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Free CME: ABAM-Approved MOC Activity!

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Alcohol, Other Drugs, and Health: Current Evidence

SEPTEMBER-OCTOBER 2015

INTERVENTIONS & ASSESSMENTS

Two Screening Questions Detect Drug Use Disorders in Primary Care

Screening questionnaires to detect substance use in primary care range from one to dozens of questions. Investigators have now validated a two-item tool* to detect drug use disorders. Of 3173 patients at two US Department of Veterans Affairs primary care sites, 41% agreed to the study and 1283 were enrolled. A diagnostic interview (Mini International Neuropsychiatric Interview) was used as a reference standard for DSM IV drug use disorder (10% met criteria), and the Inventory of Drug Use Consequences questionnaire for consequences (14% had at least one). Analyses were performed on two halves of the sample separately.

 In the replication sample, sensitivity and specificity for disorder (92% and 93%, respectively) and for consequences (83% and 97%, respectively) were high.

*The two-item tool (items asked sequentially; second item not asked if first is positive): "How many days in the past 12 months have you used drugs other than alcohol?" (7+ is positive). "How many days in the past 12 months have you used drugs more than you meant to?" (2+ is positive).

Efficacy of Electronic Interventions for Unhealthy Alcohol Use

Electronic delivery of brief interventions for unhealthy alcohol use can potentially overcome some of the barriers in clinical settings and reach a broader population. To assess their efficacy, researchers conducted a systematic review of Englishlanguage trials of at least 50 adult participants who screened positive for unhealthy alcohol use randomized to an electronic intervention (e-intervention), or control. The majority (68%) of the 28 trials that met eligibility criteria consisted of singlesession e-interventions. Comments: This study found good diagnostic test characteristics for a two-item drug use disorder screening test. However, the participation rate was low, limiting generalizability, and more importantly, the test was studied to detect only disorders and conseguences, and not the full spectrum of unhealthy use (which includes drug use). Therefore, the advantages of the tool over existing validated single-item tools and others that also detect unhealthy alcohol use are unclear. Nonetheless, given that drug use is often unrecognized in primary care settings, having another validated tool could provide—or at least inform—different ways to ask about drug use in primary care settings.

Richard Saitz, MD, MPH

Reference: Tiet QQ, Leyva YE, Moos RH, et al. Screen of drug use: diagnostic accuracy of a new brief tool for primary care. JAMA Intern Med. 2015;175(8):1371–1377.

 In college students, e-interventions were associated with a mean consumption difference of -11.7 g alcohol in a week at 6 months and -4.7 g alcohol in a week at 12 months.

- In non-college student adults, einterventions were associated with a mean difference of -25.0 g alcohol in a week at 6 months and -8.6 g in a week at 12 months.
- Two of the 3 trials focused on adults with alcohol use disorder did not find an effect, but one trial found increased odds of abstinence (odds ratio, 1.94) (continued page 2)

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Efficacy of Electronic Interventions for Unhealthy Alcohol Use (continued from page 1)

among patients who, after completing residential alcohol treatment, received a smartphone with a data plan, alcohol-focused application, and GPS-triggered alerts.

Comments: This well-done systematic review found a small effect of einterventions at 6 months but no clinically significant effect at 12 months. One of the promising features of einterventions is the capability to deliver multiple very brief intervention "moments" over time. These may produce a cumulative effect, but would need to be thoughtfully balanced against the risk of overwhelming and potentially turning off the patient. Future studies should take advantage of this capability and, as the authors note, link the eintervention with human support when needed.

Kevin L. Kraemer, MD, MSc

Reference: Dedert EA, McDuffie JR, Stein R, et al. Electronic interventions for alcohol misuse and alcohol use disorders: a systematic review. Ann Intern Med. 2015;163:205–214.

Titrated-Dose Baclofen May Have Efficacy for Treating Alcohol Use Disorder

An early small trial found baclofen to be effective for the treatment of alcohol use disorder, but subsequent studies yielded contradictory results. French practitioners have promoted a belief that very high doses have efficacy. This German study tested the efficacy of baclofen, including some high doses, in a randomized placebocontrolled trial in 56 adults with DSM-IV alcohol dependence and abstinence for up to 23 days.

