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# Alcohol, Other Drugs, and Health: Current Evidence

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## INTERVENTIONS & ASSESSMENTS

### Cutoffs for Unhealthy Alcohol Use Are Actually Lower than Those Often Suggested

Although many publications suggest a score of  $\geq 8$  on the Alcohol Use Disorders Identification Test (AUDIT) as the threshold for detecting unhealthy alcohol use, other have suggested that cutoff may not be sufficiently sensitive. Investigators analyzed data collected by research-assistant (RA) interviews with patients who visited 1 of 5 primary care practices in the southeastern US (N=625). They used the Diagnostic Interview Schedule to diagnose abuse and dependence and the timeline follow-back calendar method to detect at-risk drinking amounts as defined by the National Institute on Alcohol Abuse and Alcoholism. Unhealthy use was defined as drinking at-risk amounts, abuse, or dependence.

- For men, an AUDIT score of  $\geq 8$  was only 43% sensitive for unhealthy use (specificity was 94%). A score of  $\geq 5$  was 77% sensitive and 76% specific.
- For women, an AUDIT score of  $\geq 7$  was only 31% sensitive for unhealthy use (specificity was 98%). A score of  $\geq 3$  was 86% sensitive and 74% specific.

- Optimal sensitivity and specificity of the AUDIT-consumption (AUDIT-C) items was similar to that reported previously (scores of  $\geq 4$  for men and  $\geq 3$  for women).
- An AUDIT score of  $\geq 15$  for men and  $\geq 13$  for women was 100% specific for current alcohol dependence.

*Comments:* These results, which are consistent with other studies in primary care in the US, make a strong case for not using 8 as the AUDIT screening cutoff for unhealthy alcohol use and instead using  $\geq 5$  for men and  $\geq 3$  for women. The study also provided useful information on how to use the AUDIT as an assessment tool for advising patients who screen positive for dependence.

Richard Saitz MD, MPH

*Reference:* Johnson JA, Lee A, Vinson D, et al. Use of AUDIT-based measures to identify unhealthy alcohol use and alcohol dependence in primary care: a validation study. *Alcohol Clin Exp Res*. July 26, 2012 [Epub ahead of print]. doi: 10.1111/j.1530-0277.2012.01898.x

### Alcohol Screening and Brief Intervention in General Practice: Can You Lead a Mule to Water?

Although screening and brief intervention (SBI) can effectively address risky drinking in primary care settings, it has proven difficult to implement in routine clinical practice. This study randomized 77 general practices with 119 general practitioners (GPs) in the Netherlands to a comprehensive multifaceted program of professional, organizational, and patient-related activities designed to implement either SBI or usual care (mailed information on problem drinking). The intervention included distribution of guidelines from the Dutch College of GPs;

GP training; a reminder card; practice-level feedback on the number of risky drinkers in the practice; facilitation of cooperation with local addiction services; outreach visits to the practice by a trained facilitator; and patient information letters and personalized feedback about their drinking with advice for risky drinkers to consult their physician.

- Practices were hard to recruit: 2758 general practices were invited, but only 82 agreed (5 withdrew after randomi-  
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## Alcohol SBI in General Practice (continued from page 1)

- zation) because of the requirement that every GP agree to participate.
- Despite such agreement, only half of the 40 intervention practices met the minimum requirement that every GP attend at least 1 training session and 1 facilitator visit.
  - At baseline, the proportion of patients screened (18% in the control group, 15% in the intervention group) and given advice (3% for both groups) was very low.
  - Medical record review found that the proportion of at-risk patients screened or given advice about alcohol increased from baseline for both groups during the study period but waned at 1-year follow-up, with no differences detected.
  - On a self-report questionnaire, screening rates declined from base-

line to 1-year follow-up.

*Comments:* In this study, the difficulty recruiting practices, resistance to training, and null results demonstrate the infeasibility of getting large groups of primary care physicians to implement alcohol SBI through traditional training and support. Clearly, other implementation strategies must be developed and tested, including strong incentives or bypassing the physician altogether through the use of other providers or technology.

