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Alcohol, Other Drugs, and Health: Current Evidence

MARCH-APRIL 2021

INTERVENTIONS & ASSESSMENTS

Is Bupropion Plus Naltrexone an Effective Treatment for Methamphetamine Use Disorder?

Amphetamines are the second-most commonly used drug in the world and their use is rising in the US. There are currently no FDA-approved medications for treating methamphetamine use disorder (MUD). This multisite randomized controlled trial evaluated the efficacy and safety of extended-release naltrexone (380mg every 3 weeks) plus oral extended-release bupropion (450mg daily), compared with placebo for 6 weeks. The primary outcome was treatment response, defined as at least 3 out of 4 methamphetamine-negative urine drug tests over the last 2 weeks of the study.

- The study enrolled 403 patients with moderate or severe MUD.
- 15% of eligible patients were randomized; 69% of the participants were men.
- Overall, 13.6% of patients in the intervention group had a treatment response, compared with 2.5% in the placebo group; this translates to a number needed to treat of 9.
- The most common adverse effects were gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia.

Comments: Medications that are accessible and effective are urgently needed to treat MUD. Behavioral treatments like cognitive behavioral therapy and contingency management show favorable benefit, although their access remains very limited. This trial demonstrates a possible new treatment for MUD; however, limiting factors may be cost of the treatments and patient preference, both of which were not assessed.

Melissa Weimer, DO

Reference: Trivedi MH, Walker R, Ling W, et al. Bupropion and naltrexone in methamphetamine use disorder. *N Engl J Med*. 2021;384(2):140–153.

HEALTH OUTCOMES

Buprenorphine Treatment Retention Improved with Higher Doses and Initiation Prior to Referral to Outpatient Settings

Buprenorphine is a highly efficacious treatment for opioid use disorder (OUD). Unfortunately, buprenorphine treatment initiation and retention rates are low. This systematic review sought to identify characteristics associated with buprenorphine treatment retention among 9 randomized controlled trials meeting the study's inclusion criteria.

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Buprenorphine Treatment Retention Improved with Higher Doses and Initiation Prior to Referral to Outpatient Settings (continued from page 1)

- Buprenorphine dose of 8 mg daily resulted in higher 12-month retention (63%-78%), compared with 1–3 mg daily (17%-60%).
- Adjunctive intensive behavioral therapy did not improve buprenorphine treatment retention compared with standard behavioral therapy.
- Initiating buprenorphine prior to referral to outpatient settings resulted in higher treatment retention, compared with patients who did not initiate buprenorphine prior to referral:
  - For hospitalized patients with OUD, 6-month retention was 17% if buprenorphine was started prior to discharge, compared with 2% for those referred for outpatient treatment.
  - For incarcerated patients with OUD, individuals starting buprenorphine prior to release were retained for a mean of 66 days compared with 22 days for those referred for outpatient treatment.

Comments: Improving buprenorphine treatment retention is a critical strategy to achieve improved outcomes for individuals with OUD, but data from randomized controlled trials to identify strategies that improve retention are limited. In this study, higher buprenorphine doses and buprenorphine initiation prior to referral to outpatient treatment settings were associated with longer treatment retention, but additional strategies to improve buprenorphine treatment retention need to be identified.

Marc R. Larochelle, MD, MPH

Reference: Kennedy AJ, Wessel CB, Levine R, et al. Factors associated with long-term retention in buprenorphine-based addiction treatment programs: a systematic review. *J Gen Intern Med*. 2021;10.1007/s11606-020-06448-z.

Poisoning Deaths Associated With Buprenorphine Almost Always Involve Sedatives or Other Opioids

Buprenorphine has a favorable safety profile because of its partial agonist and ceiling respiratory depression effects. However, there are poisoning deaths associated with it. Researchers used data from autopsies of sudden and unexpected deaths in Finland, which has high rates of illicit buprenorphine use, to investigate the extent to which these deaths were associated with the use of other substances. In Finland, all sudden and unexpected deaths (12% of all deaths in this study period) are investigated with autopsy, including comprehensive toxicology in 75%.