- After a 4-week titration phase, 13 participants had relapsed or dropped out. Of the remaining 43, 8 were lost or stopped treatment early and 15 relapsed; all 23 such participants were counted as drinking. Twenty-nine participants reached the daily target dose of 270 mg; the mean dose was 180 mg and the range was 30–270 mg for 12 weeks.
- In the baclofen group, compared with placebo during the target dose phase:

more participants (15 [68%] versus 5 [24%]) were abstinent;

- cumulative abstinence duration was longer during the target dose phase (mean 68 days versus 52 [p = 0.047]).

 Abstinence was also more common (43% versus 14%) over the entire study (4 weeks of titration, 12 weeks of target dose, 4 weeks of taper). Dose was not associated with abstinence. Adverse effects were similar in both groups.

Comments: Aside from naming two outcomes as primary and excluding 23% of participants who relapsed postrandomization from the main analyses (included in secondary analyses that were consistent with the main findings), this was a well-conducted and reported study. The main limitations are the small sample size and difficulty masking high dose baclofen, which, not withstanding the temporary approval of high dose baclofen in France, preclude any recommendation for widespread clinical use. Nonetheless, these results do suggest that baclofen deserves further study for this indication, both to confirm efficacy and to better characterize safety.

Richard Saitz, MD, MPH

Reference: Müller CA, Geisel O, Pelz P, et al. High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebo-controlled trial. *Eur Neuropsychopharmacol.* 2015;25:1167– 1177.

Clinical Reminders Insufficient to Implement Alcohol Screening

Despite high rates of screening for unhealthy alcohol use in US Veterans Affairs (VA) clinics using the validated Alcohol Use Disorders Identification Test – Consumption (AUDIT-C), its sensitivity has been lower than expected. In this qualitative study, ethnographers observed participating clinical staff from 9 clinics in 7 VA sites. Of the 49 clinical staff, 3 I performed alcohol screening among 72 patients. Three themes emerged from an analysis of the field transcriptions:

- The means of administration matters. Most screening was conducted verbally, guided by a clinical reminder, but some clinics used laminated paper-based means.
- Non-verbatim screening with inferences, assumptions, and suggestions as to responses contributed to low sensitivity.
- Staff changed the recommended AUDIT-C questions to reduce discomfort and stigma, including omitting the third question about the frequency of heavy episodic drinking.

Comments: Despite the use of a clinical reminder, alcohol screening at these sites was not performed in a standardized, valid, or reliable manner; there was wide variation in how the 3 AUDIT-C questions were asked and how response sets were presented. In many cases, clinicians accepted vague replies from patients and inferred or suggested answers. Clinical reminders alone are insufficient to ensure the disciplined execution of alcohol screening. Better training might help, but patient self-administration using paper, laminated cue cards, or computerized approaches will likely do more to improve accuracy. Peter D. Friedmann, MD

Reference: Williams EC, Achtmeyer CE, Thomas RM, et al. Factors underlying quality problems with alcohol screening prompted by a clinical reminder in primary care: a multi-site qualitative study. *J Gen Intern Med.* 2015;30(8):1125–1132.

Can Brief Alcohol Intervention That Includes Referral Lead to Receipt of Treatment by Medical and Surgical Inpatients?

There is evidence that receiving specialized alcohol treatment is beneficial to people with alcohol use disorder (AUD); medical and surgical wards may present an opportunity to refer people to treatment. This systematic review of randomized controlled trials (RCTs) aimed to identify interventions for increasing subsequent alcohol treatment utilization among patients with AUD in these settings. Studies conducted among people <18 years were excluded, as were those focusing on pharmacological treatments.

- Authors identified 5 RCTs meeting the inclusion criteria.
- Two studied a single-session brief intervention (BI); I a multi-session BI; and 2 a BI with post-discharge sessions.
- Of the 5 trials, 2 reported that the intervention was associated with alcohol treatment utilization at 12 months (odds ratio [OR], 4.2 and 3.9). These trials reported on BI with post-discharge sessions. The other 3 trials showed no effect of the intervention on subsequent alcohol treatment utilization.

