Alcohol, Other Drugs, and Health: Current Evidence

JULY–AUGUST 2013

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INTERVENTIONS & ASSESSMENTS

Daily Tenofovir Pre-Exposure Prophylaxis Reduces HIV Transmission among People with Injection Drug Use in Drug Treatment

Pre-exposure prophylaxis with tenofovir/emtricitabine combination or tenofovir alone reduces the incidence of HIV infection from sexual transmission by about half, as long as adherence is adequate. Researchers conducted a randomized, placebo-controlled trial of daily pre-exposure prophylaxis with tenofovir among 2413 people in Bangkok, Thailand who injected drugs in the past year. Study sites were 17 drug treatment clinics that offered a package of HIV prevention interventions and directly observed therapy. Participants chose to receive medication via daily directly observed therapy or monthly visits and could switch monthly.

- At the beginning of the study, 33% of the sample abused methamphetamine, 22% abused heroin, 23% abused midazolam, and 22% were receiving methadone maintenance treatment.
- At the beginning of the study, the placebo group reported more sexual intercourse in the prior 12 weeks among men who had sex with men (6% versus 4%) and sex with a casual partner (40% versus 36%).
- Mean follow-up time was 4 years. Mean adherence was 84% of days. Participants received directly observed therapy 87% of the study days.
- Forty-five percent of participants reported at least one incidence of injection drug use during follow-up.
- There were 17 HIV seroconversions (incidence of 0.35 per 100 person-years) in the tenofovir group and 35 (0.68 per 100 person-years) in the placebo group, resulting in a 49% reduction in HIV incidence. HIV incidence did not differ until 36 months of follow-up.
- Nausea, vomiting (8% versus 5%), and increase in ALT (53% versus 49%) were more common in the tenofovir group.

Comments: As in previous trials in sexual risk groups, in this trial among people who inject drugs pre-exposure prophylaxis cut HIV transmission in half. Adherence was key and likely bolstered by the study sites that were drug treatment centers that offered daily observed dosing and methadone maintenance. Analyses did not account for some imbalance at baseline in sexual risk that favored the tenofovir group.

Alexander Y. Walley, MD, MSc

Reference: Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2013;381(9883):2083–2090.

Screening and Brief Intervention: USPSTF Update Affirms Recommendations and Highlights Evidence Gaps

The U.S. Preventive Services Task Force (USPSTF) has again made recommendations—to update those previously issued in 1996 and 2004—regarding screening and behavioral counseling for unhealthy alcohol use in primary care settings. These new recommendations are essentially unchanged from those of 2004.

- The Task Force recommends that clinicians screen adults and provide persons engaged in risky or hazardous drinking

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Screening and Brief Intervention: USPSTF Update Affirms Recommendations and Highlights Evidence Gaps

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(defined as drinking that results in an increased risk for health consequences) with brief behavioral counseling interventions.
- The Task Force also concludes that the current evidence is insufficient to screen adolescents.

The recommendation to screen adults is "grade B," meaning that there is high certainty that the net benefit is moderate. To screen, the USPSTF prefers validated single-item screens, the Alcohol Use Disorders Identification Test (AUDIT), and the first 3 items of the AUDIT (AUDIT-C). A positive screening test should be followed by a brief counseling intervention (at least 6–15 minutes), which is most likely to have efficacy if it is multi-contact. There is little evidence for efficacy of very brief single interventions.

Comments: The evidence and recommendations are clear though very circumscribed: for adults in primary care with hazardous but not harmful or dependent alcohol use, screening and brief—but not too brief—multi-contact counseling can reduce consumption. The USPSTF also highlighted the unknowns:
- Impact on morbidity, mortality, and quality of life.
- Efficacy for people with alcohol use disorders ("Limited evidence suggests that brief behavioral counseling interventions are generally ineffective as singular treatments for alcohol abuse or dependence," an observation that leaves clinicians in a quandary when they identify such persons by screening).
- Efficacy for adolescents.

