

# Alcohol, Other Drugs, and Health: Current Evidence

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## INTERVENTIONS & ASSESSMENTS

### Higher Doses of Buprenorphine More Effectively Treat Opioid Craving Than Lower Doses

Longer retention in buprenorphine treatment (>6 months) has shown significant benefit for the treatment of opioid use disorder (OUD). Opioid craving may be one reason why individuals with OUD prematurely discontinue buprenorphine. This systematic review sought to describe how buprenorphine impacts self-reported opioid craving during initiation and ongoing treatment, and to compare opioid craving during receipt of buprenorphine with other medications for OUD.

- Opioid craving was lower among individuals receiving buprenorphine compared with placebo.
- Opioid craving was lower among individuals receiving buprenorphine at higher daily doses (>16mg), compared with those receiving lower daily doses.
- At three months, opioid craving was lower among individuals receiving 24–32mg of buprenorphine per day, compared with those receiving 8mg.
- Opioid craving was higher among individuals receiving buprenorphine compared with extended release naltrexone at 4–12 weeks of treatment, but at 24 weeks there were no differences in craving.
- In three studies, opioid craving was higher among individuals receiving buprenorphine compared with methadone, although higher doses of buprenorphine (32mg) were more effective than methadone at reducing opioid craving.
- In three studies, opioid craving was similar between individuals receiving buprenorphine and methadone.

*Comments:* Buprenorphine is an effective treatment for OUD, but individuals may experience opioid craving throughout their treatment. This systematic review shows the need for individuals to receive effective doses of buprenorphine to reduce opioid craving, which is a risk factor for return to opioid use. Opioid craving should be discussed with patients and treated as an important component of OUD care.

Melissa B. Weimer, DO, MCR

*Reference:* Baxley C, Borsari B, Reavis JV, et al. Effects of buprenorphine on opioid craving in comparison to other medications for opioid use disorder: a systematic review of randomized controlled trials. *Addict Behav.* 2023;139:107589.

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## Which Medication for Opioid Use Disorder Is Superior for Treatment Retention and Adherence: Buprenorphine or Methadone?

Buprenorphine and methadone can be life-saving medications for opioid use disorder (MOUDs). Researchers conducted a systemic review and meta-analysis of randomized controlled trials (RCTs) and observational studies published through July 2022 that compared sublingual buprenorphine with methadone for several OUD-related outcomes, including treatment retention and MOUD adherence.

- Researchers identified 32 RCTs and 69 observational studies directly comparing buprenorphine with methadone, and an additional 51 RCTs and 124 observational studies reporting on buprenorphine retention. Overall, 1,040,827 persons aged  $\geq 18$  years were included in analyses.
- Treatment retention at 3, 6, 12, and 24 months was statistically better among people who received methadone than those who received buprenorphine, although the absolute differences were modest (e.g., 6-month retention was 52 percent for buprenorphine versus 56 percent for methadone; 12-month retention was 43 percent for buprenorphine versus 47 percent for methadone).
- Adherence did not differ between patients receiving buprenorphine and those receiving methadone.

*Comments:* This study suggests that methadone may be slightly superior to sublingual buprenorphine for long-term OUD treatment retention, but this interpretation is limited by multiple factors, including differing methods and settings for provision of buprenorphine versus methadone—particularly in the US—and changes in illicit opioid potency in recent years. Importantly, less than half of persons receiving MOUD are retained in treatment at one year, underscoring the need for efforts to increase long-term treatment retention.

Carrie Mintz, MD

*Reference:* Degenhardt L, Clark B, Macpherson G, et al. Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies. *Lancet Psychiatry*. 2023;10(6):386–402.

## Is Cytisinicline Effective for Smoking Cessation?

The medication cytisinicline (also known as “cytisine”) binds  $\alpha 4\beta 2$  nicotinic acetylcholine receptors to block the reinforcing effects of nicotine and reduce withdrawal symptoms. This double-blind, randomized, phase 3 clinical trial compared cytisinicline with placebo for smoking cessation. Adults with smoking who were ready to quit ( $N=810$ ) were randomized to 1 of 3 groups: 6 weeks cytisinicline, 12 weeks cytisinicline, or placebo (people in the intervention groups received 3mg cytisinicline 3 times daily). All participants also received weekly behavioral counseling for 12 weeks. Outcomes were continuous smoking abstinence during the last 4 weeks of treatment and through 24 weeks of follow-up. Craving and tolerability were also assessed.

