Alcohol, Other Drugs, and Health: Current Evidence

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INTERVENTIONS & ASSESSMENTS

No Effect of Extended-release Gabapentin for the Treatment of AUD

One multi-site US trial found immediate-release gabapentin reduced drinking in people with alcohol use disorder (AUD) but it has not been replicated. This multisite randomized trial tested the effect of gabapentin enacarbil extended-release (GE-XR, an FDA-approved treatment for postherpetic neuralgia and restless leg syndrome). Participants were treatment seeking, aged ≥21, with at least moderate *DSM-5* AUD, drinking ≥21 drinks/week for women, ≥28/week for men plus 1 heavy drinking day/week in the last month. Participants had to be abstinent for at least 3 days before being randomized to receive 26 weeks of either GE-XR (600mg twice/day) or a matching placebo. Those who took at least 1 dose were analyzed (338 out of 346 randomized). Intervention effects were assessed in weeks 22–25 (considered the maintenance phase of the treatment).

- Medication adherence was similar in both groups (93% in intervention group, 92% in control).
- There was no significant difference in the primary outcome, the percentage of participants with no heavy drinking days (28% in intervention group versus 22% in control).
- There were no significant differences in other drinking measures, craving, or alcohol-related consequences.

Comments: In people with moderate to severe AUD, there was no effect of extended-release gabapentin on drinking or craving, contrary to hypotheses based on previous studies conducted with immediate-release gabapentin. GE-RX cannot be recommended for the treatment of AUD, especially considering the risk of misuse and accidental drug poisoning posed by gabapentin. These findings also raise doubts regarding the effectiveness of immediate-release gabapentin to treat AUD.

Nicolas Bertholet, MD, MSc

Reference: Falk DE, Ryan ML, Fertig JB, et al. Gabapentin enacarbil extended-release for alcohol use disorder: a randomized, double-blind, placebo-controlled, multisite trial assessing efficacy and safety. *Alcohol Clin Exp Res*. 2019;43(1):158–169.

Engagement with Opioid Use Disorder Medication Improves Treatment Retention Among Youth

Multiple professional societies and government agencies recommend medication (e.g., buprenorphine, naltrexone, and methadone) for treating youth with opioid use disorder (OUD). Researchers examined the relationship between the receipt of timely treatment for OUD and retention in care among youth overall and compared adolescents (<18 years of age) and young adults (aged 18–22). Medicaid claims data for youth aged 13–22 were used to determine whether patients newly diagnosed with OUD received behavioral health services and/or medications within 3 months of the diagnosis.

- 76% of newly diagnosed youth overall received some kind of OUD treatment; there were no differences between receipt in adolescents compared with young adults.
- 89% of youth overall received behavioral health services either in combination with medication or alone.

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Engagement with Opioid Use Disorder Medication Improves Treatment Retention Among Youth (continued from page 1)

- Only 5% of adolescents received medication for OUD, compared with 27% of young adults.
- Youth overall that received timely medication were retained in care longer than those who received behavioral treatment only (67 days for behavioral treatment only, compared with 123, 150, 324 days for buprenorphine, naltrexone, and methadone, respectively).

Comments: Despite evidence-based recommendations, only a minority of youth with OUD are prescribed MOUD, and younger adolescents are less likely to receive MOUD than young adults. This study confirms that receipt of medication matters. These findings should be a call to action to healthcare providers who care for this age group to provide these services.

Sharon Levy, MD

Reference: Hadland SE, Bagley SM, Rodean J, et al. Receipt of timely addiction treatment and association of early medication treatment with retention in care among youths with opioid use disorder. *JAMA-Pediatr*. 2018;172(11):1029–1037.

HEALTH OUTCOMES

The Cancer Risk of Alcohol Consumption in Cigarette Equivalents

Alcohol is a carcinogen, but its risks have not been well-quantified and communicated. Researchers used existing data sources on alcohol and tobacco attributable fractions and UK cancer registry data to determine the absolute increase in lifetime risk of cancer from alcohol consumption (aerodigestive, breast, and liver) and tobacco smoking (bladder, aerodigestive, breast, cervical, blood, liver, lung, and pancreas).