Unfortunately, the USPSTF missed an opportunity to correct its prior poor choice to use the term "misuse." Those with alcohol dependence may take issue with this term. For clinicians, the fact that "misuse" is sometimes used to refer to risky use and at other times used to refer to dependence (i.e., "severe misuse," according to the U.S. Veterans Health Administration) is confusing at best. Little is new in this USPSTF statement, but it does again recommend a practice that should be widely disseminated.

Richard Saitz, MD, MPH

Reference: Moyer VA on behalf of the U.S. Preventive Services Task Force. Screening and Behavioral Counseling Interventions in Primary Care to Reduce Alcohol Misuse: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. May 14, 2013 [Epub ahead of print]. doi:10.7326/0003-4819-159-3-201308060-00652.

Smoking During Medically Managed Opioid Withdrawal is Associated with Increased Craving for Opioids and Nicotine

Over 80% of people with opioid addiction smoke tobacco. Smoking rates remain high among people who undergo medically managed withdrawal (detoxification). It is not known if smoking cessation during opioid detoxification treatment impacts craving, withdrawal symptoms, or subsequent substance use. Very low doses of naltrexone (0.125 mg–0.25 mg) given concurrently to patients receiving methadone for detoxification has been associated with reduced opioid withdrawal and craving. Using data from a randomized clinical trial of very low-dose naltrexone administered during detoxification, researchers conducted an observational study of craving, opioid treatment completion, and substance use in the next week among 174 subjects categorized as in-treatment smokers, nonsmokers, and smokers not allowed to smoke. Smoking cessation counseling and

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pharmacotherapy were not offered as part of treatment.

- In-treatment smokers had more severe opioid craving scores—but not more severe opioid withdrawal scores—than non-smokers and smokers not allowed to smoke.
- In-treatment smokers had higher cigarette craving scores than smokers who were not allowed to smoke.
- In-treatment smokers were less likely to complete detoxification treatment (59% versus 79%) and smoked more cigarettes in the week after treatment (20 versus 13 per day) than smokers not allowed to smoke. No differences were found in use of opioids, alcohol, cocaine, or cannabis.
- Among the in-treatment smokers, those treated with very low-dose naltrexone had lower opioid withdrawal and craving scores than those receiving placebo.

Comments: This study provides preliminary evidence that smoking cessation during opioid detoxification treatment may improve both opioid and nicotine addiction outcomes by reducing craving. Furthermore, among those who do smoke during opioid detoxification, very low-dose naltrexone may attenuate the disadvantages of continuing to smoke during treatment. Randomized clinical trials of smoking cessation and very low-dose naltrexone are warranted to determine whether they can improve opioid and nicotine addiction outcomes.

Alexander Y. Walley, MD, MSc

Reference: Mannelli P, Wu LT, Peindl KS, Gorelick DA. Smoking and Opioid Detoxification: Behavioral Changes and Response to Treatment. *Nicotine Tob Res*. Apr 9, 2013 [Epub ahead of print]. PMID: 23572466.

Trends in Ambulatory Care for People with Substance Use Disorders

The extent to which behavioral therapy and pharmacotherapy are used in U.S. ambulatory care to treat people with substance use disorders is not known. In this brief report, researchers studied data from 2 large, nationally representative, cross-sectional surveys of physicians to identify ambulatory visits from 2001 through 2009 with alcohol and/or drug use disorders (abuse, dependence, intoxication, or withdrawal) as a reason for the visit. Behavioral therapy was defined as provision of mental health counseling, stress management, or psychotherapy at the visit. Pharmacotherapy was defined as provision of naltrexone, disulfiram, acamprosate, methadone, or buprenorphine at the visit.* The complex survey design allowed for national estimates.

- Ambulatory visits for substance use disorders increased from 10.6 million in 2001–2003 to 18 million in 2007–2009; of these, visits for opioid use increased from 772,000 to 4.4 million.
- Behavioral therapy was provided in about 60% of visits and did not change over time.
- Pharmacotherapy was provided in 643,000 visits (6% of total) in 2001–2003 and 3.9 million visits (22% of total) in 2007–2009, with methadone and buprenorphine comprising 76% of medications prescribed.
- No treatment for substance use disorders was provided in 36% of visits and did not change significantly over time.

