Alcohol, Other Drugs, and Health: Current Evidence

JANUARY-FEBRUARY 2020

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INTERVENTIONS & ASSESSMENTS

Can A Single Dose of Ketamine Improve Cocaine Use Disorder Treatment Outcomes?

Currently, there are no FDA-approved medications for the treatment of cocaine use disorder. Ketamine has demonstrated antidepressant effects in randomized clinical trials and decreased cocaine craving and use in laboratory settings at sub-anesthetic doses. Investigators randomized 55 participants with *DSM-IV* cocaine dependence, past 30-day cocaine use, and no psychiatric co-morbidity to a 40-minute intravenous infusion of either ketamine or midazolam. Both groups received mindfulness-based relapse prevention (MBRP) psychotherapy. In this 5-week study, participants were hospitalized for 5 days, received the infusion on day 2, and received MRBP during the hospital stay and for 4 weeks afterwards.

- Over the last 2 weeks of the trial, 48% of participants in the ketamine group were abstinent from cocaine use, compared with 11% in the midazolam group.
- Craving scores were 58% lower in the ketamine group than the midazolam group, controlling for route of use.
- The only reported adverse effect was mild sedation lasting less 12 hours. There were no persistent psychiatric disturbances or incidences of new unhealthy substance use.

Comments: In this randomized trial, a single infusion of ketamine significantly reduced cocaine use and craving compared with midazolam. Since both groups received MBRP, it is unclear whether MBRP is necessary for ketamine to be effective. Limitations include the study's small size and exclusion of people with psychiatric co-morbidity. Furthermore, participants were hospitalized for 5 days, which may be difficult to implement in other settings.

Tae Woo (Ted) Park, MD

Reference: Dakwar E, Nunes EV, Hart CL, et al. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am J Psychiatry*. 2019;176(11):923–930.

Technology-Delivered Cognitive Behavioral Therapy for Alcohol Use Shows Benefit

Cognitive behavioral therapy (CBT) is an evidence-based treatment for alcohol use disorder, and recent efforts to increase access to CBT have involved web-based and mobile technologies. This meta-analysis was the first to synthesize the evidence for technology-delivered CBT (CBT-Tech) for reduction in unhealthy alcohol use. CBT-Tech interventions were fully computerized web-based or mobile apps that included no clinician-delivered components.

- Randomized controlled trials (15 trials, 9838 total participants) in which the majority of participants had unhealthy alcohol use* were identified and analyzed by type of

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Technology-Delivered Cognitive Behavioral Therapy for Alcohol Use Shows Benefit (continued from page 1)

control group. Content varied in length, and many incorporated elements of motivational interviewing.
- CBT-Tech compared with minimal treatment (6 trials, 8663 participants) showed a positive and significant reduction in drinking, but with a small effect size (Hedges' g, 0.2).**
- When tested as an additional intervention combined with treatment as usual (8 trials, 1125 participants), CBT-Tech demonstrated a slightly larger effect size and longer duration of benefit (Hedges' g = 0.3), compared with treatment as usual alone.
- Comparing CBT-Tech directly with treatment as usual (3 trials, 385 participants) or to clinician-delivered CBT (2 trials, 234 participants) did not show a significant difference in drinking.

* Defined here as meeting *DSM* criteria for alcohol use disorder, or scoring ≥8 on the Alcohol Use Disorders Identification Test (AUDIT).
** When assessing effect size with Hedges g, a rule of thumb is: small effect = 0.2; medium effect = 0.5; large effect = 0.8.

Comments: Technology-delivered CBT demonstrated potential benefits for people with unhealthy alcohol use as a stand-alone intervention, and potentially a stronger benefit when added to treatment as usual, although no significant benefit was seen when tested against other treatments. CBT-Tech requires patient motivation and time to complete, but offers potential advantages over other treatments, including privacy, low cost, and easy access, as well as avoiding potential deficiencies in provider training, treatment fidelity, and competency.

Joseph Merrill, MD, MPH

Reference: Kiluk BD, Ray LA, Walthers J, et al. Technology-delivered cognitive-behavioral interventions for alcohol use: a meta-analysis. *Alcohol Clin Exp Res*. 2019;43:2285–2295.

Case Series Investigates Outcomes of Initiating Buprenorphine After Naloxone-reversed Opioid Overdose in Three Patients

Emergency department (ED) visits following an opioid overdose can be an opportunity for patients with opioid use disorder (OUD) to initiate medications for OUD. However, the safety of administering buprenorphine post-naloxone-reversed opioid overdose is unknown. This single-center series of 3 patients who presented at a California ED assessed whether administering buprenorphine rapidly post-naloxone-reversed overdose was followed by serious adverse events (i.e., additive sedation with respiratory depression or precipitated withdrawal), and if it was followed by engagement in care at a linked bridge clinic.

