# Alcohol, Other Drugs, and Health: Current Evidence

SEPTEMBER-OCTOBER 2019


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## INTERVENTIONS & ASSESSMENTS

### Which Medications for Opioid Use Disorder Prevent Overdose?

Opioid overdose is a common and serious complication of opioid use disorder (OUD). One of the benefits of medication for OUD (MOUD) is reduction in overdose; this has been demonstrated in numerous studies of methadone and buprenorphine, but there are less data on the effect of naltrexone. Researchers used a database of commercially insured individuals with a diagnosis of OUD initiating MOUD to evaluate fatal and non-fatal overdose risk while on and off treatment.

- There were 46,846 individuals who received MOUD; buprenorphine was the most common (86%), followed by oral naltrexone (17%), and extended-release naltrexone (3%).
- The overdose rate while individuals were not receiving treatment was 5.0 per 100 person-years. Those taking buprenorphine had a rate of 2.1; oral naltrexone 6.2; and extended-release naltrexone 3.9.
- On multivariable analysis, receiving buprenorphine was associated with a significantly reduced risk of overdose compared with not receiving MOUD, with an adjusted hazard ratio (aHR) of 0.40, while receiving oral naltrexone (aHR, 0.93, CI 0.71–1.22) and extended-release naltrexone (aHR, 0.74, CI 0.42–1.31) were not.

*Comments*: This study supports prior research showing that buprenorphine reduces the risk of opioid overdose. It is possible that extended-release naltrexone also reduces the risk, but the numbers were too small to demonstrate this, or to assess its effect relative to buprenorphine. We can say with more confidence that oral naltrexone does not reduce the risk of overdose; this not surprising given that it is not an effective treatment for most with OUD. It is concerning that is it still being used widely for this purpose.

Darius A. Rastegar, MD


*Reference*: Morgan JR, Schackman BR, Weinstein ZM, et al. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend*. 2019;200:34–39.


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# HEALTH OUTCOMES

## Adolescent E-cigarette Use Increases Nicotine Exposure and Dependence Scores Over Time

E-cigarettes were introduced as a harm reduction product targeted to people who use cigarettes to reduce their exposure to toxins in smoke. Over the last few years, rates of adolescent e-cigarette use have risen exponentially and health consequences are poorly understood. This longitudinal study followed a cohort of 173 adolescents aged 13–18 with past-year e-cigarette use and documented trajectories of frequency of use, levels of nicotine exposure (measured via salivary cotinine), nicotine dependence scores (measured via the 10-item Penn State Electronic Cigarette Dependence Index), and preferred brands and flavors.

- 80% of participants were still using e-cigarettes at 12 month follow-up; the rate of daily use doubled from 15% to 30%.
- The mean frequency of use, nicotine exposure, and dependence scores all increased over time.
- Preference for the Juul device increased over time; fruit flavors were most popular at all time points.

*Comments*: For many adolescents, e-cigarette use is a first exposure to nicotine. While these products may represent "harm reduction" for some adult smokers, they appear to be more aptly named "harm introduction" for youth. The documented preference for one single product and high interest in flavored liquids may point the way to rational policy-making to protect youth.

Sharon Levy, MD, MPH

*Reference*: Vogel EA, Prochaska JJ, Ramo DE, et al. Adolescents' e-cigarette use: increases in frequency, dependence, and nicotine exposure over 12 months. *J Adolesc Health*. 2019;64:770–775.

## Heavy Episodic Drinking Among US Adults and Adolescents Nearly Doubles the Risk for Non-medical Use of Prescription Opioids

In 2016, 17,000 US deaths were the result of prescription opioid use. Furthermore, one in five of these deaths also involved the use of alcohol. While concurrent alcohol and opioid use has previously been shown to be a risk factor for overdose, the purpose of this study was: 1) to assess the association between past 30-day drinking patterns* and non-medical use of prescription opioids (NMUPO) among US adults and adolescents; and 2) examine the relationship between heavy episodic drinking frequency and NMUPO. Data were derived from 160,812 respondents who completed the US National Survey on Drug Use and Health between 2012 and 2014.

- 1.6% of US adults and adolescents—a weighted estimate of 4.2 million people—reported past 30-day NMUPO between 2012 and 2014, with more than half (2.2 million) also reporting heavy episodic drinking.
- Heavy episodic drinking was associated with a 1.7 times increased risk of reporting NMUPO compared with the non-drinking group, while current/non-heavy episodic drinking was not associated with NMUPO.
- Overall, the prevalence of NMUPO increased significantly with the frequency of heavy episodic drinking.

*(continued page 3)*

## Heavy Episodic Drinking Among US Adults and Adolescents Nearly Doubles the Risk for Non-medical Use of Prescription Opioids (continued from page 2)

* Defined as: Non-drinking: not having consumed any alcohol on any day in the past 30 days; Current/non-heavy episodic drinking: consuming ≥1 drink on ≥1 days in the past 30 days (but not meeting criteria for heavy episodic drinking); Heavy episodic drinking: having consumed ≥5 drinks (for males) or ≥4 drinks (for females) on ≥1 occasion in the past 30 days.