* In a personal communication (6/14/2013), Dr. Frank notes: "Methadone recorded in our study likely represents 1) methadone on the patient's medication list but not prescribed by the treating physician, or 2) methadone treatment centers captured within [the survey] sampling frame." Methadone is not approved for the treatment of opioid dependence through physicians' offices, only via opioid treatment programs.

Comments: This study indicates a national increase in ambulatory care visits for substance use disorders from 2001 through 2009. It is not clear if this is due to an increase in the underlying population prevalence of substance use disorders, better recognition and coding by providers, or greater care seeking. Certainly, the pharmacotherapy data suggest the substantial upward trend for opioid use disorders may be due to increased provision of buprenorphine, which is encouraging. Although appropriateness of management cannot be discerned from these data, the large number of individuals who received no treatment suggests an opportunity for improving care.

Kevin L. Kraemer, MD, MSc

Reference: Frank JW, Ayanian JZ, Linder JA. Management of substance use disorders in ambulatory care in the United States, 2001–2009. *Arch Intern Med.* 2012;172(22):1759–1760.

HEALTH OUTCOMES

Alcohol Use Disorders: More Deadly Than Previously Thought

Alcohol use disorders (AUDs)—comprising alcohol dependence and abuse—affect up to 12% of men and 5% of women in the United States. A seminal review of AUD and all-cause mortality from 1998 indicated a standardized mortality ratio of 1.8 for men and 3.8 for women, but

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Alcohol Use Disorders: More Deadly Than Previously Thought (continued from page 3)

many studies have appeared since then. This meta-analysis of studies up to August, 2012 seeks to update those findings.

- Eighty-one studies included 221,683 observed deaths among 853,722 people with AUDs.
- The overall relative risk of death was 2.98 for men and 4.64 for women.
- Among treatment samples with diagnosed AUD, relative risk of death was 3.38 for men and 4.57 for women.
- Among people aged 40 or younger, the relative risk of death increased 9-fold for men and 13-fold for women.

Comments: All-cause mortality from alcohol use disorders is higher than previously estimated. The higher risk among treatment samples is probably the result of higher severity of AUDs and more comorbidity, whereas the higher risk among young people is likely the result of lower mortality among the age-specific general population. It remains uncertain whether earlier identification and intervention could reduce these fatalities.

Peter D. Friedmann, MD, MPH

Reference: Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. *Addiction.* April 30, 2013 [Epub ahead of print]. doi: 10.1111/add.12231.

Heavy Episodic Drinking in Young, Healthy Adults Increases Risk for Cardiovascular Disease

Heavy episodic (binge) drinking is broadly defined as consumption of more than 4 to 5 standard drinks (13 g alcohol/drink) in a two-hour period. Among adults, heavy episodic drinking is associated with an increased risk of cardiovascular events. This increased risk may be explained, in part, by alcohol's role in endothelial dysfunction. Heavy episodic drinking is common among young, healthy adults with more than half of college students who consume alcoholic beverages reporting it. The purpose of this investigation was to determine whether young adults who participate in heavy episodic drinking have macrovascular and microvascular dysfunction and increased risk of cardiovascular disease compared with their nondrinking counterparts. The authors investigated macrovascular changes via brachial artery endothelial dependent flow mediated vasodilation (FMD) and flow independent nitroglycerin-mediated dilation, and microvascular changes via vasoreactivity of resistance arteries (isolated from gluteal fat biopsies) in 18 to 25-year-old nondrinkers (N=17) and those who participate in heavy episodic drinking (N=19).

- Subjects with heavy episodic drinking reported 6 +/- 1 heavy episodic drinking episodes per month for an average of 4 +/- 0.6 years.
- FMD was 8% (+/- 0.7) lower and nitroglycerin-mediated dilations were 20% (+/- 2) lower in people with heavy episodic drinking compared with nondrinkers.
- Two of three measures of vasoreactivity of resistance arteries were no different between the two groups.