- Continuous abstinence was greater among patients receiving the 6-week course compared with those in the placebo group at the end of treatment (25 versus 4 percent, respectively) and at 24 weeks (9 versus 3 percent).
- Continuous abstinence was greater among patients receiving the 12-week course compared with placebo at the end of treatment (33 versus 7 percent, respectively) and at 24 weeks (21 versus 5 percent).
- Craving declined more rapidly among patients in the treatment groups than among those receiving placebo.

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## Is Cytisinicline Effective for Smoking Cessation? (continued from page 2)

- Abnormal dreams and insomnia were more common in the cytisinicline groups (~10 percent), but there were no serious adverse events attributable to receipt of the medication.

*Comments:* Cytisinicline is a plant-based alkaloid that is similar to varenicline and commercially available in Europe. This trial provides strong evidence of efficacy at higher doses and longer treatment duration than what is recommended by the manufacturer (i.e., 1.5mg 6 times daily with tapering over 25 days). These dosing regimens

have not been compared head-to-head with varenicline, but cytisinicline could provide an advantage in terms of medication costs and tolerability. One limitation of the study is that people with comorbid serious mental illness or substance use disorders—groups disproportionately harmed by tobacco—were excluded from the trial.

Aaron D. Fox, MD

*Reference:* Rigotti NA, Benowitz NL, Prochaska J, et al. Cytisinicline for smoking cessation: a randomized clinical trial. *JAMA*. 2023;330(2):152–160.

## HEALTH OUTCOMES

### Cannabis Use Disorder Associated With an Increased Risk of Subsequent Major Depressive and Bipolar Disorders

Associations between cannabis use disorder (CUD) and affective psychiatric illnesses are understudied. Researchers analyzed registry data from Danish persons  $\geq 16$  years old between 1995 and 2021 to examine the associations between CUD diagnosis and subsequent diagnoses of major depressive disorder (unipolar depression) and bipolar disorder, including psychotic and non-psychotic subtypes of each illness.

- Of the 6,651,765 persons (50 percent female) analyzed, 1 percent ( $n=60,696$ ) were diagnosed with CUD and 4 percent ( $n=260,746$ ) were diagnosed with an affective disorder over the study period.
- There was an increased risk of developing both psychotic depression (adjusted hazard ratio [aHR], 1.97) and nonpsychotic depression (aHR, 1.83) among persons with CUD compared with those without CUD.
- There was an increased risk of developing psychotic bipolar disorder (aHR, 4.05) and nonpsychotic bipolar disorder (aHR, 2.96 for men; aHR, 2.60 for

women) among persons with CUD compared with those without CUD.

- Risk of developing an affective illness was highest within the first 6 months of CUD diagnosis for both unipolar depression and bipolar disorder, but the risk of developing either affective illness disorder remained elevated for 10 years following CUD diagnosis.

*Comments:* These data suggest that CUD is associated with an increased risk of developing both psychotic and nonpsychotic major depressive disorder and bipolar disorder, although a causal link has not been established. As cannabis use and CUD become increasingly prevalent, clinicians should be aware that patients with CUD may have higher likelihood of developing affective illnesses.

Carrie Mintz, MD

*Reference:* Jepsen OH, Erlangsen A, Nordentoft M, Hjorthøj C. Cannabis use disorder and subsequent risk of psychotic and nonpsychotic unipolar depression and bipolar disorder. *JAMA Psychiatry*. 2023;80(8):803–810.

### Cannabis Use Need Not Meet Criteria for Use Disorder to Be Harmful to Adolescents

Cannabis use can affect memory, motivation, attention, and mental health. Adolescents are particularly susceptible to its effects due to critical brain development during this developmental stage. As more US states legalize cannabis, adolescents are increasingly perceiving it to be safe, compared with a decade ago. This study used data from the National Survey on Drug Use and Health to investigate the association of both cannabis use disorder (CUD) and non-disordered cannabis use (NDCU)\* with adverse psychological events among US adolescents.