- Among men who do not smoke, 0.8 drinks/day increased the lifetime risk of cancer by 1 percent; for women, the same amount of consumption increased the risk by 1.4 percent.
- The corresponding risks for 1.4 cigarettes/day were 2.1 percent for men and 1.5 percent for women.
- The authors calculated that 1 bottle of wine/week was roughly equivalent to 5 cigarettes/week for men and 10 for women.
- The main reason for sex differences is that breast cancer is attributable to alcohol but not smoking.

Comments: The fact that alcohol is a carcinogen even at low consumption levels is not news. But the general public, the media, public health organizations, and the alcohol industry do not usually discuss and address alcohol as a carcinogen despite it causing 4 percent or more of cancer deaths. These investigators used existing data to present the alcohol risks alongside a more familiar, commonly addressed carcinogen that will hopefully lead to greater awareness and appropriate public health actions.

Richard Saitz, MD, MPH

Reference: Hydes TJ, Burton R, Inskip H, et al. A comparison of gender-linked population cancer risks between alcohol and tobacco: how many cigarettes are there in a bottle of wine? *BMC Public Health*. 2019;19:316.

Alcohol Consumption Within Guideline Levels Could Mean a 38% Drop in Revenue for the Alcohol Industry

A strategy to decrease harmful drinking has been to work with the alcohol industry to encourage a culture of "responsible drinking," but critics note that the industry's profitability is linked to alcohol consumption. Using data from surveys of households on alcohol spending and "typical" consumption, researchers estimated the extent of sales and revenue from consumption above guideline levels in England. Current United Kingdom (UK) guidelines recommend limiting drinking to 14 UK units per week for men and women (equivalent to 8 standard US drinks/week). They estimated the monetary value of consumption by beverage type and location: "on-trade" where alcohol is consumed on-site (i.e., bars, restaurants, etc.), versus "off-trade" where alcohol is purchased in a store and consumed elsewhere.

- An estimated 77% of all alcohol units were sold to individuals who drank above guidelines; this accounted for 44% of all sales. Furthermore, 4% of the population consumed 30% of the alcohol units, accounting for 23% of alcohol sales.
- Sales from those drinking above guideline levels accounted for an estimated 81% of revenue from "off-trade" versus 60% of "on-trade."
- Consumption within guidelines would lead to an estimated fall in revenue of 38%—a loss of £13 billion ($21 billion)—with "off-trade" revenue being most affected.
- To recoup losses through price increases, "off-trade" product prices would need to increase 80–98% while "on-trade" would need to increase 22–75%.

Comments: This study demonstrates that the alcohol industry's revenue is highly dependent on people who are drinking above guideline levels. Therefore, this industry has a significant commercial conflict of interest in promoting responsible drinking; we should be wary of their endorsement of self-regulation and involvement in research activities.

Jarratt Pytell, MD† & Darius A. Rastegar, MD

† Contributing Editorial Intern and Addiction Medicine Fellow, Johns Hopkins Medicine

Reference: Bhattacharya A, Angus C, Pryce R, et al. How dependent is the alcohol industry on heavy drinking in England? *Addiction*. 2018;113:2225–2232.

Are Reductions in Drinking To Lower Risk Levels Associated With Improvements in Quality of Life Among Individuals With AUD?

The World Health Organization (WHO) has defined risk levels for alcohol consumption.* Reducing drinking to lower risk levels of consumption have been proposed as potential alternative treatment goals to abstinence and absence of heavy drinking days. In this study, researchers assessed the association between one- and two-level reductions and improvements in quality of life and physical health using data from COMBINE study participants who received treatment for *DSM-IV* alcohol dependence (N=1142).

- At baseline, most (69%) participants were in the very high risk category.
- Four months later, 36% were abstinent; 39% were in the low risk, 10% in the medium risk, 6% in the high risk, and 8% in the very high risk categories.
- 89% of participants had at least one risk level reduction, 77% had at least two.
- One- and two-level reductions in risky drinking levels were associated with:
  - Significant reduction in systolic blood pressure (SBP): a one-level reduction was associated with 7.99 mmHg lower SBP (compared with no change or increase); a two-level reduction was associated with 7.38 mm/Hg (compared with one-level reduction, no change, or increase).
  - Small-to-medium range changes in AST, ALT, and GGT.
  - Better quality of life in all domains: physical, psychological, social, and environmental.

