

## TABLE OF CONTENTS

### RESOURCE ALERT

International Society of Addiction Journal Editors Adopts Non-Stigmatizing Language, 1

### INTERVENTIONS & ASSESSMENTS

Nalmefene May Reduce Alcohol Consumption Minimally Among People with Dependence, 1

### HEALTH OUTCOMES

Exploration of the Complex Interrelationship Between Nonmedical Use of Prescription Opioids and Heroin Use, 2

Incarceration-Related Withdrawal from Methadone Leads to Aversion to Opioid Agonist Treatment, 2

Inability to Access Addiction Treatment Is Associated with Initiation of Injection Drug Use, 3

High-Quality Motivational Interviewing Skills In Brief Interventions for Drug Use In Primary Care Are Not Associated with Better Outcomes, 3

More Restrictive DEA Scheduling of Hydrocodone Combination Products Substantially Reduced the Number of Prescriptions and Tablets Dispensed, 4

Alcohol-Related Conditions Play An Important Role In Inequalities In Total Mortality, 4

Associations Found Between Prenatal Alcohol Use and Many Co-Occurring Medical Conditions, 5

Decreased Pain Associated with Less Return to Drinking Following Alcohol Use Disorder Treatment, 5

Texas "Pill Mill" Law Reduces Opioid Dose and Volume, 5

### HIV & HCV

Do People Living with HIV and Low-to-Moderate Alcohol Use Have Improved Survival? 6

Pilot Study Suggests Efficacy of Naltrexone for Reducing Methamphetamine and Alcohol Craving and HIV Risk Behaviors Among Men Who Have Sex with Men, 7

# Alcohol, Other Drugs, and Health: Current Evidence

MARCH-APRIL 2016

## RESOURCE ALERT

### International Society of Addiction Journal Editors Adopts Non-Stigmatizing Language

*Alcohol, Other Drugs, and Health: Current Evidence* has long embraced person-first language and the avoidance of stigmatizing terms such as "abuse." Following a discussion at its 2015 meeting, the International Society of Addiction Journal Editors (ISAJE) has issued a statement encouraging the use of non-stigmatizing terminology. Of note, the statement urges authors and editors to replace the terms "abuse" and "abuser" with "substance use disorder" (or "dependence" or "addiction") and "person with a substance use disorder." The statement has been endorsed by *Journal of Addiction Medicine* and can be found on the ISAJE website: <http://www.parint.org/isajewebsite/terminology.htm>. Disclosure: The Editor of [aodhealth.org](http://aodhealth.org) is an ISAJE board member.

References: International Society of Addiction Journal Editors. "Statement on Terminology," <http://www.parint.org/isajewebsite/terminology.htm> (accessed 23 March 2016).

Saitz R. International statement recommending against the use of terminology that can stigmatize people. *J Addict Med.* 2016;10(1):1-2.

## INTERVENTIONS & ASSESSMENTS

### Nalmefene May Reduce Alcohol Consumption Minimally Among People with Dependence

The opioid antagonist nalmefene is approved for treatment of alcohol dependence in several countries, but uncertainty remains concerning its efficacy and safety. Researchers conducted a systematic review and meta-analysis to assess the efficacy and safety of nalmefene for the treatment of alcohol dependence. They identified 5 double-blind randomized controlled trials of nalmefene versus placebo, comprising 2567 participants, and assessed alcohol consumption, health, biological indices, and safety outcomes.

Compared with placebo, nalmefene was:

- Associated with fewer monthly heavy drinking days\* at 6 months (mean difference [MD], -1.65) and 12 months (MD, -1.60), and decreased total alcohol consumption (standardized mean difference [SMD], -0.20 standard deviations) and Alcohol Dependence Scale score (SMD, -0.11) at 6 months. Because the nalmefene group had a much higher study withdrawal rate, sensitivity analyses were done with "best outcome carried forward" for the participants who withdrew. These analyses indicated no difference in alcohol consumption between groups.
- Not associated with any benefit in mortality or health-related quality of life, but was associated with lower liver enzyme levels at 6 months.
- Associated with more adverse events (risk ratio [RR], 1.18 and 1.20 at 6 and 12 months, respectively) and study withdrawal for safety reasons (RR, 3.65 and 7.01 at 6 and 12 months).