Comments: One of the key findings of this study is the limited availability of data on referral to alcohol treatment among patients in medical and surgical wards. As of today, no conclusion can be drawn as to which intervention might work in increasing treatment receipt, but all identified studies that looked at Bls only conducted while patients were hospitalized failed to demonstrate an increase. But interventions with post-discharge sessions may be beneficial. Future studies should also note whether patients referred are identified by screening and unaware of their treatment need or if they are seeking help as brief interventions will likely have differing success depending on such factors.

Nicolas Bertholet, MD, MSc

Reference: Simioni N, Cottencin O, Rolland B. Interventions for increasing subsequent alcohol treatment utilisation among patients with alcohol use disorders from somatic inpatient settings: a systematic review. *Alcohol Alcohol.* 2015;50(4):420–429.

Brief Alcohol Interventions for Adolescents and Young Adults Result in Modest Reductions in Consumption

Alcohol brief interventions (BI) offer promising therapeutic approaches to reducing consumption among certain populations. This meta-analysis examined the overall effects of BI on alcohol consumption and alcohol-related problems, the variation in effects associated with BI and participant characteristics, and the persistence of those effects among adolescents (age 11–18) and young adults (age 19–30). Eligible studies examined BIs that involved \leq 5 hours of contact time and \leq 4 weeks between first and last contact time (excluding booster sessions), compared with no treatment, wait-listing, or treatment as usual.

- 185 study samples were identified (in 313 reports) and findings were synthesized using random effects meta-analytic techniques with robust standard errors.
- Alcohol BIs, which were longer for adolescents than for young adults (average 100 versus 55 total minutes spanning 5 days versus 3 days), led to reduced consumption and alcohol-related problems among adolescents and young adults.

(continued page 4)

Brief Alcohol Interventions for Adolescents and Young Adults Result in Modest Reductions in Consumption (continued from page 3)

• These effects were modest at best, but persisted at one year and did not vary across participant characteristics, intervention duration, or intervention format. Effects were stronger in adolescent populations than in young adults. The findings translated to reductions of 1.0 to 1.3 standard drinking days in a month.

Comments: These findings suggest that alcohol BI, although hardly "brief" in the traditional sense, in adolescents and young adults may result in reduced consumption and alcohol-related problems. However, the effect sizes were modest and detailed information regarding intervention delivery and the persistence of any effect is limited. Alcohol risk reduction in this population is vital and further research should delineate best practices to achieve this goal.

Jeanette M. Tetrault, MD

Reference: Tanner-Smith EE, Lipsey MW. Brief alcohol intervention for adolescents and young adults: A systematic review and meta-analysis. J Subst Abuse Treat. 2015;51:1–18.

Response to Naltrexone for Alcohol Use Disorder is Not Mediated by an Opioid Receptor Polymorphism

Naltrexone has been shown to be modestly effective for the treatment of alcohol use disorder. Post hoc analyses of previous trials suggest that the response to naltrexone may be mediated by polymorphisms of the muopioid receptor gene; specifically, individuals with 1 or 2 copies of the Asp40 allele were more likely not to relapse to heavy drinking with naltrexone treatment. This is the first prospective trial to test the hypothesis that having at least one copy of the Asp40 allele would predict a better response to treatment. In this 12-week trial, 221 individuals with *DSM-IV* alcohol dependence were stratified by genotype and randomized to naltrexone or placebo.

- There were no significant differences between the groups in demographics or drinking measures.
- For the primary outcome of heavy drinking, there

was no significant interaction between genotype and treatment.

 In the group without the Asp40 allele, the odds of heavy drinking in the naltrexone group were 0.69 times those in the placebo group. For those with the Asp40 allele, they were 1.10. Neither difference was statistically significant.