- Between 2016 and 2019, there were 792 deaths at age 15–64 years where buprenorphine or norbuprenorphine were detected in post-mortem investigations. Of these deaths, buprenorphine was implicated in 271 (34%), buprenorphine with other opioids were implicated in 99 (13%), and buprenorphine was found but not implicated in 86 (11%). In the remaining 336 cases (42%), buprenorphine was detected, but the cause of death was not poisoning.
- Among the 271 deaths where buprenorphine was implicated, concomitant benzodiazepines were found in 94%, gabapentinoids in 50%, alcohol in 41%, and antipsychotics in 28%. There were only 3 cases (1%) where alcohol, benzodiazepines, or gabapentinoids were not also present.

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Poisoning Deaths Associated With Buprenorphine Almost Always Involve Sedatives or Other Opioids (continued from page 2)

Comments: This study affirms the safety of buprenorphine in comparison with other opioids. While the use of sedatives should not be a reason to deny someone access to buprenorphine to treat opioid use disorder, we should counsel patients on the dangers of concomitant use of benzodiazepines, gabapentinoids, and alcohol. In addition, concomitant prescribing of sedating medications should be carefully considered, particularly in combination.

Darius A. Rastegar, MD

Reference: Mariottini C, Kriikku P, Ojanperä I. Concomitant drugs with buprenorphine user deaths. *Drug Alcohol Depend*. 2021;218:108345.

Medications for Opioid Use Disorder (MOUD) Improve Short-term Residential OUD Treatment Completion and Retention

Little is known about the impact of medications for opioid use disorder (MOUD) on residential OUD treatment outcomes. Researchers extracted data from a US national dataset of admissions and discharges from publicly funded substance use disorder treatment facilities. Data from adults admitted to either a short-term (ST; <30 days) or long-term (LT; >30 days) OUD residential treatment center between 2015 and 2017 were assessed to determine the effects of MOUD on the probability of treatment completion and retention (defined as a stay >10 days or >90 days for ST and LT treatment, respectively).

- A total of 87,296 and 66,623 adults with OUD received ST or LT treatment, respectively.
- Only 18% of patients received MOUD as part of their treatment plan.
- Among patients who received ST treatment, MOUD was associated with a 40% increased likelihood of treatment completion and 34% increased retention.
- For those who received LT treatment, MOUD was associated with a 26% reduced likelihood of treatment completion and no significant increase in treatment retention.
- Post hoc analyses on the effects of health insurance type on completion and length of stay revealed that Medicaid coverage upon admission could affect treatment completion and retention.

Comments: Despite its established efficacy, MOUD is underutilized in residential treatment settings. However, it may be the case that residential treatment completion does not correlate to whether or not a patient continues treatment overall. As the authors suggest, some patients who feel stable on MOUD may leave residential treatment and continue to receive their medication in another setting. Regardless, MOUD implementation should be prioritized in all treatment settings.

Eisha Lehal, BSc † and Seonaid Nolan, MD

† Contributing Editorial Intern and Clinical Research Coordinator, British Columbia Centre on Substance Use

Reference: Stahler GJ, Mennis J. The effect of medications for opioid use disorder (MOUD) on residential treatment completion and retention in the US. *Drug Alcohol Depend*. 2020;212:108067.

Non-fatal Stimulant Overdoses Are Rising Among Youth

The US overdose crisis has resulted in decreasing life expectancy. Researchers investigated trends in non-fatal overdose among children (0–10), younger adolescents (11–14), and older adolescents/young adults (15–24 years), via a retrospective analysis of national emergency department surveillance data from 47 US states between April 2016 and September 2019. Substances were identified by *International Classification of Diseases* diagnosis codes (i.e., all-drugs, opioids, heroin, and stimulants).