- In all 3 cases, no serious adverse events were observed during a 6-hour ED visit.
- All 3 patients were still taking buprenorphine (administered by the linked bridge clinic) 7 days after ED discharge.

Comments: Despite the methodological disadvantages of a small case series, vulnerability to selection bias, and low internal validity, the results suggest that administration of

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Case Series Investigates Outcomes of Initiating Buprenorphine After Naloxone-reversed Opioid Overdose in Three Patients (continued from page 2)

buprenorphine post-naloxone reversal of an opioid overdose may be safe and could be a way to initiate long term treatment. Randomized trials should test specified treatment protocols for emergency departments, which could become the new standard of care.

Raagini Jawa, MD, MPH† & Alexander Y. Walley, MD, MSc

† Contributing Editorial Intern and Infectious Disease and Addiction Medicine Fellow, Boston Medical Center

Reference: Herring AA, Schultz CW, Yang E, Greenwald MK. Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *Am J Emerg Med*. 2019;37(12):2259–2262.

HEALTH OUTCOMES

Patterns of Adolescent E-cigarette and Combustible Cigarette Use Are Evolving

The use of e-cigarettes or vaping devices by US adolescents has rapidly increased over the past several years, raising concerns. Researchers used data from a nationally representative school-based survey of 36,506 US students aged 13–16 years, collected from 2015–2017, to evaluate e-cigarette and combustible cigarette initiation patterns.

- Overall, 49% of students with e-cigarette use did not use other nicotine products. Among students who had both combustible cigarette and e-cigarette use, it was more common that use was initiated with combustible cigarettes.
- Over the 3 years of the study, initiating e-cigarettes prior to combustible cigarettes became significantly more common, while combustible cigarette-first use declined.
- Students with dual use perceived less risk related to combustible cigarette use and were more likely to report past 30-day combustible cigarette use.

Comments: While e-cigarettes continue to be promoted as a smoking cessation tool for adults who use combustible cigarettes, among adolescents they increasingly represent the first exposure to nicotine products. This suggests that combustible cigarette smoking cessation is a rare motivation for e-cigarette use among adolescents. Public health efforts should continue to focus on reducing e-cigarette use rather than promoting e-cigarettes as a harm reduction tool, particularly among youth.

Sharon Levy, MD, MPH

Reference: Evans-Polce RJ, Veliz P, Boyd CJ, McCabe SE. Initiation patterns and trends of e-cigarette and cigarette use among US adolescents. *J Adolesc Health*. 2020;66(1):27–33.

Effects of Heavy Drinking Episodes and Volume of Drinking on Liver Enzymes

This study aimed to assess whether patterns of alcohol consumption are associated with liver enzyme changes. Researchers studied the effects of heavy episodic drinking (defined as >60g of alcohol on one occasion for men, >40g for women) and levels of average daily alcohol consumption* on markers of hepatotoxicity (ALT, GGT, CRP**) in a large Finnish population survey.

- Among the 8597 men, 91% reported "low-risk" alcohol consumption, 6% "medium-risk," and 3% "high-risk."
- Among the 9733 women, 94% reported "low-risk" consumption, 5% "medium-risk," and 1% "high-risk."
- Compared with people who had no heavy episodic drinking, there was a significant increase in GGT among both men and women with any heavy drinking episodes; an increase in ALT was observed in men but not in women.
- In analyses taking into account both the total volume of alcohol consumed and the frequency of heavy drinking episodes, there was a linear increase in liver enzymes as a function of the total alcohol volume.
- Among participants reporting "low-risk" drinking, significant increases in GGT and ALT were observed in participants with more than one heavy drinking episode in a month. The same was observed for CRP among men but not women.

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Effects of Heavy Drinking Episodes and Volume of Drinking on Liver Enzymes (continued from page 3)

* Average daily alcohol consumption was classified as "low-risk" (1–40g for men, 1–20g for women), "medium-risk" (41–60g for men, 21–40g for women), and "high-risk" (61–100g for men, 41–60g for women).
** Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT), and C-reactive protein (CRP).

Comments: In addition to the negative impact of the total volume of alcohol consumed, this study suggests that there are negative effects of heavy drinking episodes even among those whose total volume of alcohol was categorized as "low-risk" drinking. Taking drinking patterns into account is therefore important when providing patients with information on unhealthy alcohol use.