Comments: This study confirmed that heavy episodic drinking has macrovascular and some microvascular consequences in a sample of young, healthy adults, suggesting an increased risk of cardiovascular events. Given the cross-sectional design and small sample size, these data should be confirmed in future studies.

Jeanette M. Tetrault, MD

Reference: Goslawski M, Piano MR, Bian JT, et al. Binge Drinking Impairs Vascular Function in Young Adults. *J Am Coll Cardiol.* April 23, 2013 [Epub ahead of print]. doi: 10.1016/j.jacc.2013.03.049.

Participation in Football and Wrestling is Associated with Nonmedical Use of Opioid Medications Among Adolescents

The prescribing of opioids and the nonmedical use of prescription opioids among adolescents in the United States has grown over the past 15 years. Participation in sports is associated with injuries that may lead to prescribed and nonprescribed opioid use. Data from the annual Monitoring the Future cross-sectional survey of U.S. 8th and 10th grade students in 2010 and 2011 were analyzed for an association between participation in sports and nonmedical use of prescription opioids (NMUPO).

- Overall, 5.5% of 13,636 respondents reported NMUPO in the past 12 months. Those who participated in any competitive sport did not have significantly higher rates of NMUPO (adjusted odds ratio [AOR], 1.17).
- Participation in football (AOR, 1.50) and wrestling (AOR, 1.49) in particular were associated with a higher rate of NMUPO. Other sports were not associated with higher rates, including ice hockey (AOR, 0.88) and soccer (AOR, 1.04).
- Hydrocodone (combined with acetaminophen) and oxycodone were the most prevalent prescription opioids used nonmedically.
- Other factors associated with NMUPO included nonurban residence, female gender, white race, having ever

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Participation in Football and Wrestling is Associated with Nonmedical Use of Opioid Medications Among Adolescents (continued from page 4)

been suspended from school and being in 10th grade (compared with 8th grade).

Comments: This study suggests that participation in certain sports is associated with nonmedical prescription opioid use. The authors cite previous research showing that football players and wrestlers have the highest rate of injury among high school athletes to explain why these two sports stood out. While much of this use is probably self-treatment of pain resulting from injuries, it raises the concern that for a minority this will lead to serious problems, including addiction and overdose.

Darius A. Rastegar, MD

Reference: Veliz PT, Boyd C, McCabe SE. Playing through pain: sports participation and nonmedical use of opioid medications among adolescents. *Am J Pub Health.* 2013;103 (5):e28–30.

Reporting of Methadone-Associated Cardiac Arrhythmias has Increased

Opioid-related deaths, which have increased substantially since the 1990s, disproportionately involve methadone. Methadone prolongs the corrected QT interval (QTc) in some patients, which increases the risk of torsade de pointes—a potentially fatal cardiac arrhythmia. In this study, researchers used data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) to describe methadone-related cardiac arrhythmia events between 1997 and 2011. They assessed whether reporting increased after the publication of a 2002 report describing an association between methadone and torsade de pointes and whether risk for arrhythmia increased with the concomitant use of methadone and other medications.

- Of 11,015 methadone-related adverse events between 1997 and 2011, 1646 (15%) were for cardiac arrest or ventricular arrhythmia and 379 (3%) were for torsade de pointes or prolonged QTc.
- Death occurred in 42% of cardiac arrest or ventricular arrhythmia events and 11% of torsade de pointes or prolonged QTc events.
- Reporting of methadone-associated torsade de pointes and prolonged QTc increased almost twelvefold from before to after the 2002 publication.
- The antiretrovirals lamivudine, ritonavir, and zidovudine were the 3 most common concomitant drugs in methadone-associated torsade de pointes and prolonged QTc events.

Comments: These findings highlight the fact that cardiac arrhythmia can be a significant adverse consequence of the provision of methadone. The increase in reporting over time may have been influenced by the 2002 report, but increased methadone prescribing may also be a contributing factor. The possibility of increased risk among HIV-infected patients receiving antiretrovirals is intriguing, but may just reflect a greater likelihood for HIV-infected patients to be prescribed methadone. I agree with the authors that improved physician training on the risks of long-acting opioid therapy is needed.

