

**New Dedicated Section:  
Prescription Drugs  
and Pain**

# Alcohol, Other Drugs, and Health: Current Evidence

JANUARY–FEBRUARY 2017

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## INTERVENTIONS & ASSESSMENTS

### How Best to Implement Alcohol Screening and Brief Advice in Primary Care?

Screening and brief advice reduce self-reported alcohol consumption in primary care patients, but the optimal methods for implementing it in practices are not known. This 5-country study cluster-randomized 120 primary care units to receive one of 6 combinations of 3 implementation strategies over 12 weeks: two 1–2 hour trainings and one telephone support call; financial reimbursement for primary care units (\$1–\$9 per screening and \$15–\$27 per advice intervention); and an electronic brief intervention (eBI), which referred patients to a country-specific electronic version of the WHO e-SBI program. All received the control intervention (a summary card of the national recommendations for screening and advice).

- At baseline, primary care units screened only 6% of adults and gave advice to 74% of those who screened positive.
- Compared with control only, an increase in screening was seen among providers who received training and support, financial reimbursement, and their combination. Availability of eBI did not impact screening rates.
- No effects were observed in the proportion of patients who screened positive and who were given advice.

*Comments:* Training with support and financial reimbursement both increased screening rates, but did not demonstrate additive effects, so policymakers seeking to increase screening rates can choose among these strategies. The authors cite a ceiling effect of the 74% baseline rate as explaining the null effect for brief advice, although one could argue that 100% of patients who screen positive should receive brief advice. The fidelity and effectiveness of the screening and brief advice was not assessed, so it remains uncertain whether these implementation strategies would lead to reduced heavy drinking among patients.

Peter D. Friedmann, MD, MPH

*Reference:* Anderson P, Bendtsen P, Spak F, et al. Improving the delivery of brief intervention for heavy drinking in primary health care: outcome results of the Optimizing Delivery of Health Care Intervention (ODHIN) five-country cluster randomized factorial trial. *Addiction*. 2016;111:1935–1945.

### Electronic Interventions for Cannabis Use Have Small Effects

Electronic interventions have been developed to target substance use, but little is known about their efficacy for cannabis use. This systematic review and meta-analysis identified randomized controlled trials that tested CD-ROM, internet, or computer-based interventions for addressing unhealthy cannabis use.

- Four studies met inclusion criteria (one from the US, one from Australia and Oceania, and 2 from Europe) with a total of 1928 participants (general population and adolescent college students).
- All interventions were web-based.
- Intervention was associated with 4 fewer days of self-reported cannabis use over the past 30 days (a small pooled standardized effect size of 0.11).

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## Free CME: ABAM-Approved MOC Activity!

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## Electronic Interventions for Cannabis Use Have Small Effects

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- The intervention with the greatest treatment effect was a web-based online chat with a trained psychotherapist in addition to an online diary, weekly personalized feedback, and written feedback based on cognitive behavioral therapy and motivational interviewing.

*Comments:* This study found evidence of efficacy for electronic interventions targeting cannabis use, but the observed treatment effects were small. Often-cited advantages of electronic interventions are that they can be made available 24/7 and do not rely on extensive

health professional resources. Nevertheless, in this review the intervention with the greatest treatment effect offered an online chat with a trained psychotherapist, a feature that shares with face-to-face interventions some limitations in terms of resources and training of providers.

Nicolas Bertholet, MD, MSc

*Reference:* Hoch E, Preuss UW, Ferri M, Simon R. Digital interventions for problematic cannabis users in non-clinical settings: findings from a systematic review and meta-analysis. *Eur Addict Res.* 2016;22:233–242.