Nicolas Bertholet, MD, MSc

Reference: Nivukoski U, Bloigu A, Bloigu R, et al. Liver enzymes in alcohol consumers with or without binge drinking. *Alcohol*. 2019;78:13–19.

Effects of Type of Alcohol and Drinking Patterns Among People With Low Socio-economic Status

Studies have indicated that people with lower socio-economic status (SES) experience more adverse effects of alcohol consumption compared with people with higher SES, even when their reported intake is similar. Researchers investigated data from 11,038 respondents to the Welsh Health Survey to determine whether alcohol consumption by beverage type, body mass index (BMI), smoking, and other factors explain inequalities in alcohol-related harm. Lower SES was determined by levels of "deprivation," an extensive definition that included geographic area of residence as well as details on education, income, and employment.

- Greater deprivation was associated with 75% higher rates of alcohol-related hospital admissions (ARHA), compared with participants with lower levels of deprivation.
- Adjustment for the number of units of alcohol consumed only reduced the risk of ARHA for participants experiencing high levels of deprivation by 4%, compared with those experiencing less deprivation.
- Adjustment for smoking and BMI reduced these inequalities by 36%, with greater reduction when other factors (e.g., self-reported health, mental health problems) were included.
- Increases of units of spirits (much higher in participants with deprivation) were positively associated with increasing risk of ARHA, more than for other drink types.

Comments: The amount of alcohol reportedly consumed by people with lower SES appears to be only a minor contributing factor to the higher rates of alcohol-related harms that they experience, compared with people with higher SES. Other comorbidities—especially smoking, obesity, living in a deprived environment, poor health status, mental health, etc—appeared to have much greater effects. This study suggests that even for alcohol-related hospital admissions, other factors associated with low SES may be important determinants of adverse health outcomes.

R. Curtis Ellison, MD

Reference: Gartner A, Trefan L, Moore S, et al. Drinking beer, wine or spirits – does it matter for inequalities in alcohol-related hospital admission? A record-linked longitudinal study in Wales. *BMC Public Health*. 2019;19:1651.

How Accessible is Office-based Buprenorphine Treatment in the US?

Buprenorphine is a highly effective treatment for opioid use disorder (OUD). Despite the ostensible availability of buprenorphine in traditional office-based US medical practices, only a minority of individuals with OUD receive it. This audit, or "secret shopper," study involved research staff posing as a 30 year-old female with heroin use to evaluate access to new patient appointments in two scenarios: one with Medicaid, the other as uninsured self-pay. The sample included 546 providers across 5 US states and Washington DC publicly listed in the Substance Abuse and Mental Health Services Administration's buprenorphine practitioner locator.

- New patient appointments were offered to 54% of Medicaid contacts and 62% of uninsured self-pay contacts.
- Buprenorphine induction on the first visit was available to 27% of Medicaid and 41% of uninsured self-pay contacts.
- The median time to a new patient appointment was 6 days for Medicaid and 5 days for uninsured self-pay contacts.

Comments: These data highlight challenges in accessing evidence-based treatment for OUD, with worse access for individuals with Medicaid compared with uninsured self-pay. Although the

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How Accessible is Office-based Buprenorphine Treatment in the US? (continued from page 4)

authors noted access and wait times for buprenorphine treatment are on par with new patient access to general primary care overall, it is unclear if this level of access is sufficient to engage individuals with OUD. Future studies should examine whether alternative low-threshold models, including those with same-day access, offer substantial improvement in treatment engagement.

Marc R. Larochelle, MD, MPH

Reference: Beetham T, Saloner B, Wakeman SE, et al. Access to office-based buprenorphine treatment in areas with high rates of opioid-related mortality: an audit study. *Ann Intern Med*. 2019;171(1):1–9.

Barriers to Continuing Medication for Opioid Use Disorder Post-incarceration in Rhode Island

In 2016, the Rhode Island Department of Corrections introduced the first state-wide correctional system-based medication for opioid use disorder (MOUD) program in the US. Between February 2017 and August 2018, researchers conducted telephone interviews with 214 individuals* post-release to ascertain whether they had been linked to community treatment and to identify any barriers.

- Overall, 54% of participants continued MOUD and 34% initiated MOUD while incarcerated; 12% received MOUD just prior to release.
- Participants received methadone (56%), buprenorphine (43%), and injectable naltrexone (1%).
- On average, surveys were conducted 29 days post-release with most participants (84%) either on probation or parole.
- Post-release, 82% of participants continued MOUD through: an opioid treatment program (74%); an office-based provider (20%); a residential treatment facility (1%); or an unclassifiable location (5%).
- Reasons for not continuing MOUD post-release included: transportation issues (23%); lack of a desire to continue (21%); perceiving treatment as a hassle (8%); time-lapse between release and connecting with an MOUD provider (8%); side effects (5%); cost (5%); and pressure from family/friends not to continue (3%).