\* Defined by the authors as days with alcohol intake of  $\geq 60$  g for men and  $\geq 40$  g for women.

**Comments:** In this meta-analysis, nalmefene's very modest impact, if any, on alcohol consumption is tempered by concerns about safety. At present, there is not enough evidence to prescribe nalmefene over naltrexone, another opioid antagonist, when considering pharmacotherapy for treatment of alcohol use disorder.

Kevin L. Kraemer, MD, MSc

Reference: Palpacuer C, Laviolle B, Boussageon R, et al. Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and meta-analysis of published and unpublished double-blind randomized controlled trials. *PLoS Med.* 2015;12(12):e1001924.

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See page 6

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## HEALTH OUTCOMES

### Exploration of the Complex Interrelationship Between Nonmedical Use of Prescription Opioids and Heroin Use

There is concern that changes in opioid prescribing practices have contributed to increases in heroin use in the United States. In this extensive review of the literature, federal representatives explore the relationship between nonmedical use of prescription opioids, policy changes regarding opioid prescribing, and the development of heroin use and its associated morbidity and mortality. Their primary findings include:

- Although both prescription opioids and heroin produce their action through similar neurobiological circuits, these substances have different properties; individual variation exists regarding how one perceives their rewarding effects.
- Available epidemiological data suggest a clear link between nonmedical use of prescription opioids and heroin use, especially among young people with frequent nonmedical use and those meeting criteria for a prescription opioid use disorder.
- Only a small proportion of individuals with nonmedical use of prescription opioids go on to use heroin. Shifts in the demographics of individuals seeking treatment for heroin use to white, non-urban

populations seem to mirror the demographic of the prescription opioid epidemic. Recent increases in heroin use appear to be due to its lower cost relative to prescription opioids and increases in purity rather than there being a direct causal link between prescription opioid use and subsequent heroin use.

- Studies suggest that a shift from prescription opioid use to heroin use was occurring before policies were enacted to address inappropriate opioid prescribing by practitioners.

*Comments:* Although nonmedical use of prescription opioids is a risk factor for heroin initiation, the transition seems to occur at a low rate and among certain subpopulations with frequent nonmedical use, or among those who already meet criteria for opioid use disorder. This article highlights the public health threat that both prescription opioids and heroin pose and suggests the need for a multi-pronged approach to addressing the epidemic.

Jeanette M. Tetrault, MD

*Reference:* Compton WM, Jones CM, Baldwin GT. Relationship between non-medical prescription-opioid use and heroin use. *N Engl J Med.* 2016;374(2):154–163.

### Incarceration-Related Withdrawal from Methadone Leads to Aversion to Opioid Agonist Treatment

Up to 25% of incarcerated people meet criteria for opioid use disorder (OUD), but few jails and prisons offer opioid agonist treatment (OAT), and some limit it to certain populations (i.e., pregnant women). This qualitative study explored attitudes toward medications for treatment of OUD among 21 former inmates (defined as ≥1 day of incarceration in the previous 5 years) with OUD. Interviews were one hour in length and were conducted by a trained research assistant. An interview guide was used to elicit partici-

pants' experiences with treatment for OUD, incarceration, community reentry, and attitudes toward methadone and buprenorphine.

- The median age of the sample was 49 years; all were African American or Hispanic; 18 were male. Participants were incarcerated for a median of 16 years (interquartile range 5.5–26 years) and prison or jail release was a median of 7.5 months prior to the interview (median 10 days to 4 years).

(continued page 3)

## Incarceration-Related Withdrawal from Methadone Leads to Aversion to Opioid Agonist Treatment

(continued from page 2)

- 20 out of 21 participants received non-pharmacologic treatment for OUD while incarcerated; at the time of the interview 6 were receiving buprenorphine and 3 were receiving methadone.
- Participants who received methadone treatment immediately prior to an incarceration episode reported severe and prolonged withdrawal symptoms from rapid dose reductions or disruption of their methadone treatment during incarceration, leading to a subsequent aversion to reengagement in OAT post release.

*Comments:* Although the sample is drawn from a single region, the results of this study underscore the negative effect that OAT disruption can have on retention in care and should inform policy change with regard to medication administration during incarceration.