Peter D. Friedmann, MD, MPH

*Reference:* van Beurden I, Anderson P, Akkermans RP, et al. Involvement of general practitioners in managing alcohol problems: a randomized controlled trial of a tailored improvement programme. *Addiction*. 2012;107(9):1601–1611.

## Is Low-Risk Drinking an Appropriate Treatment Outcome for Individuals with Alcohol Use Disorders?

Although the Food and Drug Administration now recommends “no heavy drinking” (defined as abstinence or low-risk drinking) as the primary outcome for clinical trials of alcohol treatment, it is not clear if this is an appropriate outcome for patients who enter treatment with more severe alcohol use disorders. In this study, researchers examined data from 2 large randomized studies of alcohol and drug treatment delivery in an integrated health-care system. The analysis was restricted to 995 participants with alcohol abuse or dependence at baseline who provided data on past 30-day alcohol consumption and completed the Addiction Severity Index (ASI) at 6 and 12 months post-treatment.

- At 6 months, 66% of participants were abstinent, 14% drank low-risk amounts,\* and 20% drank heavy amounts.\*\* By 12 months, 7% of par-

ticipants who were abstinent and 31% with low-risk drinking had progressed to heavy drinking.

- Compared with those with heavy drinking at 6 months, participants who were abstinent were more likely to be abstinent or to consume low-risk amounts at 12 months (odds ratio [OR], 16.7) and to have lower ASI psychiatric (OR, 1.8), family/social (OR, 2.2), and employment (OR, 1.9) problem severity.
- Compared with those with heavy drinking at 6 months, participants with low-risk drinking were more likely to be abstinent or to consume low-risk amounts at 12 months (OR, 3.4) and to have lower ASI psychiatric (OR, 2.2) and family/social (OR, 2.2) problem severity.

*Comments:* This study indicates that, compared with those who drink heavily, individuals who drink low-risk amounts 6 months after treatment for alcohol use disorders have a similar decrease in alco-

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\*Defined in this study as nonabstinence and no days with consumption of 5+ drinks (grams of alcohol per standard drink not provided).

\*\*Defined in this study as 1 or more days with consumption of 5+ drinks.

## Low-Risk Drinking: An Appropriate Outcome for AUD Treatment? (continued from page 2)

hol problem severity as that seen in abstinent individuals. This suggests low-risk drinking may be an appropriate harm reduction target. However, it should also be noted that people consuming low-risk amounts had a higher rate of progression to heavy drinking than those who were abstinent, which may lead to adverse consequences later on.

Kevin L. Kraemer, MD, MSc

*Reference:* Kline-Simon AH, Falk DE, Litten RZ, et al. Post-treatment low-risk drinking as a predictor of future drinking and problem outcomes among individuals with alcohol use disorders. *Alcohol Clin Exp Res.* July 24, 2012 [Epub ahead of print]. doi: 10.1111/j.1530-0277.2012.01908.x

## Naltrexone for Alcohol Dependence May Be Particularly Beneficial among People Who Smoke

Cigarette smoking predicts more severe alcohol dependence and is associated with greater urges to drink and increased risk of relapse. Responsiveness to pharmacotherapies for alcohol dependence is moderate, and some characteristics (genetic polymorphism, for example) can influence treatment response. In this study, researchers conducted a secondary analysis of COMBINE\* study data to assess whether smoking moderated responsiveness to naltrexone in people with alcohol dependence (N=1383) and whether naltrexone impacted smoking. Fifty-five percent of participants in the sample were tobacco smokers (mean use, 17 cigarettes per day).

- Overall, smoking was associated with less treatment retention and worse drinking outcomes. Smokers assigned to naltrexone, compared with those who were not, reported a higher percentage of days abstinent (PDA) (mean, 78.4 versus 71.7), lower scores on drinking consequences\*\* (mean, 13.57 versus 17.50), and a lower percentage of heavy drinking days (mean, 14.5 versus 20.4).