## HEALTH OUTCOMES

### Factors Associated with Hazardous Alcohol Use Among Individuals Who Inject Drugs

Hazardous alcohol use has not been well studied among people who inject drugs (PWID). To assess the risk factors in this population, researchers analyzed data from a prospective cohort of 1114 HIV-uninfected PWID. Participants were recruited from 2005 to 2012 and completed baseline and semi-annual questionnaires over a median follow-up period of 63 months. The researchers used multivariable methods to assess the independent association of potential risk factors with the outcome of hazardous alcohol use.\*

- 17% (n = 186) of participants at baseline and 37% (n = 415) over the study period reported hazardous alcohol use.
- In multivariable analyses, the following factors were associated with an increased risk of hazardous alcohol use: sexually transmitted infection (adjusted odds ratio [aOR], 1.41), victim of violence (aOR, 1.33), number of sex partners (2–10 versus <1; aOR, 1.25),

and incarceration (aOR, 1.24). Factors associated with a decreased risk of hazardous alcohol use were: addiction treatment (aOR, 0.83), daily heroin injection (aOR, 0.72), and white race (aOR, 0.59).

\*Hazardous alcohol use defined as: >14 drinks in a week or >4 drinks on a single occasion for men, and >7 drinks in a week or >3 drinks on a single occasion for women.

*Comments:* Although these findings shed light on who is most at risk for unhealthy alcohol use among PWID, perhaps the most important finding is the prevalence of hazardous alcohol use in this population. This suggests the need to screen all PWID for hazardous alcohol use and intervene as appropriate.

Kevin L. Kraemer, MD, MSc

*Reference:* Fairbairn N, Hayashi K, Milloy MJ, et al. Hazardous alcohol use associated with increased sexual risk behaviors among people who inject drugs. *Alcohol Clin Exp Res.* 2016;40(11):2394–2400.

## Heavy Drinking Is Common and Problematic in Primary Care Patients with Drug Use

The prevalence and adverse consequences of unhealthy alcohol use in primary care patients who screen positive for drug use are unclear. Researchers conducted a secondary analysis of 589 primary care patients with drug use who participated in a randomized trial of brief intervention for drug use and completed assessments at baseline and 6 months. For this analysis, the main independent variable was baseline heavy drinking, assessed with the question “In the past month, how many times have you had X or more drinks in a day?” (X=4 for women, 5 for men).

- The main drugs of choice were marijuana (64%), cocaine (18%), and opioids (16%). At baseline, 48% of participants reported  $\geq 1$  heavy drinking day (25% with 1–4 heavy drinking days, 23% with  $>4$  heavy drinking days) in the past month.
- In adjusted analyses, any heavy drinking at baseline was significantly associated with:
  - ◊ At baseline: DSM-IV drug dependence (odds ratio [OR], 1.74), use of  $>1$  drug (OR, 1.64), drug problems (OR, 1.46), any unsafe sex (OR, 1.90), and occurrences of unsafe sex (incidence rate ratio [IRR], 1.87).

- ◊ At 6 months: Number of days in past month using the main drug (IRR, 0.75), DSM-IV drug dependence (OR, 1.77), use of  $>1$  drug (OR, 1.73), any unsafe sex (OR, 1.90), and any arrest or incarceration (OR, 2.01).

*Comments:* This secondary analysis indicates a high prevalence of heavy drinking and adverse consequences in primary care patients with drug use at a single urban site. Although prevalence and associations could potentially differ with other clinical populations, the study’s findings certainly suggest that clinicians should carefully screen for unhealthy alcohol use in their primary care patients who have drug use.

Kevin L. Kraemer, MD, MSc

*Reference:* Maynié-François C, Cheng DM, Samet JH, et al. Unhealthy alcohol use in primary care patients who screen positive for drug use. *Subst Abus.* 2016 [Epub ahead of print]. doi: 10.1080/08897077.2016.1216920.

## No Association Between State-Controlled Substance Regulation and Adverse Opioid-Related Outcomes Among Vulnerable Patients

In the US, one response to tackling the surging rate of prescription opioid-related overdose deaths has been the passage of legislation restricting the prescribing and dispensing of opioids, but these laws may have the unintended consequence of restricting patients’ access to pain management medications. Researchers examined the relationship between state-controlled substance regulations and adverse prescription opioid outcomes (e.g., multiple prescribers, high doses, and nonfatal overdoses). They examined 81 laws implemented from 2006-2012 that included 8 regulations (quantitative prescription limits, patient identification requirements, requirements with respect to physician examination or pharmacist verification, “doctor-shopping” restrictions, prescription drug monitoring programs, tamper-resistant prescription forms, and pain clinic regulations) over a 7-year period ( $>8$  million person-years of observation) among disabled Medicare beneficiaries  $\leq 65$  years of age (2.2 million patients), half of whom received opioid prescriptions.