Jeanette M. Tetrault, MD

*Reference:* Maradiaga JA, Nahvi S, Cunningham CO, et al. "I kicked the hard way. I got incarcerated." Withdrawal from methadone during incarceration and subsequent aversion to medication assisted treatments. *J Subst Abuse Treat.* 2016;62:49–54.

## Inability to Access Addiction Treatment Is Associated with Initiation of Injection Drug Use

Use of needles increases the risk of complications from unhealthy drug use. Addiction treatment may provide an opportunity to prevent young people who have unhealthy drug use from initiation of injection drug use. Researchers used data from the At-Risk Youth Study, a prospective cohort of street-involved youth (age 14–26) in Vancouver, Canada. For this study, they included 462 youth who had never injected drugs at baseline and had at least one follow-up visit.

- The median age of the cohort was 21.5 years and 31% were female. Participants were followed for a median of 22.4 months and 21% initiated injection drug use during follow-up. The median number of years between initiation of "hard" drug use (heroin, cocaine, or methamphetamine) and injection drug use was 7.1. Of the cohort, 28% reported being unable to access treatment at some point during the study period.

- On multivariable analyses, inability to access treatment was associated with initiation of injection drug use (adjusted hazard ratio [aHR], 2.02). The only other factor with a significant association was methamphetamine use (aHR, 2.00).

*Comments:* This study reinforces the importance of accessible and timely treatment for substance use disorder. More needs to be done to reach out to vulnerable youth to prevent progression to more serious problems.

Darius A. Rastegar, MD

*Reference:* DeBeck K, Kerr T, Nolan S, et al. Inability to access addiction treatment predicts injection initiation among street-involved youth in a Canadian setting. *Subst Abuse Treat Prev Policy.* 2016;11:1.

## High-Quality Motivational Interviewing Skills In Brief Interventions for Drug Use In Primary Care Are Not Associated with Better Outcomes

Motivational interviewing (MI) is a strategy to address unhealthy drug use that is often employed as part of screening and brief intervention. However, the evidence for its efficacy in primary care is limited and even less is known about the association between the quality of MI skills and patient outcomes. A recent randomized controlled trial examined the efficacy of 2 types of brief interventions for unhealthy drug use among primary care patients identified through screening. One intervention was a brief intervention based on MI (BNI); the other a more intensive intervention that also used MI techniques (MOTIV). The original study found that these interventions did not have a significant effect on drug use at 6 weeks and 6 months. For this study, the researchers graded the quality of these interventions based on review of recordings and analyzed the association between the quality of the intervention and outcomes.

- There were 171 participants in this study; 69% were male and 63% reported marijuana as their main drug.

- On multivariable analyses, there was little evidence that ratings of the quality of MI skills for either intervention were associated with drug use at 6 weeks or 6 months.

*Comments:* This study suggests that a brief intervention is insufficient to address unhealthy drug use in primary care, no matter how well it is delivered. For most individuals with substance use disorder, and perhaps even for those with risky use, the problem is probably better approached like other chronic conditions, with longitudinal care over an extended period of time. MI techniques may prove to be effective in this context.

Darius A. Rastegar, MD

*Reference:* Palfai TP, Cheng DM, Bernstein JA, et al. Is the quality of brief motivational interventions for drug use in primary care associated with subsequent drug use? *Addict Behav.* 2016;56:8–14.

## More Restrictive DEA Scheduling of Hydrocodone Combination Products Substantially Reduced the Number of Prescriptions and Tablets Dispensed

Hydrocodone combined with non-opioid analgesics (e.g., acetaminophen) have been among the most commonly prescribed medications and were involved in over 100,000 substance-related US emergency department visits in 2011. When the Drug Enforcement Agency shifted hydrocodone products from Schedule III to II in 2014, prescription refills were no longer permitted. Researchers used prescription dispensing in a large national pharmacy database and prescriber specialty data to determine how dispensing of hydrocodone products changed when the more restrictive scheduling went into effect.