\*COMBINE = Combining Medications and Behavioral Interventions study for alcohol dependence.

\*\*Assessed using the 50-item Drinker Inventory of Consequences (DRI-C) questionnaire.

- Nonsmokers in the naltrexone and placebo groups reported similar PDA (mean, 74.0 and 74.6, respectively) and scores on drinking consequences (mean, 9.69 and 9.49, respectively).
- There was no interaction between smoking and naltrexone on time to relapse or number of drinks per drinking day.
- Naltrexone had no impact on smoking.

*Comments:* This analysis confirms that smoking is a predictor of more negative outcomes in people with alcohol dependence, but that it also moderates naltrexone's effect. Therefore, smoking status could be used to identify patients more likely to respond to naltrexone. Smoking is highly prevalent among people with alcohol dependence and does not require expensive testing. These results should encourage clinicians to prescribe naltrexone to patients who smoke, especially since it can alleviate the negative impact of smoking on the course of alcohol dependence.

Nicolas Bertholet, MD, MSc

*Reference:* Fucito LM, Park A, Gulliver SB, et al. Cigarette smoking predicts differential benefit from naltrexone for alcohol dependence. *Biol Psychiatry.* 2012;72(10):832–838.

## Topiramate Did Not Increase Abstinence from Methamphetamine but Might Reduce Use

Topiramate has shown promise for the treatment of cocaine dependence. This study randomized 140 methamphetamine-dependent adults from 8 sites to 13 weeks of topiramate (50 mg per day increasing to  $\leq 200$  mg per day) or placebo. All subjects received counseling to enhance adherence.

- Intent-to-treat analyses did not show differences in abstinence during weeks 6–12.
- More subjects in the topiramate (64%) than placebo (42%) group reduced their weekly median quantitative urine methamphetamine levels by  $\geq 25\%$  from baseline ( $p=0.05$ ) during weeks 6–12.
- More subjects in the topiramate (38%) than placebo (14%) group reported a  $\geq 50\%$  reduction in methamphetamine use from baseline ( $p=0.003$ ) during weeks 6–12.
- Subjects in the topiramate group experienced improved observer-rated global severity-of-dependence scores and had a trend toward decreased craving.

- Topiramate was associated with increased paresthesias and dysgeusia but was generally well-tolerated.

*Comments:* Discovery of a medication to treat methamphetamine dependence would be a major advance in addiction science. Topiramate did not increase abstinence in this study, but results indicate it might reduce methamphetamine use over time. It appears to take 6 or more weeks to see effects, so a medical-management-type intervention to enhance adherence seems imperative. Perhaps topiramate will be useful for selected patients, but we still await a medication that will be widely effective for abuse of stimulants, especially among the most severely afflicted.

Peter D. Friedmann, MD, MPH

*Reference:* Elkashef A, Khan R, Yu E, et al. Topiramate for the treatment of methamphetamine addiction: a multicenter placebo-controlled trial. *Addiction.* 2012;107(7):1297–1306.

## Voluntary Brief Intervention for Multiple Substances Is of Questionable Benefit in Young Adult Men

Evidence exists for the efficacy of brief interventions (BI) following a positive screen for at-risk or harmful drinking. Multi-substance use is the more common pattern in the general young adult population, however. The authors of this effectiveness trial investigated multi-substance\* BI in a Swiss cohort of young adult men undergoing army conscription who voluntarily sought BI, without prior screening. Switzerland has a mandatory 2-day army recruitment conscription process for young men at age 19. During this process, conscripts complete a physical, medical, and cognitive assessment of fitness. Between 2008–2009, all conscripts were invited to a counseling session on tobacco, alcohol, and cannabis. Of 4767 conscripts available to participate in the study, 1052 voluntarily sought BI. Participants were randomized to receive assessment and BI (n=362) versus assessment only (control group, n=461). The authors also tested the incremental benefit of a 3-month booster session in the BI group.