*Comments*: In this study, the prevalence of NMUPO increased significantly with the frequency of heavy episodic drinking. Accordingly, strategies focused on preventing heavy episodic drinking may also serve to reduce NMUPO and overdoses involving alcohol.

Seonaid Nolan, MD

*Reference*: Esser MB, Guy GP Jr, Zhang K, Brewer RD. Binge drinking and prescription opioid misuse in the US, 2012–2014. *Am J Prev Med*. 2019;57(2):197–208.

## Maintenance of Drinking Reductions to Lower Risk Over Time

Recently, we summarized a research report by Witkiewitz et al (March-April 2019) on the association between reduction of alcohol consumption by risk levels defined by the World Health Organization* and quality of life. Whether non-abstinent reductions are stable over time remained an open question. To study the maintenance over time of 1- and 2-level reductions and associations with functioning, researchers used data from COMBINE study participants who received treatment for *DSM-IV* alcohol dependence.

- 1- and 2-level reductions at the end of treatment (week 16 of the COMBINE trial) were significantly associated with WHO risk level reductions at 1 year (odds ratio [OR], 10.25 for at least a 1-level reduction; OR, 9.40 for at least a 2-level reduction).
- Among participants with a 1-level reduction at the end of treatment, 86% reported at least the same reduction at 1 year.
- Among those with a 2-level reduction at the end of treatment, 78% reported at least the same reduction at 1 year.
- Reductions over time were associated with fewer alcohol-related consequences and with lower systolic blood pressure and liver tests.

* 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*: In this cohort of participants in a trial of treatment for alcohol use disorder, reductions in risk levels as defined by the WHO were stable at 1 year. Reductions in risk levels were associated with better functioning. This study adds valuable information on the maintenance over time of non-abstinent drinking reductions and further supports its use as a clinical goal.

Nicolas Bertholet, MD, MSc

*Reference*: Witkiewitz K, Falk DE, Litten RZ, et al. Maintenance of World Health Organization risk drinking level reductions and posttreatment functioning following a large alcohol use disorder clinical trial. *Alcohol Clin Exp Res*. 2019;43(5):979–987.

## Existing Buprenorphine Prescription for Opioid Use Disorder Reduces Hospital Readmission Risk

Prior studies have shown that hospital initiation of medication for opioid use disorder (MOUD) can improve OUD treatment retention post-discharge. This single-site retrospective cohort study of 470 patients with OUD sought to determine factors associated with hospital readmission. The study identified patients with OUD by ICD-9 or ICD-10 diagnostic codes, but additionally required that patients received at least 24 hours of opioid analgesics during the hospitalizations.

- Overall, the percentage of patients with OUD who were readmitted at 30 days (18%) and 90 days (32%) was similar to that of older patients with complex chronic illnesses.
- At the time of hospital admission, 23% of patients had existing prescriptions for buprenorphine and 27% were receiving methadone treatment.
  - Patients with an existing prescription for buprenorphine were 53% less likely to be readmitted at 30 days (adjusted odds ratio [aOR], 0.47), and 43% less likely to be readmitted at 90 days (aOR, 0.57), compared with patients without an existing prescription for buprenorphine.
  - Readmission risk at 30 and 90 days was not significantly increased for patients who were receiving methadone at the time of hospital admission, compared with patients not receiving methadone treatment.
- Patients with heroin use were 41% less likely to be readmitted at 90 days (aOR, 0.59), compared with those with non-medical use of prescription opioids.
- Buprenorphine initiated during the hospitalization did not change readmission risk, although this practice occurred rarely.

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## Existing Buprenorphine Prescription for Opioid Use Disorder Reduces Hospital Readmission Risk (continued from page 3)

*Comments*: This study provides observational evidence that patients with OUD have high rates of readmission to the hospital. Being enrolled in buprenorphine treatment at the time of hospital admission appears to reduce patients' with OUD overall risk of readmission at both 30 and 90 days, although overall hospital initiation of buprenorphine in the study was low.

Melissa Weimer, DO, MCR

*Reference*: Moreno JL, Wakeman SE, Duprey MS, et al. Predictors for 30-day and 90-day hospital readmission among patients with opioid use disorder. *J Addict Med*. 2019;13(4):306–313.

## Increasing Worldwide Evidence of Harms Associated With Gabapentinoids, Particularly Pregabalin

With increased use of gabapentinoids (gabapentin and pregabalin) for a wide a variety of indications, there has been growing evidence of harms. Two recent studies—one in Sweden and the other in Australia—looked at national data to investigate harms associated with gabapentinoid use.

Swedish researchers used national data to investigate the association between receiving a gabapentinoid prescription and a variety of adverse outcomes from 2006 to 2013.

- Overall, 191,973 individuals (2.1% of the population aged ≥15) received ≥2 consecutive prescriptions for a gabapentinoid.
- Gabapentinoids were associated with suicidal behavior and deaths by suicide (age-adjusted hazard ratio [aHR], 1.26), unintentional overdoses (aHR, 1.24), head/body injuries (aHR, 1.22), and traffic incidents and offenses (aHR, 1.13).
- The hazards were highest for those aged 15–24 and among those prescribed pregabalin.