Kevin L. Kraemer, MD, MSc

Reference: Kao D, Bartelson BB, Khatri V, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997–2011. *Ann Intern Med.* 2013;158:735–740.

Relation of Alcohol Intake to the Risk of Dying from Cancer

In this study, researchers performed a meta-analysis relating alcohol consumption to all-cancer mortality based on almost 50,000 deaths reported in the literature from 18 prospective cohort studies. The authors report the following:

- In comparison with abstainers or people with occasional alcohol use, the average consumption of ≥50 g of alcohol per day (approximately 4 U.S. standard drinks) was associated with an estimated 32% increased risk of dying from cancer.
- There was no significant increase in the estimated risk of cancer death for subjects classified as "moderate drinkers" (defined in this study as people who consume 12.6 g to 49.9 g of alcohol per day).
- There was a slight but statistically significant *decrease* in cancer mortality risk among "light drinkers" (defined in this study as people who consume ≤12.5 g of alcohol per day). With adjustment for source of cohort, geographic area, and potential related factors, for people with "light" alcohol use the relative risk for cancer death among men was 0.91; among women it was 0.94.

Comments: The decrease in all-cancer deaths for people with "light" alcohol use is somewhat surprising, but it is

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Relation of Alcohol Intake to the Risk of Dying from Cancer (continued from page 5)

possible that misclassification of cause of death (e.g., attributing a cardiovascular-related death to an underlying cancer) or residual confounding could play a role. On the other hand, in this large meta-analysis the only significant *increase* in risk in cancer mortality was among people who consume ≥50 g of alcohol per day. This suggests that the overall risk of death from cancer associated with alcohol consumption may be primarily from heavy alcohol use.

R. Curtis Ellison, MD

Reference: Jin M, Cai S, Guo J, et al. Alcohol drinking and all cancer mortality: a meta-analysis. *Ann Oncol.* 2013;24(3):807–816.

Systematic Review of Opioids for Pain and Opioid Dependence: The Risks Cannot be Estimated

The epidemic of prescription opioid dependence in the United States has raised concern about whether management of non-cancer pain with opioids is to blame. This systematic review examined 135 potentially relevant studies of this association. Data were extracted from 17 studies that reported the incidence or prevalence of opioid dependence in patients prescribed opioids for treatment of acute or chronic pain. Most studies included adult patients with chronic non-malignant pain; two also included patients with cancer pain.

- Studies were very heterogeneous and of very low quality.
- Only one study included patients with a previous history of drug dependence.
- Incidence ranged from 0 to 24% (median 0.5%).
- Prevalence ranged from 0 to 31% (median 4.5%).

*Comments***:** The authors conclude that "available evidence suggests that opioid analgesics for chronic pain conditions are not associated with a major risk for developing dependence," but admit that the quality of the evidence is very weak. A scathing critique (McAuliffe, 2013) emphasizes that "studies with very low methodological quality undermine the scientific and medical value of a systematic review." Unfortunately for clinicians, the existing literature is unable to estimate the incidence of iatrogenic opioid dependence among patients receiving treatment for pain. Better primary research is clearly needed.

Peter D. Friedmann, MD, MPH

References: Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction.* 2013;108(4):688–698.
McAuliffe WE. A critique of Minozzi et al.'s pain relief and dependence systematic review. *Addiction.* 2013;108(6):1162–1169.

Subarachnoid Hemorrhage after Cocaine Use Associated with Aneurysm Re-Rupture and Death

Cocaine use has been linked to aneurysmal subarachnoid hemorrhage (aSAH). This retrospective review of all patients admitted with aSAH to Johns Hopkins medical institutions over 2 decades sought to examine the impact of recent cocaine use on initial presentation, complications, and outcomes. Of the 1134 aSAH patients, 142 (13%) had recent cocaine exposure identified by a urine toxicology test or self-reported cocaine use within 72 hours. Compared to those without known recent cocaine use:

- People with cocaine use were younger (mean age 49 versus 53).
- Aneurysm re-rupture incidence was higher among people with cocaine use (8% versus 3%).
- In-hospital mortality for people with cocaine use was 3 times higher in multivariable analysis and mortality rates remained higher even after exclusion of patients from both cohorts with aneurysm re-rupture (25% versus 16%).