- Although the BI subjects reported nonsignificant reductions in substance use on 10 of 12 measures at 6 months compared with controls, the only significant

\*Alcohol, cannabis, and tobacco.

- between-group difference was for cannabis use (from 45% to 39% in the control group versus 46% to 34% in the BI group [ $p=0.013$ ]).
- There were no differences in outcomes in subjects who received a booster session at 3 months compared with those who did not.

*Comments:* Although this study offered a possible model for a distinct population of young Swiss men who voluntarily sought a multi-substance BI, no differences were seen in alcohol or tobacco use outcomes, only a small decrease was seen in cannabis use, and there was no added benefit of BI booster sessions. Current screening and BI models—either with or without booster sessions—should be implemented to detect and treat substance use only in settings and for substance use patterns where efficacy is proven.

Jeanette M. Tetrault, MD

*Reference:* Gmel G, Gaume J, Bertholet N, et al. Effectiveness of a brief integrative multiple substance use intervention among young men with and without booster sessions. *J Subst Abuse Treat.* August 10, 2012 [Epub ahead of print]. doi: 10.1016/j.sat.2012.07.005

## Alcohol-Related Deaths in Scotland: Care for People with Dependence is Available, but High-Quality Care Is Lacking

Alcohol-related death rates have increased in some countries, including Scotland. Researchers there sought to determine whether primary-care interventions or other opportunities might have prevented the deaths. They analyzed 2003 death records from a large metropolitan area and identified 501 alcohol-related deaths (average age at death, 57.5 years; 72% men). They then conducted a comprehensive review of lifetime primary-care, inpatient (medical and psychiatric), social-work, forensic, charity, and police records for a subsample of 65 decedents (74% men). Actual care received by this subsample was compared with evidence-based recommendations for the management of alcohol use disorders.

- The majority of deaths were due to alcoholic liver disease (58%) and alcohol-related psychiatric disorders (14%).
- There were 24 lifetime primary-care or hospital outpatient visits among men and only 5 among women.
- Seventy-nine percent of patients received advice to

abstain from alcohol.

- Twenty-three percent received brief interventions, but only 17% complied.
- Fifty-eight percent were referred to specialized treatment, but compliance was poor.

*Comments:* This retrospective study suggests individuals who died from alcohol-related causes did not receive evidence-based care despite ample contact with clinical and other services. The findings are consistent with other research showing that only a small minority of individuals with alcohol use disorders receive high-quality evidence-based care. It is difficult to draw other conclusions from this study due to the small, single-city subsample and sampling of only decedents.

Kevin L. Kraemer, MD, MSc

*Reference:* Morris M, Johnson D, Morrison DS. Opportunities for prevention of alcohol-related death in primary care: results from a population-based cross-sectional study. *Alcohol.* 2012;46(7):703–707.

## HEALTH OUTCOMES

### Light Drinking May Relate to an Increased Risk for Certain Cancers

The majority of observational studies have shown that alcohol intake, especially heavy drinking, increases a number of upper aerodigestive tract and other cancers, and even

lower risk drinking is associated with an increase in the risk of breast cancer. This meta-analysis of 222 articles com-  
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## Light Drinking and Increased Risk of Certain Cancers (continued from page 4)

pared the effects of “light” drinking (an average reported intake of  $\leq 1$  drinks per typical drinking day) versus non-drinking in terms of relative risks for a number of cancers. The analysis included roughly 92,000 light drinkers and 60,000 nondrinkers.

- The authors found small but significant increases in risk from light drinking for cancers of the oral cavity and pharynx (relative risk [RR], 1.17), esophageal squamous cell carcinoma (RR, 1.30), and breast cancer in women (RR, 1.05).
- No increased risk from light drinking was found for cancers of the colorectum, liver, or larynx.