- NDCU was found to be 4 times more prevalent than CUD. Youth with NDCU averaged meeting 0.5 DSM-5 CUD criteria, while those with CUD met an average of 3.5 criteria.
- Both NDCU and CUD were associated with poor mental health, but the difference between the two was not significant.
- NDCU was associated with difficulty concentrating (adjusted odds ratio [aOR], 1.8) and truancy (aOR, 2.4), compared with non-use; the odds were greater for those with CUD (aOR, 2.4 and 3.0, respectively).

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## Cannabis Use Need Not Meet Criteria for Use Disorder to Be Harmful to Adolescents (continued from page 3)

- NDCU was also associated with past-year arrests (aOR, 4.2) and the association was stronger among those with CUD (aOR, 10.5); both NDCU and CUD were associated with aggression when compared with non-use.

\* CUD defined as meeting DSM-5 CUD criteria; NDCU defined as recent cannabis use that does not meet criteria for CUD.

*Comments:* This study suggests that cannabis use is potentially harmful for all adolescents, even when it does not meet criteria for a use disorder. This reinforces the importance of screening all adolescents for cannabis use. All cannabis use in

adolescence should be taken seriously, particularly in this time of increasing legalization in the US, where attitudes towards cannabis use are becoming more positive and availability has increased.

Corey McBrayer, DO, MPH\*\* & Darius A. Rastegar, MD

\*\* 2022–23 Rich Saitz Editorial Intern & Grant Medical Center Addiction Medicine Fellow, OhioHealth.

*Reference:* Sultan RS, Zhang AW, Olfson M, et al. Nondisordered cannabis use among US adolescents. *JAMA Netw Open.* 2023;6(5):e2311294.

## Prenatal and Childhood Exposure to Secondhand Smoke is Associated With Attention Problems

Many children are exposed to second hand chemicals from smoked tobacco and vaped nicotine, but the impact of this exposure has not been extensively studied. Nicotine binds to acetyl choline receptors in the central nervous system and causes the release of neurotransmitters, impacting many parts of the brain. This study followed a cohort of mother-child dyads (N=386) from pregnancy through childhood to assess the association between cotinine levels in children—an objective measure of prenatal and childhood smoke exposure—and behavioral symptoms (assessed via the Behavior Assessment System for Children, 2nd edition [BASC-2]).

- Increased cotinine concentrations in children were associated with poorer performance on cognitive (B=-1.29), memory (B=-0.97), and attention tasks (B=-1.59).
- Prenatal cotinine concentration was not associated with behavioral problems in childhood.

*Comments:* Nicotine use during pregnancy has long been associated with fetal growth retardation. This study found that tobacco exposure in childhood is associated poorer performance on cognition, learning, and attention tasks. Together, these findings suggest that tobacco exposure has adverse effects on children with outcomes that vary across developmental windows.

Sharon Levy, MD, MPH

*Reference:* Fuemmeler BF, Glasgow TE, Schechter JC, et al. Prenatal and childhood smoke exposure associations with cognition, language, and attention-deficit/hyperactivity disorder. *J Pediatr.* 2023;256:77–84.e1.

## White Individuals Are More Likely to Receive Medication for Opioid Use Disorder During and After Pregnancy Than Black and Hispanic Individuals

Administration of the medications for opioid use disorder (MOUDs) methadone and buprenorphine during pregnancy can reduce fetal risks associated with exposure to illicit opioids. MOUDs also reduce the risk of maternal overdose during and after pregnancy, when the risk is highest. The earlier in pregnancy MOUD is initiated, the more likely it is to be continued post-birth. This study used Medicaid data on pregnant persons with a diagnosis of OUD from 6 US states to investigate the receipt of MOUD and the proportion of days covered (PDC) during and after pregnancy, by race.

- White individuals were more likely to receive any MOUD in the first 90 days post-partum than Hispanic and Black individuals (61 percent, 53 percent, and 33

percent receiving MOUD, respectively).

- White individuals received MOUD earlier than Hispanic and Black individuals (MOUD receipt at 69, 72, and 91 average days' gestation, respectively).
- White individuals were more likely to be prescribed buprenorphine, compared with the other groups.
- Black individuals were more likely to receive methadone than White or Hispanic individuals, but had substantially lower PDC for methadone compared with those other groups (0.09, 0.16, and 0.18 PDC, respectively).