- The number of hydrocodone combination prescriptions declined by 22% and tablets dispensed declined by 16% in the 12 months after rescheduling compared with the 12 months before rescheduling,
- The number of non-hydrocodone opioid-containing pain combination prescriptions increased by 4.9% and tablets dispensed increased by 1.2% in the 12 months after rescheduling compared with the 12

months before rescheduling,

- Primary care physicians and surgeons accounted for the largest decreases in hydrocodone prescriptions and tablets dispensed.

*Comments:* More restrictive rules on prescribing hydrocodone combination products resulted in fewer prescriptions and tablets dispensed. While increases in non-hydrocodone opioid combination products did occur, these did not fully offset the hydrocodone reductions. This study does not report whether these reductions are offset by opioids that are not combined with other analgesics, are sustained beyond 12 months, or are associated with changes in pain treatment, addiction risk, or overdose in patients.

Alexander Y. Walley, MD, MSc

*Reference:* Jones CM, Lurie PG, Throckmorton DC. Effect of US Drug Enforcement Administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. *JAMA Intern Med.* 2016;176:399–402.

## Alcohol-Related Conditions Play An Important Role In Inequalities In Total Mortality

Alcohol consumption patterns are linked to socioeconomic status (SES) and most studies find that mortality from alcohol-related conditions is higher in low-SES groups compared with high-SES groups. This study, based on national and regional mortality registries in 17 European countries, assessed the magnitude of SES inequalities in alcohol-related mortality.

- Mortality from alcohol-related conditions was highest in Hungary where the age-standardized mortality rate per 100,000 person-years was 198 deaths among men and 51 among women. This was mostly due to alcohol-related liver cirrhosis. Alcohol use disorder mortality was highest in Denmark and alcohol poisoning mortality highest in Estonia.
- Inequality in mortality from alcohol-related causes was found in all populations, and mortality rates were higher in low-SES groups compared with high-SES groups. Nevertheless, the gap between low and high education groups varied substantially between populations (from small in Southern Europe to large in Eastern Europe, Finland, and Denmark).

- Over time there was a rise in inequalities in alcohol-related mortality due to a large increase in mortality among individuals with low education levels, while mortality was stable or only moderately increased among high-SES groups. This was mostly explained by the rapid rise in mortality in low-SES groups in Eastern Europe, Denmark, and Finland.

*Comments:* This study demonstrates important inequalities in total mortality in many European countries due to alcohol-related conditions. The rise in inequalities is of great concern. Dealing with the impact of alcohol-related conditions in low-SES groups is crucial to reducing inequalities in mortality. Among other factors, these changes might be explained by the increased affordability of alcohol in some countries, or the liberalization of the alcohol market in Eastern countries since low-SES groups are more responsive to price changes.

Nicolas Bertholet, MD, MSc

*Reference:* Mackenbach JP, Kulhánová I, Bopp M, et al. Inequalities in alcohol-related mortality in 17 European countries: a retrospective analysis of mortality registers. *PLoS Med.* 2015;12(12):e1001909.



## Associations Found Between Prenatal Alcohol Use and Many Co-Occurring Medical Conditions

Alcohol exposure is known to cause a spectrum of harms to the developing fetus. Researchers conducted a meta-analysis of 127 studies examining the prevalence of co-occurring medical conditions in individuals with fetal alcohol spectrum disorders (FASD). Co-occurring conditions were coded according to the International Classification of Diseases, tenth revision (ICD-10). Pooled prevalence data for each condition was compared with the US population.

- Data abstraction identified 428 conditions—excluding diagnostic criteria for fetal alcohol syndrome (FAS). Eighteen conditions had a pooled prevalence of > 50% in individuals with FASD.
- For many conditions, pooled prevalence in individuals with FAS was substantially higher than the general population. For example, individuals with FAS had a prevalence of visual impairment 31 times higher and blindness 71 times higher than the US population.

*Comments:* The current naming convention that uses fetal alcohol spectrum disorders as an umbrella term to include fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder underscores the variability of clinical presentation. This review suggests that the impact of alcohol on the fetus may be even greater than generally recognized. The findings are perhaps not surprising; unlike most psychoactive substances, which have their effect through a specific neuronal receptor, alcohol is known to have many sites of action both intra and extra-cellular throughout the body.

Sharon Levy, MD, MPH

*Reference:* Popova S, Lange S, Shield K, et al. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. *Lancet*. 2016 [Epub ahead of print]. doi: 10.1016/S0140-6736(15)01345-8.