*Comments:* Although the increases in cancer risk found in this study were small, they could lead to large numbers of

cancer cases, since most drinkers are “light” consumers. The statistical methodology was correct and done appropriately; however, there are methodological limitations. For example, both ex-drinkers and never-drinkers were included in the reference group, and estimates of effect were not adjusted based on other lifestyle habits, including smoking. The authors also did not address the net health effects of light drinking. Since alcohol is a known carcinogen, the results remain plausible, but additional studies with fewer limitations are needed to better delineate the potential risks of “light” drinking.

R. Curtis Ellison, MD

*Reference:* Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol*. August 21, 2012 [Epub ahead of print]. doi:10.1093/annonc/mds337

## African-American Adolescents Are Less Likely to Sell or Use Illicit Drugs but More Likely to Be Arrested

African-American youths have higher arrest rates than their white counterparts. To assess the relationship between race, illicit substance use, criminal behaviors, and arrest rates, researchers analyzed data from the National Longitudinal Survey of Youth in 1997 and included 5796 youths who were reinterviewed in 2003. The baseline survey included information on arrests, alcohol or illicit drug use, selling drugs, and other illegal activity. Multivariable analysis took into account family income, urbanicity, and living in a high-crime or high-unemployment area. The youth were divided into 2 age groups: 12–14 years or 15–17 years at baseline.

- African-American youths were more likely than white youths to have been arrested more than once (3.1% versus 1.3% in the younger group; 6.5% versus 4.1% in the older group).
- White youths had higher rates of alcohol and other drug use and were more likely to report drug-selling activity. There was no significant difference between groups in other illegal behaviors.
- In multivariable analysis, African-American youths were significantly more likely to be arrested once (adjusted odds ratio [AOR], 2.18) or multiple times (AOR, 2.20).

- African Americans with arrest histories at baseline were less likely than their white counterparts to have completed high school (AOR, 2.43).

*Comments:* This study sheds some light on the ways in which African Americans are disproportionately involved in the criminal-justice system. The findings are particularly disturbing in that these arrests will have lifelong implications. Unfortunately, the study did not collect data on why the subjects were arrested; while it is likely that many (if not most) of the arrests were for drug-related crimes, we need more detailed data before drawing any conclusions on the implications with regard to US drug laws and the ways in which they are enforced. In the meantime, as clinicians, we need to be aware of this disparity and the affect that it has on vulnerable youth.

Darius A. Rastegar, MD

*Reference:* Kakade M, Duarte CS, Liu X, et al. Adolescent substance use and other illegal behaviors and racial disparities in criminal justice system involvement: findings from a US national survey. *Am J Pub Health*. 2012;102(7):1307–1310.

## HIV AND HCV

### Pretreatment Alcohol Intake and Duration of Pretreatment Abstinence Do Not Impact HCV Treatment Outcomes

Prior studies of alcohol consumption and HCV treatment suggest current and past heavy drinking are associated with treatment failure, which may provide a rationale for withholding HCV treatment or requiring pretreatment abstinence from patients with heavy alcohol use. This retrospective observational study evaluated the relationship between pretreatment alcohol intake and sustained

virologic response (SVR) in a cohort of privately insured patients who initiated HCV treatment between 2002 and 2008. Eligible participants\* underwent a retrospective  
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\*Reasons for ineligibility included the following: not treatment-naïve; left health plan; died; post-transplant; coinfection with HBV or HIV; non-English speaking; too ill; provider recommendation not to participate.

## Pretreatment Alcohol Intake and Abstinence: Impact on HCV Treatment Outcomes (continued from page 5)

assessment of lifetime drinking patterns, which was used to calculate total alcohol consumption (kg) prior to treatment. Multivariable logistic regression analyses adjusted for demographic and viral-related factors.

- Of 421 patients eligible for the study, only 259 (62%) completed study interviews.
- There was no significant association between pretreatment alcohol intake and failure to achieve SVR (adjusted odds ratio [AOR], 1.00).
- There was no significant association between months of abstinence leading up to treatment and failure to achieve SVR (AOR, 0.998).