* Low (1–40g ethanol/day for men, 1–20g/day for women); medium (41–60g/day for men, 21–40g/day for women); high (61–100g/day for men, 41–60g/day for women); and very high (≥101g/day for men, ≥61g/day for women).

Comments: Whether the observed changes in SBP or liver enzymes can be linked to more distal outcomes (like cardiovascular events or survival) remains to be seen. Nevertheless, drinking risk level reduction as a clinical outcome, notably in a harm reduction approach, can be appropriate and is associated with better quality of life.

Nicolas Bertholet, MD, MSc

Reference: Witkiewitz K, Kranzler HR, Hallgren KA, et al. Drinking risk level reductions associated with improvements in physical health and quality of life among individuals with alcohol use disorder. *Alcohol Clin Exp Res*. 2018;42(12):2453–2465.

Health Care Utilization Effects of Integrating Addiction Treatment Resources Into Primary Care Practices

Integrating addiction treatment into primary care has been shown to improve clinical outcomes; less is known about the impact on health care utilization. In 2014, a large hospital-based health system launched a substance use disorder (SUD) initiative integrating buprenorphine and extended-release naltrexone, counseling, and recovery coaches alongside addiction training into selected primary care practices. Investigators compared health care utilization of 1353 patients in intervention and control practices (offering referral to an addiction treatment clinic only), matched on baseline healthcare utilization by propensity score.

- Over time, across the intervention and control groups, hospitalizations and emergency department visits increased, and primary care visits decreased.
- Patients in the intervention group had more buprenorphine and naltrexone prescriptions as well as contact with recovery coaches, compared with patients in the control group.
- During the 9-month follow-up period, there was no difference in frequency of inpatient admissions after the intervention (13.5 in the intervention group versus 13.3 in control, per 100 patients). Compared with controls, the intervention group had shorter length of inpatient stay (74 versus 81 in control, per 100 patients), fewer ED visits (36 versus 43 in control, per 100 patients), and less of a decline in primary care visits (317 versus 270 in control, per 100 patients over 9 months).

Comments: Overall, people with SUD in primary care had increased acute care and decreased primary care utilization over time, but these changes were attenuated among patients in primary care practices that integrated addiction treatment resources. Recovery coaching was included as part of the intervention package, which is an emerging, previously unstudied, addiction intervention in primary care. Limitations include unmeasured differences between the groups and incomplete observation of utilization, as measurement was restricted to a single institution.

Simeon Kimmel, MD† & Alexander Y. Walley, MD, MSc

† Contributing Editorial Intern and Research Fellow in Infectious Diseases and Addiction Medicine, Boston Medical Center/Boston University School of Medicine

Reference: Wakeman SE, Rigotti NA, Chang Y, et al. Effect of integrating substance use disorder treatment into primary care on inpatient and emergency department utilization. *J Gen Intern Med.* 2019 [Epub ahead of print]. doi: 10.1007/s11606-018-4807-x.

Mortality Due to Comorbidities Following Nonfatal Opioid Overdose

Increases in opioid overdose deaths in the United States are well documented. However, the mortality and morbidity associated with opioids extend well beyond overdose deaths. This study used a national Medicaid sample of 76,325 individuals surviving an opioid overdose between 2001 and 2007 and identified cause-specific standardized mortality rate ratios (SMRs), standardizing to the general population by age, sex, and race/ethnicity.

- The crude mortality rate was 778 per 100,000 person-years, and all-cause SMR was 24.
- SMRs were elevated for several causes in the year following overdose, including: suicide (SMR, 24); HIV (SMR, 46); viral hepatitis (SMR, 31); influenza and pneumonia (SMR, 24); cirrhosis and alcohol-related liver disease (SMR, 16); and cancer (SMR, 9).

Comments: Although dated, these results demonstrate that opioid overdose survivors have mortality attributable to myriad causes beyond overdose, including mental health, infectious diseases, liver disease, and malignancy. Care for individuals with severe opioid use disorder should address both the substance use disorder and associated comorbidities. These results support the need for Medicaid expansion as funding for substance use treatment and adequate coverage to treat associated comorbidities.