Comments: Personalized medicine guided by genomics has been touted as the future of health care, but so far it has had limited clinical application. This study suggests that the Asp40 allele does not moderate response to naltrexone and that we cannot use this to guide treatment decisions for individuals with alcohol use disorder.

Darius A. Rastegar, MD

Reference: Oslin DW, Leong SH, Lynch KG, et al. Naltrexone vs. placebo for the treatment of alcohol dependence: a randomized clinical trial. JAMA Psychiatry. 2015;72(5):430–437.

Does Opioid Agonist Therapy for Prisoners Reduce Drug-Related Deaths After Prison Release?

Incarcerated people with opioid use are at high risk of drug-related death after release from prison, partly because they can lose opioid tolerance during imprisonment. Opioid agonist therapy during imprisonment may mitigate this risk. To assess the effect of a national prison -based opioid agonist program on mortality, researchers linked the records of all Scottish prisons to a national death index and then compared drug-related death rates before (1996–2002) and after (2003–2007) the opioid agonist program implementation. Eligible prisoners were those released after a minimum 14-day imprisonment.

- 150,157 prisoners were released between January 1996 and December 2007.
- Drug-related death rates at 12 weeks post-release were 3.8 per 1000 releases pre-implementation of the opioid agonist program, versus 2.2 per 1000 releases post-implementation.
- 57% of pre-implementation and 56% of postimplementation drug-related deaths were within 14

days of release.

 Overall, 61% of opioid-related deaths occurred within 14 days of release; this did not differ pre- and postimplementation.

Comments: Overall drug-related death rates decreased among former prisoners after implementation of an in-prison opioid agonist program. However, the proportion of deaths within 14 days of prison release remained the same; this was the outcome thought to be most sensitive to the in-prison program. The researchers attributed the decrease to the improved quality of community methadone programs and access to drug treatment. Additional post-release programs—such as early engagement in community opioid agonist programs or ready access to naloxone—may be necessary to further decrease the rate of drugrelated deaths occurring soon after release.

Kevin L. Kraemer, MD, MSc

Reference: Bird SM, Fischbacher C, Graham L, Fraser A. Impact of opioid substitution therapy for Scotland's prisoners on drug-related deaths soon after prisoner release. *Addiction*. 2015;110:1617–1624.

HEALTH OUTCOMES

Effects of Alcohol on Blood Pressure Among Women: A Randomized Trial

Researchers examined the effects on blood pressure of the administration of two levels of alcohol in the form of red wine among 24 normotensive pre-menopausal women (all of whom had at baseline an average alcohol consumption of 2-3 standard drinks in a day), compared with changes in blood pressure when they were given dealcoholized red wine. Participants were divided into two groups based on reported average consumption. Those consuming < 200 g alcohol in a week were administered 100 ml/day of red wine on 4 days per week (an average of 46 g/week of alcohol, about 0.5 drinks per day), 200 ml/day of red wine daily (average of 146 g/week of alcohol, about 1.5-2 drinks/day), and then similar amounts of dealcoholized red wine consecutively over three 4-week periods. Participants who at baseline reported an average consumption of > 200 g alcohol in a week were administered 100 ml/day of red wine daily (an average of 73 g/week of alcohol, about one drink per day), 300 ml/day of red wine daily (218 g/week of alcohol, about 2-3 drinks/day), and then similar amounts of dealcoholized red wine consecutively over three 4-week periods.

With higher alcohol intake, there were significant increases in 24-hour average blood pressure (+2.0±0.6 mmHg systolic, +1.2±0.4 mmHg diastolic) over the

effects of dealcoholized wine.

 With lower intake, there were no significant differences (+0.4±0.6 mmHg systolic, -0.3±0.4 mmHg diastolic), compared with dealcoholized wine.

Comments: The slight increase in blood pressure from higher levels of alcohol (versus no alcohol) supports previous research; the findings of no significant effect from lower levels of intake are consistent with either a slight increase or a slight decrease in blood pressure among people with the participants' baseline level of alcohol consumption. It is not known how the effects of short-term interventions with alcohol may relate to the regular intake of alcohol for many years. Further, the fact that the study group was based on participants who averaged 2–3 drinks in a day prior to the intervention (yet were still normotensive) might suggest that their blood pressure was not "sensitive" to alcohol, and could limit the applicability of these results to the general public.