*Comments:* This study did not find an association between

total lifetime alcohol intake or duration of pretreatment abstinence and HCV treatment failure. Study strengths included a large sample size and detailed measurement of alcohol use. Limitations included a large number of patients who were either ineligible or did not complete the study interview (potential to introduce bias) and a retrospective study design. Nevertheless, results suggest prior heavy alcohol use should not be viewed as a barrier to HCV treatment.

Judith Tsui, MD, MPH

*Reference:* Russell M, Pauly MP, Moore CD, et al. The impact of lifetime alcohol use on hepatitis C treatment outcomes in privately insured members of an integrated health care plan. *Hepatology*. 2012;56(4):1223–1230.

## Decreased Quality of Care for HIV-Infected People Who Use Alcohol and Other Drugs

Combined antiretroviral treatment has had a significant impact on survival of HIV-infected individuals. With HIV now considered a chronic medical condition, providers must consider certain quality indicators (QIs) when caring for HIV-infected patients. Researchers examined the association between self-reported past-year unhealthy alcohol use\* and illicit drug use and quality of HIV care among HIV-infected Veterans Affairs (VA) patients based on 9 QIs. The sample consisted of 3410 HIV-infected patients enrolled in the Veterans Aging Cohort Study (mean age, 49 years; 97% male).

- Twenty-six percent of the sample had unhealthy alcohol use, 29% had illicit drug use, and 12% had both.
- Patients infected with HIV received 82% (standard deviation [SD], 18.9) of the 9 QIs.
- Receipt of QI was lower among patients with unhealthy alcohol use versus those without (59% versus 70%) and

\*Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score  $\geq 4$ .

among patients with illicit drug use versus those without (58% versus 71%). Unhealthy alcohol and illicit drug use were inversely associated with receipt of QI after adjusting for age, gender, race, history of homelessness, diabetes, depressed mood, and study site.

*Comments:* Overall, quality of HIV care in this sample of HIV-infected veterans was high, but it was lower among patients reporting unhealthy alcohol and illicit drug use. Although generalizability may be limited as the sample was primarily men and QIs delivered at non-VA sites are not reflected, this work suggests targeted interventions to improve quality of care for HIV-infected substance users are needed.

Jeanette M. Tetrault, MD

*Reference:* Korthuis PT, Fiellin DA, McGinnis KA, et al. Unhealthy alcohol and illicit drug use are associated with decreased quality of HIV care. *J Acquir Immune Defic Syndr*. 2012;61(2):171–178.

## Methadone Maintenance after Prison Release Reduces HIV Injection-Risk Behaviors but Not Sex-Risk Behaviors

This study analyzed HIV risk behaviors of 211 adult men with opioid dependence after release from prison in Baltimore, MD. Subjects were randomly assigned to 1 of 3 treatment conditions: counseling only (CO), counseling + opioid agonist treatment (OAT) after release (CR), or counseling + OAT initiated while in prison (CM). The primary outcome measure was self-reported participation in drug- and sex-risk behaviors as measured by Texas Christian University's AIDS Risk Assessment (ARA) administered at baseline (30-day recall prior to incarceration) and at several intervals up to 12 months post-release.

- In the entire cohort, there was a significant decline in overall ARA sex-risk score but not in drug-risk score.
- When comparing the 3 treatment conditions, participants in the CR and CM groups had significantly lower drug-risk scores than those in the CO group. Those in the CM group had lower scores than those in the CR

group, but the difference was not statistically significant.

- There was no significant difference in post-release sex-risk scores between the 3 groups.

*Comments:* This study adds to established research on the benefits of providing OAT to opioid-dependent prisoners at the time of release. As would be expected, OAT was associated with less post-release injection-risk behavior. Initiating OAT prior to release may be better in this regard, but this study failed to demonstrate it. As shown in other studies, OAT alone did not appear to have any effect on sex-risk behaviors, although the counseling all subjects received may have had a beneficial effect.

Darius A. Rastegar, MD

*Reference:* Wilson ME, Kinlock TW, Gordon MS, et al. Postprison release HIV-risk behaviors in a randomized trial of methadone treatment for prisoners. *Am J Addict*. 2012;21(5):476–487.