## Decreased Pain Associated with Less Return to Drinking Following Alcohol Use Disorder Treatment

Persistent pain is associated with heavy drinking among people with alcohol use disorder. Researchers prospectively studied 366 adults who entered abstinence-based treatment for DSM-IV alcohol dependence and were interviewed approximately 12 months later. At entry, 75% reported any pain, but the presence of pain was not associated with subsequent drinking. At follow-up:

- 50% of the sample was lost.
- 30% reported past-month drinking (94% had heavy use).
- 91% reported any pain and 23% reported decreased pain.
- Decreased pain was associated with a lower odds of any drinking (odds ratio, 0.15) in an analysis adjusted

for depressive symptoms, baseline drinking, social support, age, sex, and education; the association at follow-up was similar (0.34).

*Comments:* With loss of half of the sample, it is difficult to interpret these results. Nonetheless, it is plausible and makes clinical sense that for some, pain plays a role in return to drinking. Whether interventions that reduce pain can improve outcomes for those with pain and alcohol use disorder is an important area for study.

Richard Saitz, MD, MPH

*Reference:* Jakubczyk A, Ilgen MA, Kopera M, et al. Reductions in physical pain predict lower risk of relapse following alcohol treatment. *Drug Alcohol Depend*. 2016; 158:167–171.

## Texas “Pill Mill” Law Reduces Opioid Dose and Volume

The impact of “pill mills,” which prescribe opioids but provide inadequate clinical management, on opioid supply at the population-level is largely unknown. This study examined the effect of the 2010 Texas “pill mill” law. Using prescription claims data that included 65% of retail prescription transactions nationally, investigators created a cohort of 8.3 million patients with prescription claims during a 24-month period. Patient and provider-level outcomes were compared over 12 months pre-intervention (September 2009–August 2010) and post-intervention (September 2010–August 2011).

- 12 months after the policy change, average morphine equivalent dose (MED) per transaction was 48.2 mg in a month; 8.1% lower than the expected 52.5 mg.

- Opioid volume declined by 9.99 kg in a month. Opioid volume, total number of opioid prescriptions, and quantity of opioid pills dispensed were 24%, 23%, and 20% lower, respectively, than expected at one year.
- Prescribers with highest quartile opioid volume prescribing at baseline had the greatest change compared with prescribers with lower prescribing volumes; among prescribers in the lowest prescribing quartile there was no decrease in prescribing.
- Investigators estimated the decrease in opioids in circulation at one year could have supplied every person aged 45–49 in Texas for a week of around-the-clock hydrocodone/acetaminophen (Vicodin).

(continued page 6)

## Texas “Pill Mill” Law Reduces Opioid Dose and Volume (continued from page 5)

*Comments:* The study was limited by absence of a control group to compare changes in states without policy change; secular changes in opioid-prescribing patterns could explain observed differences. Nonetheless, policy approaches that decrease the supply of opioids at the population level are critical to support clinical-level interventions to reduce unnecessary exposure to opioids and reduce morbidity and mortality.

Hillary Kunins, MD, MPH, MS

*Reference:* Lyapustina T, Rutkow L, Chang HY, et al. Effect of a “pill mill” law on opioid prescribing and utilization: the case of Texas. *Drug Alcohol Depend.* 2016;159:190–197.

## HIV AND HCV

### Do People Living with HIV and Low-to-Moderate Alcohol Use Have Improved Survival?

Unhealthy alcohol use is associated with many adverse health outcomes in people living with HIV (PLWH). Researchers analyzed data from 9741 PLWH in the Swiss HIV Cohort Study to determine any potential benefits from low to “moderate” alcohol use\* in this population. Participants completed alcohol use questionnaires every 6 months. Cox proportional hazards models, adjusted for multiple confounders, were used to test the association of alcohol use categories (time-updated every 6 months) with the primary outcome (composite of death or cardiovascular disease event).