- The sample consisted of 2.2 million patients providing  $>8$  million person-years of observation.
- From 2006 through 2012, states added 81 controlled-substance laws.

- On average, 45% of beneficiaries filled opioid prescriptions in a given year; 8% had  $\geq 4$  opioid prescribers; 5% had prescriptions yielding a daily morphine equivalent dose of  $>120$  mg in any calendar quarter; and 0.3% were treated for a nonfatal prescription-opioid overdose.
- No significant associations between specific types or numbers of regulations and adverse opioid-related outcomes were observed.

*Comments:* Although researchers found no associations between passage of prescription opioid regulations and opioid-related adverse outcomes, these data rely on administrative coding and a significant amount of legislation was passed and enacted after the study period. It would be prudent to invest in robust evaluation of current legislation while also considering other methods to tackle the opioid epidemic, including clinician education.

Jeanette M. Tetrault, MD

*Reference:* Meara E, Horwitz JR, Powell WW, et al. State legal restrictions and prescription-opioid use among disabled adults. *N Engl J Med.* 2016;375(1):44–53.

## Does Alcohol Screening Score Predict Alcohol-Related Health Outcomes?

A validated surrogate marker that predicts alcohol-related health outcomes would be useful for patient monitoring, research, and program evaluation. The 3-question Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) is increasingly available in electronic health records. This retrospective cohort study analyzed data from 486,115 outpatients at 24 Veterans Affairs health care systems from 2004–2007 to determine the AUDIT-C's predictive validity for high-density lipoprotein (HDL, an alcohol biomarker) and 2 alcohol-related health outcomes: gastrointestinal (GI) hospitalizations and physical trauma (any fractures or hospital discharge diagnosis of trauma) over the subsequent year.

- A baseline AUDIT-C score of 0 was associated with a subsequent mean HDL of 41.4 mg/l and a score of 12 with an HDL of 53.5 mg/l in the follow-up year.
- The probability of GI hospitalization increased from 0.49% for a baseline AUDIT-C score of 0, to 1.8% for a score of 12. Similarly, the probability of physi-

cal trauma increased from 3% for an AUDIT-C score of 0, to 6% for a score of 12.

- Compared with stable patients, those whose AUDIT-C score increased over time experienced increased HDL, and vice-versa. Probabilities of GI hospitalization and trauma increased with increases in AUDIT-C.

*Comments:* Although this descriptive study suggests that changes in AUDIT-C correlate with changes in some alcohol-related health outcomes, measures of association, explanatory power and predictive ability are not presented. AUDIT-C might be a useful surrogate outcome for research and evaluation, but the prognostic importance of AUDIT-C, beyond its role as an indicator of alcohol consumption, remains difficult to infer for individual patients.

Peter D. Friedmann, MD, MPH

*Reference:* Bradley KA, Rubinsky AD, Lapham GT, et al. Predictive validity of clinical AUDIT-C alcohol screening scores and changes in scores for three objective alcohol-related outcomes in a Veterans Affairs population. *Addiction*. 2016;111:1975–1984.

## Adolescent Nonmedical Use of Sedatives/Anxiolytics Is Associated with Substance Use Disorder Later in Life

An increasing number of individuals are prescribed sedatives/anxiolytics. There is a concern that exposure through prescriptions may lead to substance use disorder (SUD), particularly when they are prescribed to adolescents. This study used data from a cohort of 8373 individuals in the Monitoring the Future study to examine the association between medical and nonmedical prescription sedative/anxiolytic use at age 18 and subsequent SUD symptoms at age 35.