## ETHICAL CONDUCT OF ALCOHOL AND OTHER DRUG RESEARCH: FEATURE ARTICLE

### Ethical Considerations in Research Using the Drug of Addiction as Treatment: What Can Researchers Learn from Heroin Prescription Studies?

Sylvia Baedorf Kassis, MPH

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Alcohol and other drug (AOD) research is rife with ethical quandaries and controversy. Particularly polarizing have been studies investigating the use of the addictive agent as a treatment, such as recent research involving heroin (diacetylmorphine) maintenance therapy. Although not permitted in the US, pharmaceutical diacetylmorphine prescription is being studied in other countries, and many of the ethical considerations of those studies are relevant to any research covering sensitive topics and/or enrolling vulnerable populations. This article provides an overview of the ethical issues surrounding diacetylmorphine prescription research and methods to address those concerns that may be applicable to other AOD research.

#### Background

Research testing the agent of addiction as a potential treatment is not novel. Alcohol has been administered to subjects with alcohol dependence to treat withdrawal,<sup>1</sup> and nicotine has been used as a therapeutic agent to decrease smoking.<sup>2</sup> These studies have not generated enough controversy in the US to halt the research, however; alcohol and nicotine are legal drugs in the US, and, in general, accepted by society. Opioid agonist treatment is a related example. Although not exactly the agent of addiction, opioid agonists (methadone and buprenorphine) are among the most efficacious treatments for opioid (i.e., heroin and/or prescription-opioid) dependence. These agonists are also legal medications, which facilitates their study, although many people remain “against” these treatments.

Heroin addiction is highly stigmatized in the US. Although heroin was developed as a cough suppressant by Bayer Pharmaceuticals in the 1890s and was prescribed as a treatment for opioid dependence in the early 1900s, its use was restricted by the Harrison Narcotic Act in 1914, and by 1919, doctors risked prosecution for prescribing it to people with addiction.<sup>3</sup> Nonetheless, diacetylmorphine has been used as a therapeutic agent on a limited basis in Britain since the early 1960s, and the first reported controlled clinical trial of diacetylmorphine prescription was conducted there.<sup>4</sup>

Over the last 20 years, governments and public-health authorities in Switzerland,<sup>5</sup> the Netherlands,<sup>6</sup> Germany,<sup>7</sup> and Canada,<sup>8</sup> to name a few, have supported the investigation of diacetylmorphine as a treatment for heroin dependence due largely to an alarming increase in HIV transmission among people with injectable drug use<sup>9</sup> and a desire to reduce drug-related crime.<sup>10</sup> In the US, however, the overall attitude toward illicit drug use, and in particular, injection drug use, has blocked the study of diacetylmorphine as a potential treatment for heroin dependence.

Diacetylmorphine prescription, in and of itself, presents several ethical challenges. Even before considering a research study, debates over allocation of resources, reduction in use or consequences versus abstinence as treatment goals, addiction as a medical or social problem, and whether diacetylmorphine prescription unintentionally promotes heroin addiction, would need to be considered. These challenges will not be discussed here; rather, the ethical issues that have been raised in existing diacetylmorphine studies are presented.

#### Considerations for Ethical Research

##### Consent

Informed consent is considered one of the fundamental tenets of ethical research.<sup>11,12</sup> For consent to be valid, it must be voluntary, and the potential subject must be competent. Whether individuals addicted to heroin are capable of consenting to participate in research, especially studies that provide the drug of addiction as a potential treatment, is fiercely debated. Intoxication may impair capacity. A clinical determination can be made as to whether the potential subject is intoxicated. Most people using heroin will have tolerance and also have periods between drug administration when they are not intoxicated despite recent use.