- Baseline alcohol use was 51% abstinent/very low, 20% low, 22% “moderate,” and 7% high.
- Over 46,719 person-years of follow-up, there were 491 deaths and 343 non-fatal cardiovascular events.
- Compared with abstinent/very low alcohol use, low and “moderate” use were associated with lower risk for the primary composite outcome (hazard ratio [HR], 0.79 and 0.78, respectively) and for death alone (HR, 0.57 and 0.60). Incidence of non-fatal cardiovascular events did not differ significantly across alcohol use categories.

\* Categorized by the authors as: abstinence/very low (<1 g/day), low (1–9 g/day), “moderate” (women, 10–29 g/day; men, 10–39 g/day), and high (exceeding “moderate” limits).

*Comments:* This study suggests a J-curve relationship between alcohol use and overall mortality in PLWH, with decreased risk observed among those with low to “moderate” alcohol use. However, it is perplexing that cardiovascular events, the purported mechanism for decreased mortality among low-to-moderate drinkers, did not differ by alcohol use categories. Although the researchers did sensitivity analyses omitting some “sick quitters” (i.e., those with illnesses that result in decreased alcohol use and increased mortality) and found similar results, concerns remain given the high prevalence of abstinence/very low alcohol use in this cohort and the potential of the last time-updated alcohol use category to change towards abstinence/very low in advance of death. Similar analyses should be done in other prospective HIV cohorts with the addition of competing risks models and, as the researchers suggest, attention to types of alcoholic beverage and patterns of use.

Kevin L. Kraemer, MD, MSc

*Reference:* Wandeler G, Kraus D, Fehr J, et al. The J-curve in HIV: low and moderate alcohol intake predicts mortality but not the occurrence of major cardiovascular events. *J Acquir Immune Defic Syndr.* 2016;71(3):302–309.

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Addiction Science & Clinical Practice  
Addictive Behaviors  
AIDS  
Alcohol  
Alcohol & Alcoholism  
Alcoholism: Clinical & Experimental Research  
American Journal of Drug & Alcohol Abuse  
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Many others periodically reviewed (see [www.aodhealth.org](http://www.aodhealth.org)).

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## Pilot Study Suggests Efficacy of Naltrexone for Reducing Methamphetamine and Alcohol Craving and HIV Risk Behaviors Among Men Who Have Sex with Men

Methamphetamine use and heavy episodic drinking (> 5 drinks on a single occasion) are associated with HIV risk behaviors and are highly prevalent among men who have sex with men (MSM). This 8-week pilot study among 30 MSM with methamphetamine use (> 2 times per month) and heavy episodic drinking (but no diagnosis of *DSM-IV* dependence) and high-risk sexual behaviors evaluated the feasibility, acceptability, and tolerability of targeted naltrexone (i.e., during craving or in anticipation of methamphetamine or alcohol use), compared with placebo. All received one 15–20 minute session of substance use counseling every two weeks.

- Targeted naltrexone was found to be:
  - \* Feasible: trial completion rate was 93%; visit completion rate was 95%. There were no between-arm differences.
  - \* Acceptable: mean weekly number of medication pills taken was 2; patient satisfaction was 96%. There were no between-arm differences.
  - \* Tolerable: there were no serious adverse events in either treatment arm.
- While analyses revealed no differences in methamphetamine use or drinking overall, subgroup analyses revealed

greater reductions in methamphetamine-using days among patients using > weekly receiving naltrexone compared with placebo (incidence rate ratio [IRR], 0.78), and greater reductions in heavy episodic drinking days among people who took >3 naltrexone pills in a week (IRR, 0.72).

- Patients in the naltrexone group were also found to have greater reductions in serodiscordant receptive anal intercourse (IRR, 0.15) and condomless receptive anal intercourse (IRR, 0.11).

*Comments:* Given the prevalence of non-dependent methamphetamine use and heavy episodic drinking and associated HIV risk behaviors among MSM, the results of this study are of importance but are limited by the very small sample size. Much larger efficacy trials examining the impact of targeted naltrexone on substance use outcomes and sexual risk behaviors among this patient population are warranted.

Seonaid Nolan, MD

*Reference:* Santos GM, Coffin P, Santos D, et al. Feasibility, acceptability and tolerability of targeted naltrexone for non-dependent methamphetamine using and binge-drinking men who have sex with men. *J Acquir Immune Defic Syndr*. 2015 [Epub ahead of print]. doi: 10.1097/QAI.0000000000000922.



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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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