Comments: Cocaine use is associated with higher in-hospital mortality after aSAH, likely due in part to higher rates of aneurysm re-rupture. Patients presenting with aSAH who have recently used cocaine may require closer monitoring. Efforts to reduce risk for aneurysm re-rupture, such as blood pressure control or even antifibrinolytic medications, warrant further investigation.

Nadia Fairbairn, MD,† and Richard Saitz, MD, MPH

†Contributing Editorial Intern and Resident in Internal Medicine, University of British Columbia, Vancouver, Canada.

Reference: Chang TR, Kowalski RG, Caserta F, et al. Impact of acute cocaine use on aneurysmal subarachnoid hemorrhage. *Stroke.* 2013;44(7):1825–1829.

HIV AND HCV

Persons Coinfected with HIV and Hepatitis C have Liver Fibrosis Measures Equal to Those with Hepatitis C Only who are Nearly a Decade Older

Persons with HIV infection manifest an increased risk for a variety of conditions at ages younger than those without HIV. Researchers analyzed data from a cohort of people with current and former injection drug use in Baltimore to investigate whether HIV reduces the age at which hepatitis

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Persons Coinfected with HIV and Hepatitis C have Liver Fibrosis Measures Equal to Those with Hepatitis C Only who are Nearly a Decade Older (continued from page 6)

C virus (HCV)-associated liver disease occurs. The study included 1176 participants who had positive antibodies for HCV and at least one valid liver fibrosis assessment by transient elastography.

- Overall, 13.9% of participants had cirrhosis at baseline and 10.6% had clinically significant fibrosis. Liver fibrosis was associated with older age, HIV infection, black race, having ever using alcohol daily, chronic hepatitis B infection, greater body mass index, and higher HCV viral load level. In multivariable analysis, liver fibrosis remained significantly associated with all of these factors, except race.
- Among those infected with HIV, lower CD4 counts and higher HIV viral loads were associated with liver fibrosis.
- Participants with HIV had liver fibrosis measurements equal to those without HIV who were, on average, 9.2 years older.

Comments: This study indicates that people with current and former injection drug use who are coinfected with HIV and hepatitis C have a more rapid progression to fibrosis. Another novel finding was that HCV viral load level was also associated with fibrosis. Characteristics associated with fibrosis that can be addressed in patients include alcohol use, hepatitis B prophylaxis, and excessive weight gain. The association between age and progression likely reflects the duration of infection. Now that persons with HIV are surviving longer and more effective treatments for HCV have become available, the need for expanded delivery of treatment has become more urgent.

Darius A. Rastegar, MD

Reference: Kirk GD, Mehta SH, Astemborski J, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. *Ann Intern Med.* 2013;158 (9):658–666.

Response to HCV Treatment Among People with Heavy Alcohol Use is Similar to Those who Abstain

Management of hepatitis C virus (HCV) infection among people with heavy alcohol use is often challenging. In a sample of patients with chronic HCV infection (defined by detectable HCV RNA for at least 6 months), French researchers conducted a retrospective case-control study* to compare access to antiviral therapy and response to treatment between patients with and without heavy alcohol use (≥60 g, or ≥4–5 U.S. standard drinks, per day for at least 1 year at the time of referral versus below 40 g per day without previous periods of heavy use). Sixty-nine participants with heavy alcohol use were included and matched to controls. Of those, 31 received treatment.

- The percentage of patients with a recommendation for treatment according to French guidelines was similar in cases and controls (75%).**
- The proportion of patients accessing treatment was lower among those with heavy alcohol use than those without (45% versus 71%).
- Among people with heavy alcohol use, the main reason not to treat despite indication was the absence of abstinence. Factors associated with treatment access were fibrosis stage, employment, and alcohol consumption of ≤170 g per day.
- Of those who received antiviral therapy, a sustained virological response was obtained in 32% of people with heavy alcohol use versus 26% of controls.
- Among patients with heavy alcohol use, response to treatment was similar whether or not patients were abstinent for 6 months before treatment initiation.