R. Curtis Ellison, MD

Reference: Mori TA, Burke V, Beilin LJ, Puddey IB. Randomized controlled intervention of the effects of alcohol on blood pressure in premenopausal women. *Hypertension*. 2015;66 (3):517–523.

HIV AND HCV

Buprenorphine Treatment of Opioid Use Disorder Improves Primary Care-Based Addiction Treatment Engagement Among People With and At Risk for HIV

Some agencies recognize the need for integrated chronic disease, behavioral health, and addiction management within a medical home model, which may be particularly useful for people with HIV. The FAST PATH program was developed to increase capacity to provide addiction treatment to patients with HIV, or at high risk of HIV infection, at an urban medical center. Researchers assessed whether certain predisposing characteristics (depression, housing status, and polysubstance use) and an enabling resource (provision of on-site buprenorphine treatment for those with opioid use disorder) were associated with engagement in an integrated primary care-based addiction treatment program and persistent *DSM-IV* substance dependence at 6 months.

- At enrollment, 61% of participants were HIV-infected, 71% had depression, 19% were homeless, and 53% had polysubstance use. At 6 months, 60% were receiving treatment with buprenorphine.
- 64% of patients were engaged in care (defined as 2 visits within the first 2 weeks and 2 additional visits within 30 days). Patients receiving buprenorphine for opioid

use disorder (OUD) were 8 times more likely to be engaged in care.

 Baseline depression was associated with polysubstance use at 6 months (adjusted odds ratio, 3.32). Neither baseline housing status nor polysubstance use were associated with either outcome.

Comments: This cohort study confirms prior reports that buprenorphine treatment for OUD delivered within an integrated primary care setting is associated with improved treatment engagement among a cohort of patients with SUD who are infected with or at high risk for HIV infection. However, these data suggest that integrated care models should also address patients' mental health needs.

Jeanette M. Tetrault, MD

Reference: Walley AY, Palmisano J, Sorensen-Alawad A, et al. Engagement and substance dependence in a primary care-based addiction treatment program for people infected with HIV and people at highrisk for HIV infection. *J Subst Abuse Treat.* 2015 [Epub ahead of print]. doi: 10.1016/j.jsat.2015.07.007.

Alcohol-Related Diagnoses Increase the Risk of Hospitalization Among People with HIV

Combination antiretroviral treatment (ART) prolongs survival for individuals living with HIV infection. Increasingly, people with HIV are hospitalized for non AIDS-defining conditions. Alcohol use disorders and other alcohol-related diagnoses (ARD) are common among this population and these individuals may be more susceptible to harm from alcohol. Researchers studied the impact of ARDs on hospitalizations using US Veterans Administration Healthcare System data from 1997 to 2011, comparing patients with HIV (HIV+) with their uninfected counterparts (HIV-).

- There were 46,428 HIV+ and 93,997 HIV- patients included in this study. During this period, 72% of the HIV+ patients were hospitalized compared with 58% of the HIV- patients.
- Hospitalization rates declined over the study period for HIV+ patients (32% decline) and HIV- patients (21%). It also declined for ARD+ patients (21%) and ARD- patients (22%).
- On multivariable analysis of factors associated with the risk of hospitalization, compared with the HIV-/ARD- cohort, the HIV+/ARD+ cohort had an adjusted hazard ratio (HR) of 3.24, the HIV+/ARD- had an HR of 1.85, and the HIV-/ARD+ had an HR of 2.08.

Comments: This study suggests that ARDs increase the risk of hospitalization for everyone, and particularly for people with HIV. The association between ARDs and smoking may account for some of the increased risk. It remains to be seen whether increased efforts to address ARDs can reduce hospitalizations among this population.