In Australia, researchers used national data to explore trends in adverse events associated with pregabalin between 2005 (when it first became available) and 2017, compared with gabapentin.

- Pregabalin dispensing increased from 132,000 in 2013 (when it was first covered under the national Pharmaceutical Benefits Scheme) to 353,000 in 2016, a 2.7-fold increase, while gabapentin remained stable and at much lower levels.
- There were a total of 1,158 intentional pregabalin poisonings reported to the Poisons Information Centre during this period, increasing from 0 in 2005 to 375 in 2016.
- There were a total of 88 pregabalin-associated deaths during this period; most also involved opioids (80%) and benzodiazepines (67%).

*Comments*: These studies highlight a number of harms associated with gabapentinoid use, particularly pregabalin. Clinicians should exercise caution before prescribing these medications, especially to younger people and those with substance use disorders.

Darius A. Rastegar, MD

*References*: Molero Y, Larsson H, D'Onofrio BM, et al. Associations between gabapentinoids and suicidal behavior, unintentional overdoses, road traffic accidents and violent crime: population based cohort study in Sweden. *BMJ*. 2019;365:l2147.

Cairns R, Schaffer AL, Ryan N, et al. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. *Addiction*. 2019;114:1026–1034.

## Children of Parents Prescribed Opioids Are at Increased Risk of Suicide Attempt

Youth suicide has increased in the US over the last 15 years and little is known about why. This pharmacoepidemiologic study linked medical claims for parental opioid prescriptions with medical claims for suicide attempts by their children. In a large privately insured sample, propensity matching was used to compare suicide attempt claims in 148,395 10–19 year old children of parents who were not prescribed opioids and 184,142 matched children of parents who were prescribed opioids covering at least one year between 2010 and 2016.

- Of the children with parents not prescribed opioids, 212 (0.014%) had claims related to a suicide attempt, while 678 (0.037%) children of parents prescribed opioids had a suicide attempt claim.

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## Children of Parents Prescribed Opioids Are at Increased Risk of Suicide Attempt (continued from page 4)

- Children of parents prescribed opioids had an increased rate of suicide attempts compared with children of matched controls (odds ratio [OR], 1.99) with rates of 11.68 versus 5.87 per 10,000 person-years. Similar differences were found when stratified by sex and age.
- After controlling for parental substance use disorder (SUD) and depression as well as child age, sex, depression, opioid use disorder, and SUD, the association between parental opioid prescription and child suicide attempt was still significant, though the odds ratio was reduced (OR, 1.46).
- Additional analyses accounting for the number of parents prescribed opioids, parental history of suicide attempt, method of suicide attempt (overdose versus other), and geographic region did not change the results. Controlling for sleep medication use reduced the adjusted odds ratio (OR, 1.26).

*Comments*: This study provides observational support for the association between parental opioid prescriptions and suicide attempts by their children. The association was seen after controlling for multiple potential confounders, although the magnitude of the effect was reduced, raising the possibility that unmeasured or incompletely measured factors might explain the association. Whether this association explains the recent increase in youth suicide cannot be directly assessed by this study.

Joseph Merrill, MD, MPH

*Reference*: Brent DA, Hur K, Gibbons RD. Association between parental medical claims for opioid prescriptions and risk of suicide attempt by their children. *JAMA Psychiatry*. 2019 [Epub ahead of print]. doi: 10.1001/jamapsychiatry.2019.0940.

## Unhealthy Substance Use Is Associated with Heart Failure Hospital Encounters

Unhealthy substance use complicates the management of chronic medical conditions such as heart failure. This retrospective cohort study investigated whether unhealthy use* of a number of substances—excluding tobacco—was associated with heart failure hospital encounters and all-cause mortality. Medical records for 11,268 adult patients with heart failure diagnoses from one California hospital system were examined for the years 2005–2016.

- Unhealthy substance use was documented in 15% of heart failure patients during the study period.
- Several substances were associated with hospital encounters for heart failure: methamphetamine (5% prevalence, incidence rate ratio [IRR] 2.0), opioids (8% prevalence, IRR 1.5), and alcohol (5% prevalence, IRR 1.5).
- Unhealthy substance use was not associated with all-cause mortality.

* Defined by authors as having a documented ICD-9 diagnosis of "substance abuse" or positive urine drug test.

*Comments*: In this study, unhealthy substance use was common and associated with negative heart failure outcomes. This sample's high prevalence of methamphetamine use may not generalize to the entire US; however, methamphetamine is cardiotoxic and its use is increasing. The authors did not control for tobacco use, which at least in part explains the observed association between substance use and hospitalizations.

Aaron D. Fox, MD

*Reference*: Nishimura M, Bhatia H, Ma J, et al. The impact of substance abuse on heart failure hospitalizations. *Am J Med*. 2019 [Epub ahead of print]. doi: 10.1016/j.amjmed.2019.07.017.

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