- All non-fatal overdoses increased among children and younger adolescents over the study period (average increase of 2% and 2.3%, respectively).
- Non-fatal overdose attributed to heroin decreased among older adolescents/young adults (average 3.3% decrease per quarter over the study period).
- Non-fatal stimulant overdoses increased among all 3 age groups over the study period (average increase of 3.3% for children, 4% for younger adolescents, 2.3% for older adolescents/young adults).

Comments: Public health interventions to address the overdose crisis, including access to medication and naloxone distribution, have largely targeted opioids. Even with a level of success with these measures, rates of overdose continue to rise; this analysis demonstrates that stimulants are a major contributor. These findings suggest that to reverse the overdose epidemic, broad measures that focus on substance use prevention and addiction treatment for all classes of substances must supplement current efforts.

Sharon Levy, MD

Reference: Roehler DR, Olsen EO, Mustaquim D, Vivolo-Kantor AM. Suspected nonfatal drug-related overdoses among youth in the US: 2016-2019. *Pediatrics*. 2021;147(1):e2020003491.

Cannabis Use Is Associated With Suicidal Ideation Among Individuals With Opioid Use Disorder Receiving Opioid Agonist Therapy

Cannabis use is associated with suicidal behavior in the general population. This Canadian study investigated the association between cannabis use and suicidal ideation in cohort of participants aged 16 or older with opioid use disorder who were receiving opioid agonist therapy. Suicidal ideation was assessed by self-report as part of the Maudsley Addiction Profile (MAP), which also includes a 10-item psychological health scale. Participants were also asked about cannabis use and frequency.

- Of the 2335 participants, approximately half reported current cannabis use. Among those with cannabis use, 24% reported suicidal ideation in the last 30 days compared with 17% of those without.
- In multivariable analyses, suicidal ideation was associated with cannabis use (odds ratio [OR], 1.4), male sex (OR, 1.8), and symptoms of anxiety and depression on the MAP (OR, 1.2 for every 1-point increase). The following factors were not associated with suicidal ideation: current tobacco or alcohol use, or being employed or married.
- Frequency of cannabis use was not significantly associated with suicidal ideation.

Comments: This study raises concerns about the potential effect of cannabis on the psychological health of individuals with opioid use disorder. This is particularly important in the context of legalization of cannabis in Canada and many US states. However, this is far from demonstrating a cause and effect relationship, especially given that the observed association was modest and there did not appear to be a dose-response effect.

Darius A. Rastegar, MD

Reference: Naji L, Rosic T, Sanger N, et al. The role of cannabis use in suicidal ideation among patients with opioid use disorder. *J Addict Med*. [Epub ahead of print] 2020. doi:10.1097/ADM.0000000000000781.

Is Age at First Alcohol Intoxication Associated With Mortality in Adulthood?

Among young adults, a significant portion of alcohol-related mortality comes from heavy alcohol consumption, which can lead to an increased risk of intentional and unintentional injuries. Early age at first drink or first intoxication may be associated with increased mortality, even in the absence of an alcohol use disorder. This study used data from the Northern Finland Birth Cohort 1986 Study to examine the association between age at onset of drinking and age at first alcohol intoxication and the risk of death by the age of 30.

- By the age of 30, 47 of the 6564 participants had died (0.7%); males represented 81% of deaths.
- The most common causes of death were suicide (47%) and accidents (32%).
- There was no association between age at first drink and mortality at age 30.
- In analyses adjusted for confounders, age of ≤14 years at first intoxication was associated with all-cause mortality (hazard ratio [HR], 2.33) and death by suicide or accident (HR, 2.99).

Comments: This study shows that first intoxication at an early age is associated with negative consequences later in life. These results support preventive interventions targeting alcohol intoxication in adolescents.

Nicolas Bertholet, MD, MSc

Reference: Levola J, Rose RJ, Mustonen A, et al. Association of age at first drink and first alcohol intoxication as predictors of mortality: a birth cohort study. *Eur J Public Health*. 2020;30(6):1189–1193.