* To compare access to treatment, participants were matched according to stage of fibrosis, genotype, and, when possible, gender and age. To compare response to treatment, participants were matched to type of antiviral therapy, genotype, and, when possible, stage of fibrosis, gender, and age.
** HCV genotype 2 or 3 or bridging fibrosis.

Comments: This case-control study suggests that, when delivered by a multidisciplinary team (including an addiction specialist), HCV treatment among people with heavy alcohol use is feasible and allows for satisfactory response to treatment. These data call for efficacy trials of integrated care among patients with HCV and recent heavy drinking.

Nicolas Bertholet, MD, MSc

Reference: Costentin CE, Trabut JB, Mallet V, et al. Management of hepatitis C infection in heavy drinkers. *Alcohol Alcohol*. 2013;48(3):337–342.

FEATURE ARTICLE: ETHICAL CONDUCT OF ALCOHOL AND OTHER DRUG RESEARCH

Confidentiality Protections in Research Involving People with Substance Use Disorders

Sylvia Baedorf Kassis, MPH

Clinical Research Manager, Center for Human Genetic Research and Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Boston, MA, USA

As described in previous issues of this newsletter, there are numerous ethical considerations surrounding the conduct of research involving people with substance use disorders.[1,2,3] Weighing the potential risks of the studies' interventions, as well as determining capacity and obtaining informed consent, are just a few of the ethical issues. Protecting the confidentiality of research subjects and their data is another imperative.

Under the Code of Federal Regulations 45 CFR 46.111 – Criteria for IRB Approval of Research, the seventh criterion requires "adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data" in human subjects research.[4] Thus, while all researchers must afford their subjects confidentiality protections, given the inherent vulnerability of individuals who are most likely to be recruited into research on substance use disorders and the sensitive information likely to be collected, additional attention must be paid to protecting this kind of research data from breaches as well as subpoena for use in legal proceedings.

According to the National Institutes of Health (NIH), *sensitive information* "includes (but is not limited to) information relating to sexual attitudes, preferences, or practices; information relating to the use of alcohol, drugs, or other addictive products; information pertaining to illegal conduct; information that, if released, might be damaging to an individual's financial standing, employability, or reputation within the community or might lead to social stigmatization or discrimination; information pertaining to an individual's psychological well-being or mental health; and genetic information or tissue samples."[5]

While it is important to acknowledge that CFR 42 Part 2 – Confidentiality of Alcohol and Drug Abuse Patient Records[6] is a regulation that provides some guidance on the protection of clinically derived information, it does not speak to the more conservative provisions that are necessary to safeguard sensitive research data. The bar is set much higher in conduct of research studies because, in general, the information being collected is not primarily for the care and treatment of the individual patient, but rather for the purpose of answering a research question and contributing to generalizable knowledge. This article discusses the features that are particularly salient to ensuring the protection of research subjects who participate in studies on substance use disorders.

Anonymous Versus Identifiable Research Data

Research studies frequently involve the collection of sensitive information beyond that which would usually be collected in a clinical context and included in a medical record. The onus is on researchers to safeguard this data to the greatest extent possible, especially if it is in any way identifiable. A complete understanding of the difference between anonymous and identifiable research data is essential to devising the most appropriate plan to protect research subjects' confidentiality.

Identifiable research data contains identifying characteristics or a code that links to identifying characteristics, even when that code is stored separately. According to the NIH, *identifying characteristics* include a subject's "name, address, social security or other identifying number, fingerprints, voiceprints, photographs, genetic information or tissue samples, or any other item or combination of data about a research participant which could reasonably lead, directly or indirectly by reference to other information, to identification of that research subject."[7] In contrast, *anonymous* means that there are no identifying characteristics and there exists no link to any identifying characteristics. Simply put, if a researcher is able to link research data to an individual subject's identity, that data is identifiable. Thus, coded data linked to a master list that includes identifying characteristics is not considered anonymous and requires special confidentiality protections.