- At age 18, 20% of the cohort reported lifetime use of sedatives or anxiolytics; 7.6% reported only medical use, 6.2% reported medical and nonmedical use, and 6.3% reported only nonmedical use.
- At age 35, compared with participants who reported no medical or nonmedical use, those who reported medical and nonmedical use were more likely to have alcohol use disorder symptoms (adjusted odds ratio [aOR], 1.5) and other drug use disorder symp-

toms (aOR, 3.0). Participants who reported nonmedical use only also had increased odds of alcohol (aOR, 2.1) and other drug use disorder symptoms (aOR, 3.0).

- Those who reported only medical use did not have significantly higher odds of SUD symptoms at age 35, compared with adolescents with no medical or nonmedical use.

*Comments:* This study shows that many adolescents are exposed to sedative/anxiolytics. Almost half of those who are prescribed these medications also take them nonmedically and these individuals are at risk for SUD later in life. Although this does not establish a cause and effect relationship, it does reinforce the need to administer these agents judiciously and to monitor closely when they are prescribed.

Darius A. Rastegar, MD

*Reference:* McCabe SE, Veliz P, Boyd CJ, Schulenberg JE. Medical and nonmedical use of prescription sedatives and anxiolytics: adolescents' use and substance use disorder symptoms in adulthood. *Addict Behav*. 2017;65:296–301.

## Parents' Attitudes About Adolescent Marijuana Use May Be Changing

In 2014, Washington State legalized marijuana for adults. Researchers analyzed data from 395 participants in a 30-year longitudinal who were recruited at age 10 in 1985, were parents, and were still living in Washington in 2014 to assess their perceptions of adolescent marijuana use.

- 82% agreed that regular marijuana use is harmful to teens.

- 89% of respondents disapproved of marijuana use where children can see it and 93% disapproved of parental use while caring for children.
- 19% said they would allow high school-aged children to decide whether or not to use marijuana, compared with 6% of parents who answered the same question in 1991.

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## Parents' Attitudes About Adolescent Marijuana Use May Be Changing (continued from page 4)

*Comments:* A majority of adult parent respondents believed that teen marijuana use is harmful and disapproved of adult role modeling, although the proportion of parents willing to tolerate marijuana use by their children tripled in one generation. It is unknown whether this finding is generalizable to states where marijuana remains illegal. This softening of parental attitudes may result in greater adolescent marijuana use over time. Clinicians can play an important role by

educating both children and parents about the harms of marijuana use on the developing brain, and coaching parents on setting expectations in an era of legalized marijuana.

Sharon Levy, MD, MPH

*Reference:* Kosterman R, Bailey JA, Guttmannova K, et al. Marijuana legalization and parents' attitudes, use and parenting in Washington State. *J Adolesc Health.* 2016;59(4):450–456.

## HIV AND HCV

### Do Patient Navigation and Financial Incentives Improve HIV Viral Suppression in Hospitalized Patients with Substance Use Disorder?

Patients with HIV and substance use disorder (SUD) are at high risk of viral non-suppression and other poor clinical outcomes. Patient navigation may improve viral suppression rates in this population. Researchers randomized 801 inpatient adults with HIV and SUD from 11 US hospitals to 6 months of one of the following: patient navigation (care coordination with case management); navigation + financial incentives (up to \$1160); or usual care. The primary outcome was HIV viral suppression versus non-suppression or death at 12 months.

- Viral suppression rates at 12 months did not differ significantly between usual care (34%) and patient navigation (36%) or navigation + incentives (39%).
- Patients in the navigation and the navigation + incentives arms were more likely than those in usual care to engage in HIV and SUD treatment at 6 months, but these improvements were not sustained at 12 months.
- Stimulant use, enrollment in the South, and black race were associated with lower rates of viral suppression.

- Few patients were linked to medication treatment for addiction at 12 months (8%).

*Comments:* Patient navigation with or without financial incentives was not effective in producing sustained improvements in HIV viral load suppression. However, engagement in HIV and SUD treatment improved in both intervention groups over 6 months, though they did not persist. Among complex patients with chronic SUD and HIV, sustained intervention will likely be needed to see ongoing benefits in treatment engagement that translate into long-term viral suppression. Tailoring the incentives and the elements of the navigation to individuals' responses also warrants further investigation.