But Charland<sup>9</sup> argues that the compulsive need to seek and use heroin leaves potential subjects with impaired decisional capacity, rendering them incapable of giving valid consent. In contrast, Foddy and Savulescu<sup>13</sup> reject the notion that people with addiction lack free will, arguing that heroin does not present an irresistible force but rather a strong appetitive desire that does not compromise consent. They further assert that a desire to engage in heroin use, a “harmful act,” should not be construed as evidence of irrational or compulsive thinking.<sup>13</sup> The type of study may be relevant here—a study that dispenses carefully measured and regulated amounts of diacetylmorphine at a daily clinic visit may not be a study that a person with heroin addiction would find irresistible, whereas a supply for home use might be associated with impaired decisional capacity. In any case, both authors promote a better consent process—but what should that consist of?

If you determine that the population under investigation is not competent to provide consent, the study may still be able to proceed; however, additional safeguards would have to be incorporated. For example, Charland<sup>9</sup> argued that substitute decision making in the form of a surrogate should be pursued. In cases where there is concern about obtaining valid consent but incompetence is unlikely to be an issue, a

## Ethical Considerations in Research Using the Drug of Addiction as Treatment (continued from page 8)

less stringent approach would be to include an impartial third party or research subject advocate in the process. An additional measure suggested by Foddy and Savulescu<sup>13</sup> is to put sufficient time between the consent process and study participation to prevent craving for the drug or other influences (including the persuasion of researchers) from impacting consent.

### Risk/Benefit Assessment

A thoughtful principal investigator carefully evaluates the potential risks and benefits of a research study, discussion of which should be included as part the consent process. Is the study of diacetylmorphine for heroin addiction considered minimal risk or greater than minimal risk?

Under US Federal Regulations,<sup>14</sup> minimal risk means the probability and magnitude of harm anticipated in the research are not greater than those ordinarily encountered in daily life. The latter part of this definition may be open to interpretation depending on the population under study. What does the standard “ordinarily encountered in daily life” mean in a population engaged in behaviors associated with social stigma, infectious disease risk, and criminal activity that will most certainly be brought to light by research participation? Which is riskier—use of illicitly obtained heroin or use of prescribed diacetylmorphine under strict clinical supervision?

Orr and Wynia<sup>15</sup> argue that researchers must be forthright about whether the primary goal of a study is to give subjects an opportunity to move toward recovery and avoid harms associated with addiction (health risks, financial costs, risk of arrest, etc.) or to reduce societal harms, such as crime. (A study of heroin prescription could be either.) In their view, the avoidance of therapeutic misconception—the belief that a study is for one’s benefit when this is not the case—requires the consent discussion to very clearly address study aims. Although altruistic participation is still possible in research addressing societal harms, the risks associated with a study are likely to be minimized if the primary goal is to benefit the subject.

### Confidentiality Protections

Finally, risk discussion during the consent process will almost certainly include information about confidentiality. Since AOD research is likely to include the collection of sensitive personal information about substance use and illegal activities, there exists the real possibility of direct harm to participants if confidentiality is not protected.<sup>16</sup> Such harms could include risks to employability, insurability, and/or reputation. As a result, US investigators are encouraged to seek a Certificate of Confidentiality<sup>17</sup> to protect research data from compulsory disclosure, such as through a subpoena. Further, it is prudent to collect only the minimum information about subjects necessary to meet the scientific aims of the study.

## Conclusion

There are certainly additional ethical issues to take into account when planning AOD research, particularly a study involving diacetylmorphine prescription (e.g., whether and how to provide financial compensation for participants, what to do after the trial ends, and what to do if results are positive). These have been discussed in relation to Canada’s North American Opiate Medication Initiative (NAOMI) trial<sup>8</sup> but are beyond the scope of this article.

Informed consent, as discussed above, is the paramount characteristic of ethical research, and whether or not heroin addiction renders individuals incompetent to consent must be carefully evaluated. Although diacetylmorphine prescription may not be studied in the US in the foreseeable future, awareness of the fundamental ethical issues inherent in such research may allow researchers to improve how well they incorporate protections into studies exploring similar topics.

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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.

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