* N=227, but 13 participants were re-incarcerated during the study period. Participants were majority white and male, with an average age of 37.

Comments: With a large majority of program participants continuing to receive MOUD approximately one month post-release, these results emphasize the potential role of universal access to MOUD in correctional settings. To improve retention, interventions should focus on minimizing the delay between release from a correctional facility and contact with a community MOUD provider, as well as addressing transportation challenges.

Seonaid Nolan, MD

Reference: Martin RA, Gresko SA, Brinkley-Rubinstein L, et al. Post-release treatment uptake among participants of the Rhode Island Department of Corrections comprehensive medication assisted treatment program. *Prev Med*. 2019;128:1057666.

PRESCRIPTION DRUGS & PAIN

Over 40% of US Adults Have Taken a Prescription Opioid or Sedative in the Past Year; 8% Have Taken Both

The use of opioids and benzodiazepines—both prescribed and non-medically—has increased in the US in the last two decades. This is a major public health concern because concomitant use increases the risk of overdose. In this study, researchers used data from the 2015 and 2016 National Survey of Drug Use and Health to estimate the proportion of US adults who had taken an opioid (including methadone and buprenorphine) or sedative (including benzodiazepines, cyclobenzaprine, and carisoprodol) in the past year, and demographic factors associated with use.

- Overall, 41% of participants reported any use (prescribed and non-medical) of a prescription opioid or sedative in the past year; 29% reported only opioids, 4% only sedatives, and 8% reported both. Among those who reported any use of both opioids and sedatives, 72% had been prescribed these medications.
- Use of these substances (prescribed and non-medical) was associated with older age, female gender, non-Hispanic white ethnicity, being unmarried, and not being in the workforce.
- Non-medical use (versus prescribed) was associated with younger age, male gender, non-white/Hispanic ethnicity, being unmarried, and not being in the workforce.

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Over 40% of US Adults Have Taken a Prescription Opioid or Sedative in the Past Year; 8% Have Taken Both (continued from page 5)

Comments: This study shows that prescribed and non-medical use of prescription opioids and sedatives in the US is a common experience; an alarmingly high number of adults (one in twelve), are using both. This is particularly concerning given the risks associated with the use of these medications, especially concomitantly.

Darius A. Rastegar, MD

Reference: Li C, Santaella-Tenorio J, Mauro PM, Martins SS. Past-year use of prescription opioids and/or benzodiazepines among adults in the United States: estimating medical and non-medical use in 2015–2016. *Drug Alcohol Depend*. 2019;204:107458.

Out of Eight Countries, US Patients Were Most Likely to Receive Opioid Medications During Hospitalization and at Discharge

Receipt of opioid medications during hospitalization may be a risk factor for long-term use of prescription opioids, which can lead to poor health outcomes in some patients. This cross-sectional survey of 981 adult patients in the US and 7 other countries compared receipt of opioid medication during hospitalization and patients' perception of analgesic benefits. Patients were included if they reported pain within the first 24–36 hours of hospitalization.

Satisfaction with hospital pain management did not differ between patients in the US or other countries. Compared with patients in non-US countries (n=478), patients in the US (n=503) were more likely to:

- Have a history of "illicit drug use" (33% in US patients versus 6% in all others) and psychiatric illness (27% versus 8%).
- Receive opioid medications prior to hospitalization (38% versus 17%).
- Report greater pain severity.
- Receive opioid medications during hospitalization whether they were prescribed opioids prior to hospitalization (adjusted odds ratio [aOR], 3.2) or not (aOR, 2.8) and at higher doses.
- Have opioid medications prescribed at hospital discharge.

Comments: This study provides evidence that patients who are hospitalized in the US report higher pain severity and are more likely to receive opioid medications during hospitalization and at hospital discharge compared with patients from other countries. Although receipt of opioids during hospitalization can increase the risk of ongoing and unhealthy opioid use long-term, this must be balanced with the need for adequate analgesia in hospitalized patients.

Melissa Weimer, DO, MCR

Reference: Burden M, Keniston A, Wallace MA, et al. Opioid utilization and perception of pain control in hospitalized patients: a cross-sectional study of 11 sites in 8 countries. *J Hosp Med*. 2019;14(12):737–745.

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