Jessica L. Taylor, MD† and Alexander Y. Walley, MD, MSc

† Contributing Editorial Intern and Assistant Professor of Medicine, Boston Medical Center

*Reference:* Metsch LR, Feaster DJ, Gooden L, et al. Effect of patient navigation with or without financial incentives on viral suppression among hospitalized patients with HIV infection and substance use: a randomized clinical trial. *JAMA.* 2016;316(2):156–170.

### HCV Treatment Is Effective Among People with Drug Use and/or Receiving Opioid Agonist Treatment

Many insurance payers in the US restrict access to direct-acting antivirals (DAA) for chronic hepatitis C (HCV) infection if patients have illicit substance use or are receiving opioid agonist treatment (OAT). Three phase 3 multi-center trials (the "ION" trials) evaluated the efficacy and safety of ledipasvir/sofosbuvir ± ribavirin in patients with chronic genotype 1 HCV infection. People receiving OAT were eligible, but those with drug use in the year prior to study initiation were excluded. Illicit drug use in the period following treatment initiation did not lead to discontinuation from these trials. In this post hoc analysis, researchers evaluated the impact of OAT (among patients enrolled in all phase 3 ION trials) and

illicit drug use measured by serum toxicology testing on stored samples during therapy on: HCV treatment completion (among patients enrolled in the ION 1 trial only), adherence, sustained virologic response (negative HCV RNA viral load) 12 weeks post-treatment (SVR12), and safety of ledipasvir/sofosbuvir ± ribavirin.

- Among 1952 patients enrolled in the ION trials, 4% (n = 70) were receiving OAT. Compared with those who were not, there were no significant differences in treatment completion (97% versus 98%), ≥80% medication adherence (93% versus 92%), SVR12 (94% versus 97%), or serious adverse events (4% versus 3%).

(continued page 6)

## HCV Treatment Is Effective Among People with Drug Use and/or Receiving Opioid Agonist Treatment (continued from page 5)

- 23% (n = 196) of patients in the ION 1 trial had toxicology testing consistent with illicit drug use during HCV therapy (15% cannabinoids alone; 8% other illicit drugs ± cannabinoids). There were no differences in treatment completion, ≥80% adherence, SVR12, or serious adverse events in those with no drug use during treatment compared with those who used cannabinoids and/or other illicit drugs.

*Comments:* These trials included highly select populations, included a small number of people receiving OAT, and excluded people with recent drug use at treatment initiation, so the findings may not be representative of the general population of patients with drug use. However, these data suggest that HCV treatment outcomes in patients who have drug use and/or are receiving OAT can be comparable with regard to treatment completion, medication adherence, SVR12, and safety to those of other patients treated for HCV. These data add to the growing body of literature that indicates active substance use should not be considered a contraindication to HCV treatment with DAAs.

Jeanette M. Tetrault, MD

*Reference:* Grebely J, Mauss S, Brown A, et al. Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: analysis of phase 3 ION trials. *Clin Infect Dis.* 2016;63(11):1405–1411.

## Opioid Agonist Treatment Improves Antiretroviral Treatment Engagement and Outcomes

People who inject drugs (PWID) are at risk for HIV infection. In addition to other benefits, opioid agonist treatment (OAT) has the potential to improve antiretroviral treatment (ART) engagement and outcomes. The authors conducted a systematic review examining the impact of OAT on ART. They found 32 observational studies that met their criteria with 36,327 participants and a median follow-up of 24 months.

- OAT was associated with increased odds of being prescribed ART (odds ratio [OR], 1.5), adherence to ART (OR, 2.1), and HIV suppression (OR, 1.5). Receipt of OAT was associated with a decreased odds of ART discontinuation (OR, 0.8).
- The review failed to find a significant association between OAT and CD4 counts or mortality.

*Comments:* This study adds to the growing evidence that OAT helps engage PWID in treatment of other conditions. Most of the studies included in this review were of individuals receiving methadone; we need more research on the impact of buprenorphine, especially since it can be more easily integrated with treatment of other medical conditions. Moreover, integration of OAT with other medical treatment may further improve treatment engagement and outcomes. In any case, providing access to OAT should be part of the standard of care of treatment of people with HIV and opioid use disorder.