Darius A. Rastegar, MD

Reference: Rentsch C, Tate JP, Akgün KM, et al. Alcohol-related diagnoses and allcause hospitalization among HIV-infected and uninfected patients: a longitudinal analysis of United States Veterans from 1997 to 2011. AIDS Behav. 2015 [Epub ahead of print]. doi: 10.1007/s10461-015-1025-y.

Receipt of Both Antiretroviral Therapy and Opioid Agonist Therapy Associated with Decreased Mortality Among People with HIV and Injection Drug Use

The pathways by which antiretroviral therapy (ART) and opioid agonist therapy (OAT) impact drug and HIV-related mortality are interrelated and complex. This prospective cohort study investigated all-cause and cause-specific mortality among 1727 Canadians with HIV and a history of injection drug use (IDU) receiving OAT and ART alone and concurrently between January 1996 and March 2010. Participants initiated ART at study enrollment.

- At baseline, 35% of participants were receiving OAT.
- Over the 14-year study period, 29% of participants died.
- In marginal structural models, the hazard of all-cause mortality was significantly reduced in individuals receiving ART (hazard ratio [HR], 0.39) and OAT (HR, 0.34).
- ART was negatively associated with drug-related deaths (HR, 0.49), while OAT was not. ART and OAT were both negatively associated with HIV-related deaths (HR, 0.34 and 0.33, respectively) and death from other causes (HR, 0.37 and 0.45).
- The greatest reductions were in individuals receiving both ART and OAT (allcause mortality HR, 0.16; drug-related HR, 0.40; HIV-related HR, 0.14; other causes HR, 0.08).

(continued page 7)

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Receipt of Both Antiretroviral Therapy and Opioid Agonist Therapy Associated with Decreased Mortality Among People with HIV and Injection Drug Use (continued from page 6)

Comments: In this observational study, patients receiving OAT may have more severe substance use disorders than patients not receiving OAT, increasing their risk of death compared with others with a remote history of IDU. On the other hand, this study may underestimate the contemporary impact of OAT on mortality, as the models do not account for increasing tolerability and effectiveness of ART over the study period, and OAT is known to lead to improved ART adherence. These findings are particularly noteworthy because ART is widely available to individuals with HIV in resource-rich settings; effective strategies targeted at expanding access to OAT

(e.g., HIV clinic-based buprenorphine) are needed. Finally, it is important to note the limitations of accurately determining cause-specific mortality, especially drug-related mortality, in observational studies.

Jessica S. Merlin, MD, MBA

Reference: Nosyk B, Min JE, Evans E, et al. The effects of opioid substitution treatment and highly active antiretroviral therapy on the cause-specific risk of mortality among HIV-positive people who inject drugs. Clin Infect Dis. 2015;61(7):1157–1165.

Benzodiazepine Use is an Independent Risk Factor for HIV Infection Among People with Injection Drug Use

People who inject drugs (PWID) are at risk for contracting HIV, and benzodiazepine use is an established risk factor for hazardous behaviors associated with HIV transmission. However, no direct association between benzodiazepine use and HIV infection has previously been demonstrated among this population. Researchers prospectively tracked a cohort of 1682 HIV-negative PWID to determine whether selfreported benzodiazepine use was directly associated with HIV seroconversion.

- At baseline, 501 participants reported benzodiazepine use; of these, 99% reported the mode of use to be noninjection.
- Among the overall population, 176 seroconverted for an incidence density of 1.5 cases per 100 person-years.
- Participants who reported benzodiazepine use at baseline were more likely to seroconvert over the course of

the study period.

Multivariable models controlling for age, ancestry, and at least daily injection cocaine use demonstrated that benzodiazepine use was independently and positively associated with an elevated risk of HIV seroconversion (adjusted rate ratio, 1.50).

Comments: These findings emphasize not only the need for targeted HIV prevention programs for this population, but also the importance of prescriber education regarding the limited proven clinical benefits and known risks of benzodiazepines.

Seonaid Nolan, MD

Reference: Ickowicz S, Hayashi K, Dong H, et al. Benzodiazepine use as an independent risk factor for HIV infection in a Canadian setting. Drug Alcohol Depend. 2015;155:190-194.



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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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