2018 and 2019.

- During the study period, an average of 400 people per day consumed substances at the OPS.
- The risk of any "social nuisance" in the area around the OPS declined by nearly 7 percent, while it increased by 5 percent in the control area.
- The difference-in-difference in risk of any reported "social nuisance" in the area surrounding the OPS—from pre- to post-intervention to that of the control area—was -0.12.

* Defined as: "people smoking crack/meth/fentanyl," "people injecting," "people dealing drugs," "discarded needle caps," "discarded full needles," "discarded baggies, cookers, pipes, etc.," "human excrement visible," "people sleeping or laying on the ground," "tents or other sleeping structures," and "shopping trolleys and other property."

Comments: This study adds to the growing evidence of the benefits of OPS services for individuals with substance use and the areas in which the OPS services are located. It should provide some reassurance to people who live or work near a proposed OPS, and facilitate the establishment of more sites like this, which provide critical services to a vulnerable population.

Darius A. Rastegar, MD

Reference: Davidson PJ, Wenger LD, Morris T, et al. Impact of a high-volume overdose prevention site on social and drug disorder in surrounding areas in San Francisco. *Drug Alcohol Depend*. 2023;252:110969.

PRESCRIPTION DRUGS & PAIN

Chronic Pain Associated With Increased Cannabis Use and Adverse Effects Among Young Adults

Nonmedical cannabis use is on this rise in adults suffering from pain, despite evidence demonstrating negative clinical outcomes. Researchers investigated the relationship between cannabis use, adverse consequences, and chronic pain in a US-based cohort of young adults aged 18–25 years.

- The sample of 403 young adults reported a mean cannabis use of 47 days in the prior 90 days; of this sample, 20 percent reported chronic pain.
- Participants with chronic pain used cannabis at significantly greater frequency (incident rate ratio [IRR], 1.35), intensity (IRR, 1.61), and reported more negative consequences (IRR, 1.23), compared with those without chronic pain.

Comments: This study contributes to a growing body of evidence that young people with chronic pain have increased cannabis use compared with their peers and experience more adverse effects. Youth are neuro-developmentally vulnerable to cannabis's effects, with brain maturation occurring through the mid-twenties. Cultural messages that promote cannabis as a "medication" appear to be drowning out accurate information about the risks of use for this age group. Given the implications, young adults should be advised of non-cannabis alternatives to mitigate chronic pain.

Emily Nields, DO

Reference: Hayaki J, Abrantes AM, Anderson B, Stein MD. Chronic pain and cannabis use frequency, intensity, and severity in young adults. *Subst Use Misuse*. 2024;59(4):576–582.

Listen to our podcast, "**Behind the Evidence**," supported by the Grayken Center for Addiction at Boston Medical Center.

Hosted by addiction medicine specialists Honora L. Englander, MD (Oregon Health & Science University) and Marc R. Larochelle, MD, MPH (Boston Medical Center/ Boston University Chobanian & Avedisian School of Medicine), each episode of "Behind the Evidence" offers thoughtful discussion of one or more recent significant publications in the clinical addiction literature. Through author interviews and expert insights, "Behind the Evidence" will appeal to clinicians, as well as anyone who is interested in the latest developments in addiction medicine research.

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Alcohol: Clinical & Experimental Research
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New England Journal of Medicine
Preventive Medicine
Psychiatric Services
Substance Abuse
Substance Use & Misuse

Many others periodically reviewed (see www.aodhealth.org).

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