Darius A. Rastegar, MD

*Reference:* Low AJ, Mburu G, Welton NJ, et al. Impact of opioid substitution therapy on antiretroviral therapy outcomes: a systematic review and meta-analysis. *Clin Infect Dis.* 2016;63:1094–1104.

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The major journals regularly reviewed for the newsletter include:

Addiction  
Addiction Science & Clinical Practice  
Addictive Behaviors  
AIDS  
Alcohol  
Alcohol & Alcoholism  
Alcoholism: Clinical & Experimental Research  
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Journal of Substance Abuse Treatment  
Journal of the American Medical Association  
Journal of Viral Hepatitis  
Lancet  
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Many others periodically reviewed (see [www.aodhealth.org](http://www.aodhealth.org)).

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## PRESCRIPTION DRUGS & PAIN

### Recent Pain Severity Associated with Subsequent Opioid Use in Patients with Prescription Opioid Use Disorder and Chronic Pain

Chronic pain affects a substantial proportion of patients entering treatment for prescription opioid use disorder. Pain severity has not been consistently associated with non-medical use of prescription opioids (NMUPO) during treatment, but measurement issues and pain variability may have clouded an association. This secondary analysis investigated the association between past-week pain severity and subsequent-week NMUPO in 148 patients with both chronic pain and *DSM-IV* prescription opioid dependence who participated in a 12-week trial of buprenorphine/naloxone and counseling. NMUPO was measured by weekly self-report and urine drug testing, while pain severity was measured weekly with the 2-item Brief Pain Inventory (Short Form).

- Over the course of the study, 66% of weekly urine drug test samples were negative for opioids, while 68% of patients demonstrated significant pain severity variability, defined as crossing over between mild, moderate, and severe pain categories.

- Multivariable logistic regression adjusted for baseline characteristics and past-week opioid use demonstrated that increased pain severity in a given week was associated with an increased risk of NMUPO in the subsequent week (adjusted odds ratio, 1.15).

*Comments:* These data support the association of recent pain severity with subsequent return to NMUPO among patients with co-occurring chronic pain and prescription opioid use disorder. Interventions to reduce return to NMUPO in this population would benefit from better understanding the causes of the variability in pain severity. These findings raise questions of whether assessment of pain severity—versus assessment of function—is most salient in the management of chronic pain.

Joseph Merrill, MD, MPH

*Reference:* Griffin ML, McDermott KA, McHugh RK, et al. Longitudinal association between pain severity and subsequent opioid use in prescription opioid dependent patients with chronic pain. *Drug Alcohol Depend.* 2016;163:216–221.



ADDICTION SCIENCE &  
CLINICAL PRACTICE

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Jeffrey H. Samet, MD, MA, MPH

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### Target Audience

The target audience is generalist clinicians, many of whom have received limited training on detecting and treating substance abuse.

### Educational Needs Addressed

Primary-care clinicians often miss the diagnosis of alcohol or drug problems and cannot stay abreast of the current substance-abuse literature in the context of a busy practice. Because of the effects of alcohol and drugs on adherence to care plans and physician-patient relationships, patients with alcohol or drug problems may receive suboptimal treatment for other conditions. Further, physicians sometimes perceive alcohol or drug dependence as less treatable than other medical conditions, and thus delegate responsibilities for screening and intervention to others. At the root of the screening and treatment gap is the inadequate provision of substance-abuse education in medical schools and mental-health fields. The newsletter addresses this not only by research dissemination but by providing free downloadable teaching tools for use by educators.

### Educational Objectives

At the conclusion of this program, participants will be able to state the latest research findings on alcohol, illicit drugs, and health; incorporate the latest research findings on alcohol, illicit drugs, and health into their clinical practices, when appropriate; and recognize the importance of addressing alcohol and drug problems in primary care settings. In sum, the purpose of the newsletter is to raise the status of alcohol and drug problems in both academic and clinical culture to promote evidence-based screening and treatment and ultimately improve patient care.

### Disclosure Statement

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