HIV & HCV

Does Unhealthy Substance Use Impact HIV Viral Loads?

Unhealthy substance use may affect HIV disease progression indirectly via antiretroviral therapy (ART) adherence, or directly through biological mechanisms, such as immune function. This Canadian prospective cohort study examined whether non-injection substance use (crack cocaine, powdered cocaine, opioids, methamphetamine, alcohol, and cannabis) was associated with HIV-1 RNA viral load levels. Participants were 843 people living with HIV and illicit drug use who were assessed every 6 months with questionnaires and blood tests between 2005 and 2018.

- The cohort was 67% male with a median age of 43; 31% were homeless. The median baseline CD4 count was 340 (cells/μl), and median HIV viral load was 3.1 (log10 copies/ml).

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Does Unhealthy Substance Use Impact HIV Viral Loads? (continued from page 4)

- At baseline, 79% of participants had injection drug use, 79% had crack cocaine use, and 53% had alcohol use.
- Periods of crack cocaine use were associated with higher HIV viral load (while adjusting for age, sex, injection drug use, homelessness, CD4 count, and ART exposure), but there were no significant associations between the use of other substances—including powder cocaine—and HIV viral load.
- Participants received ART for a median of 180 days per 6-month period.

Comments: These findings regarding crack cocaine use reinforce prior studies, but the longitudinal design and availability of data on ART exposure from pharmacy records (as opposed to self-report) are strengths. Due to the high ART exposure, the authors suggest that data support a biological mechanism for crack cocaine leading to HIV disease progression. However, it is possible that crack cocaine use affected ART adherence in ways not captured by pharmacy dispensing records, especially since no association was found with powder cocaine. ART availability and adherence supports remain high priorities for people living with HIV and substance use.

Aaron D. Fox, MD

Reference: Liang J, Nosova E, Reddon H, et al. Longitudinal patterns of illicit drug use, antiretroviral therapy exposure and plasma HIV-1 RNA viral load among HIV-positive people who use illicit drugs. *AIDS*. 2020;34(9):1389–1396.

PRESCRIPTION DRUGS & PAIN

New Opioid Prescriptions among Medicaid Patients Do Not Explain Rising Opioid Overdose Rates

The relationship between prescribed opioid medications and opioid overdose is complex. This study identified patients with apparent new prescriptions for opioid medications in 4 large US state Medicaid programs, and calculated incidence rates of subsequent opioid overdose. Eligible patients were enrolled in Medicaid for 3 years without any prior opioid overdose or prescribed opioid medications before the index opioid prescription.

- 1.3 million patients met criteria, contributing 246,466 person-years of follow-up data. The median age was 50 years, 64% were female, 38% were white, 7% had a prior substance use disorder (SUD) diagnosis, and 20% had a mental health diagnosis.
- Between 2002 and 2012, 609 opioid overdose events were identified in the cohort. There was a slight, insignificant linear reduction in overdose incidence rates per year of cohort entry.
- Risk factors for incident opioid overdose included younger age, white race/ethnicity, higher initial daily opioid dose, prior SUD, mental health conditions, and prior benzodiazepine prescription (within 30 days of cohort entry).

Comments: This study used data from a time period when prescription opioid overdose rates were rising in the 4 state Medicaid programs studied, yet opioid overdose incidence rates among patients with apparent new prescriptions for opioid medications showed a decreasing—albeit insignificant—trend. It is possible that an increase in illicit prescription opioid use, rather than newly prescribed opioids, was responsible for these disparate trends. Risk factors for opioid overdose in this study largely mirrored those in other populations studied.

Joseph Merrill, MD, MPH

Reference: Nam YH, Bilker WB, DeMayo FJ, et al. Incidence rates of and risk factors for opioid overdose in new users of prescription opioids among US Medicaid enrollees: a cohort study. *Pharmacoepidemiol Drug Saf*. 2020:29(8):931–938.

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