Strategies to Improve Protection

Conduct anonymous research studies

Whenever possible, researchers should avoid collecting direct identifiers such as name, medical record number (MRN), social security number (SSN), date of birth, etc. While conducting a study anonymously is likely only feasible in studies involving a single study visit that does not require any follow-up activities—whether they be additional study visits or repeated reviews of the subjects' medical records—collecting anonymous research data is the best way to protect research subjects' confidentiality. Although most studies that require more than one participant contact will not be able to be done anonymously, some can be done this way by using a participant generated code or password that allows linking of the data collected at the contacts without identifying the participant. The downside is that if the participant forgets the code or cannot easily regenerate it, the ability to link to the data is lost.

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Another option to consider when conducting research of a more ethnographic/qualitative nature is to ask subjects to assign themselves a pseudonym, which ultimately also renders their data anonymous.[8] This is most appropriate in research where follow-up occurs but personally identifying characteristics (like name or date of birth) and linking to other records (via MRN or SSN) are not required to answer the research question. In these cases, the researchers never learn the identities of their subjects even when working with them directly and can more easily safeguard their confidentiality.

Destroy the link to identifying characteristics as soon as possible

When some identifiers are required, for example, to link research subjects' survey responses to information in the medical record, one safeguard is to conduct the study in such a way that the data is anonymized as soon after collection as possible. This means that there would be no link to identifying characteristics and, therefore, no way to collect additional data. When considering this option, researchers often express concerns about being unable to confirm or correct data points and/or add new data to their analyses if an error is found or additional hypotheses emerge. While these are legitimate questions, paying careful attention to the development of complete data collection tools and implementing quality control safeguards during data entry can minimize these concerns. In deciding whether or not, and when, to anonymize their data, researchers should take into account the risk-benefit ratio of the study, thereby balancing the need for confidentiality protections with the study's scientific and analytic needs and the value of the research's contribution to generalizable knowledge.

Take precautions to prevent breaches in confidentiality

In many cases it is simply not feasible to conduct a research study without collecting any identifiers about research subjects. When the gathering of identifying characteristics is absolutely necessary, researchers should consider the following:

- Using passwords to protect all electronic data and securing paper records in locked cabinets and offices.
- Limiting the number of individuals who have access to identifying characteristics and master codes, whether electronic or paper records.
- Storing any master code files that contain identifiers separately from study data.
- Ensuring paper research records and documents (e.g., surveys, data collection forms, etc.) are coded, do not contain any identifying characteristics, and are stored separately from any master code files that contain identifiers.
- Never traveling between study sites or to study visits with identifiable information and the research records stored within the same folder or bag.
- If sending letters or postcards to research subjects, avoiding making any details about the study visible to others at the recipient's address. If initiating contact via phone, taking care not to reveal details of study participation if the subject is unavailable or a voice message has to be left.

Protect research data from subpoena

Since research on substance use disorders often includes the collection of information beyond what would normally be recorded in a clinical context, extra protection of identifiable research information from forced disclosure is recommended through a NIH-issued Certificate of Confidentiality (COC).[9] All types of research studies—regardless of funding source or status—that collect identifiable research data on sensitive matters are eligible to apply. Retroactive to the start of the study, a COC permits anyone on the research team who has access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, COCs help achieve the research objectives and promote participation in studies by helping to assure confidentiality and privacy to participants.

Conclusion

The protection of subject confidentiality is essential in all research studies, but is particularly important when enrolling people into research on substance use disorders. Understanding the difference between anonymous and identifiable data is necessary for researchers to implement the most appropriate plan to protect their subjects' research data. Some of the best practices in protecting the confidentiality of sensitive data have been elucidated above and include collecting anonymous research data or anonymizing it as soon as possible, instituting precautions to prevent breaches of confidentiality, and obtaining a Certificate of Confidentiality to prevent subpoena of subjects' personal information. A thoughtful and well-executed plan of protection is an ethical imperative.

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Contact Information:
Alcohol, Other Drugs, and Health: Current Evidence
Boston University School of Medicine/Boston Medical Center
801 Massachusetts Ave., 2nd floor
Boston, MA 02118