Marc R. Larochelle, MD, MPH

Reference: Olfson M, Crystal S, Wall M, et al. Causes of death after nonfatal opioid overdose. *JAMA Psychiatry*. 2018;75(8):820–827.

HIV AND HCV

Unhealthy Opioid Use Among People Living With HIV Associated With Adverse Health Outcomes

People living with HIV (PLWH) are more likely to be prescribed opioids and have higher prevalence of mental health and substance use disorders compared with those without HIV. Additionally, PLWH who have unhealthy opioid use are less likely to be prescribed standard HIV treatment, leading to adverse health outcomes. The authors of this study used data from the 2009–2014 cycles of the Medical Monitoring Project (MMP) to assess prevalence and correlates of unhealthy substance use among PLWH who had opioid misuse.* The MMP is a surveillance system collecting nationally representative data on the sociodemographic, clinical, and behavioral characteristics of adults receiving HIV care in the US.

- Of 28,162 PLWH included in the MMP, 3% (975) had opioid misuse.
- PLWH with opioid misuse were less likely to have been prescribed antiretroviral therapy (ART, 89% versus 93%), report being adherent to ART medications in the past 3 days (78% versus 88%), and have durable viral suppression (54% versus 65%), compared with PLWH who did not have opioid misuse.
- Among PLWH with opioid misuse, the prevalence of engaging in condomless sex with HIV-negative or unknown HIV status partners while not durably virally suppressed was more than 3 times greater than it was among those without opioid misuse.

* Defined as any self-reported injection use or use of prescription opioids for nonmedical purposes.

Comments: Although these data rely on patient self-report and a cross-sectional survey and therefore causation cannot be conclusively determined, this analysis is the first nationally representative survey of its kind. It adds to the growing body of literature suggesting the need for tailored treatment and risk reduction efforts for PLWH with opioid misuse.

Jeanette M. Tetrault, MD

Reference: Lemons A, DeGroote N, Peréz A, et al. Opioid misuse among HIV-positive adults in medical care: results from the Medical Monitoring Project, 2009–2014. *J Acquir Immune Defic Syndr*. 2019;80:127–134.

PRESCRIPTION DRUGS & PAIN

Dual Enrollment in VA and Medicare Part D Associated With Overlapping Opioid and Benzodiazepine Prescribing

Concurrent use of opioids and benzodiazepines is associated with an increased risk of overdose and guidelines recommend against co-prescribing these agents. Patients cared for in the US Veterans Health Administration (VA) often receive medications outside of the system and this can complicate management. Investigators used data from the VA and Medicare Part D to study the association between "dual use" (i.e., use of both VA and Medicare drug benefits) and receipt of overlapping prescriptions for opioids and benzodiazepines.

- In 2013, 368,891 patients received ≥2 opioid prescriptions (for a supply of ≥15 days) from the VA or Medicare Part D (18% VA-only, 30% Medicare-only, and 51% dual use).
- Of these, 102,450 (28%) received an overlapping prescription for a benzodiazepine; the rate was highest among those with dual use (31%), followed by Medicare-only (26%) and VA-only (21%).
- In adjusted analyses, those with dual use were more likely than VA-only to have an overlap (adjusted relative risk [aRR], 1.27); less so when compared with Medicare-only (aRR, 1.12). Overlap of high-dose opioids (defined as a daily morphine milligram equivalent of ≥120) and benzodiazepines was more likely among those with dual use when compared with VA-only (aRR, 2.23) and Medicare-only (aRR, 1.06).

Comments: This report shows that co-prescribing of opioids and benzodiazepines is common and that receiving care from different sources is a risk factor. It is likely that efforts to limit co-prescribing within the VA have led some to seek prescriptions from other sources. It is also possible that prescribers are more comfortable—or feel less responsible—in situations in which someone else is prescribing one of these medications. Further integration of care and health records may help to minimize this problem.

Darius A. Rastegar, MD

Reference: Carico R, Zhao X, Thorpe CT, et al. Receipt of overlapping opioid and benzodiazepine prescriptions among veterans dually enrolled in Medicare Part D and the Department of Veterans Affairs: a cross-sectional study. *Ann Intern Med*. 2018;169:593–602.

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Jeffrey H. Samet, MD, MA, MPH

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