*Comments:* This study reinforces previous studies showing disparities within the US healthcare system. In the US,

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## White Individuals Are More Likely to Receive Medication for Opioid Use Disorder During and After Pregnancy Than Black and Hispanic Individuals (continued from page 4)

methadone is highly regulated and must initially be dosed daily at a certified opioid treatment program, whereas buprenorphine can be prescribed and dispensed monthly at a pharmacy. The proportion of Black individuals receiving methadone may partially explain the reduced proportion of days covered in this population, given the pervasive barriers to accessing this medication in the US.

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\* 2022–23 Rich Saitz Editorial Intern & Grant Medical Center Addiction Medicine Fellow, Ohio-Health.

*Reference:* Austin AE, Durrance CP, Ahrens KA, et al. Duration of medication for opioid use disorder during pregnancy and postpartum by race/ethnicity: results from 6 state Medicaid programs. *Drug Alcohol Depend.* 2023;247:109868.

## Racial Disparities in Workplace Drug Testing and Termination Following a First Positive Test

Workplace drug testing is common, but its impact is unclear. While some studies suggest that it reduces substance use, there are concerns that its implementation targets minorities disproportionately. Researchers used data from the 2002–2019 US National Survey on Drug Use and Health to examine differences in drug testing and positive drug test policies between ethnoracial groups (Black, Hispanic, or White). The sample included 121,988 employed individuals aged  $\geq 18$  years.

- Black workers were more likely to report being subject to workplace drug testing than White or Hispanic workers (adjusted odds ratio, 2.0).
- Following a first positive drug test, Black and Hispanic workers were more likely to be fired than White workers (relative risk [RR], 1.6 and 1.4, respectively).
- Black workers were more likely to be referred to treatment (RR, 1.4), while Hispanic workers were less likely to be referred to treatment (RR, 0.8), compared with White workers.

*Comments:* This study shows another way in which policies exacerbate disparities. Even if some of the differences may be due to the type of work that these groups were engaged in, policies that result in the firing of workers rather than providing them with supportive services are unnecessarily punitive and contribute to harmful outcomes.

Darius A. Rastegar, MD

*Reference:* Oh S, Hodges J, Salas-Wright C, et al. Ethnoracial differences in workplace drug testing and policies on positive drug tests in the United States. *Drug Alcohol Depend.* 2023;247:109898.

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## PRESCRIPTION DRUGS & PAIN

### Case Review was Associated with Increased Mortality Among Patients Prescribed Opioids with Newly Diagnosed Opioid Use Disorder

In the US, the liberal prescribing of opioids that began in the 1990s led to many harms. In response, policies were implemented to reduce high-risk opioid prescribing. The US Veterans Health Administration (VHA) implemented a clinical decision support tool to assess the risk of serious adverse events among patients prescribed opioids. To evaluate this tool, a previous study randomized facilities to case review the top 1 or 5 percent of high-risk patients identified. This secondary analysis examined the effect of the expansion of case review on individuals with newly diagnosed opioid use disorder (OUD).

- There were 28,251 patients newly diagnosed with OUD during the study period; 19,321 were assigned to the control group and 8930 were assigned to case review.
- All-cause mortality within 90 days for the entire sample was 1.4 percent. In adjusted analyses, the odds of mortality were greater in the case review group (adjusted odds ratio, 1.7), compared with the control group.
- In a post-hoc exploratory analysis, among patients who received an opioid prescription prior to—but not after—OUD diagnosis, the odds of 90-day mortality was 5.9 compared with patients in the control group.

*Comments:* This is another study suggesting that the US response to the prescription opioid epidemic may be leading to unintended harms. The observed increase in mortality associated with case review could be due a number of factors, including rapid discontinuation or tapering of opioid analgesics, and limited resources to support individuals with newly diagnosed OUD. In any case, this study demonstrates the vulnerability of patients with newly diagnosed OUD, particularly those who are being prescribed opioids.

Darius A. Rastegar, MD

*Reference:* Auty SG, Barr KD, Frakt AB, et al. Effect of a Veterans Health Administration mandate to case review patients with opioid prescription on mortality among patients with opioid use disorder: a secondary analysis of the STORM randomized control trial. *Addiction*. 2023;118:870–879.



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**Episode 5** features an interview with **Dr Sumeet Singh-Tan, DO** on her article, “Addiction consult service and inpatient outcomes among patients with alcohol use disorder;” that was recently summarized in *AODH*.

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