Alcohol, Other Drugs, and Health: Current Evidence

SEPTEMBER–OCTOBER 2013

INTERVENTIONS & ASSESSMENTS

Counseling General Hospital Patients Reporting Heavy Alcohol Use: Single Brief Sessions Not Enough; More Not Clearly Better

Prior systematic reviews have identified mixed results regarding the efficacy of brief counseling interventions for heavy drinking in general hospital patients. The most recent Cochrane Review found brief interventions associated with short-term reductions in alcohol consumption, although effects disappeared when the methodologically weakest study was excluded from analysis, and the reviewers aggregated interventions of varying intensity. This review grouped studies by intervention intensity (number and duration of sessions) and strategy (face-to-face versus pamphlets), summarizing their impact on alcohol consumption and numerous secondary outcomes. Twenty-two randomized and nonrandomized trials met the inclusion criteria for a total of 5307 patients in general hospitals internationally. The heterogeneity of trials precluded meta-analytic techniques. The authors found:

- When compared with usual care, the 12 studies of single-session interventions found largely no impact on alcohol consumption, while the 5 studies of 2–3 session interventions found some decreased alcohol consumption among people with "non-dependent" alcohol use.
- Three studies comparing a 2–3 session intervention with a single-session intervention (N=2), and another study comparing a longer versus shorter 2-session intervention did not find reduced alcohol consumption between groups.
- Two studies comparing a brief intervention with self-help literature found no difference in alcohol consumption.
- No studies found that counseling had any impact on other outcomes.

Comments: On the one hand, trials comparing multiple intervention sessions to usual care were positive, suggesting that interventions of more than a single session may be effective among this population. On the other hand, the few trials that compared interventions of different intensities found no benefit for greater intensity. The question of how best to intervene with hospital inpatients who have heavy alcohol use remains open.

Hillary Kunins, MD, MPH

Reference: Mdege ND, Fayter D, Watson JM, et al. Interventions for reducing alcohol consumption among general hospital inpatient heavy alcohol users: a systematic review. *Drug Alcohol Depend.* 2013;131(1–2):1–22.

Implications of Team-Based Approach to Screening and Brief Intervention for Unhealthy Alcohol and Other Drug Use

The use of health educators to perform screening and brief intervention (SBI) for unhealthy alcohol and other drug use among primary care patients has the potential to decrease the burden on clinicians. This study sought to determine how reliably primary care clinicians' notes document SBI as delivered by a health educator. Researchers performed a retrospective chart review of the Massachusetts Screening, Brief Intervention and Referral to Treatment (MASBIRT) program. Health educators

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Implications of Team-Based Approach to Screening and Brief Intervention for Unhealthy Alcohol and Other Drug Use (continued from page 1)

completed a paper communication form to convey the results of the screening and brief intervention to clinicians. Of 3905 unique primary care patients screened by health educators during the 6-month study period, 13% (495 patients) screened positive for unhealthy alcohol (>3 drinks in a day for women, >4 drinks in a day for men) or other drug use.

- Sixty-nine percent of primary care clinician notes documented information related to screening data obtained by health educators.
- Clinician documentation was 100% for patients with likely dependent alcohol or other drug use, but only 64% and 59% for those with risky alcohol or other drug use, respectively.
- Clinician documentation of cocaine or opioid use was greater than that of alcohol or marijuana use.

Comments: A team-based approach to health care is an appealing option. However, this study demonstrates that sharing of information among team members may suffer as a result of divisions of labor. The impact of these "handoffs" on care delivery is not known. Electronic medical records with shared documentation capabilities may address some of this fragmentation of care.

Jeanette M. Tetrault, MD

Reference: Kim TW, Saitz R, Kretsch N, et al. Screening for unhealthy alcohol and other drug use by health educators: do primary care clinicians document screening results? *J Addict Med.* 2013;7(3):204–209.

Knowing Someone Who is Receiving Buprenorphine Therapy May Increase Interest in Seeking Treatment

Buprenorphine is a safe and effective treatment for opioid dependence, but some eligible individuals do not utilize it because they are either unaware or not interested. In this study, researchers conducted a cross-sectional interview of 158 participants (mean age 48 years, 69% male, 71% Latino, 91% lifetime history of heroin use) in an urban needle exchange program to assess the association of exposure and awareness with interest in buprenorphine treatment.

- Most (70%) participants were aware of buprenorphine treatment but only 32% had direct exposure (prior treatment with buprenorphine), and 31% had indirect exposure (knew someone treated with buprenorphine). Fifty-six percent had an interest in buprenorphine treatment.
- In analyses adjusted for history of methadone maintenance and current cocaine use, indirect exposure to buprenorphine was significantly associated with interest in treatment. Awareness of and direct exposure to buprenorphine treatment were not associated with interest in treatment.

Comments: This study found that high-risk individuals in a needle exchange program were generally aware of buprenorphine and a little over half expressed an interest in treatment. The finding that awareness of and direct exposure to buprenorphine treatment are not associated with interest in treatment is surprising and may reflect lack of accurate knowledge or a prior adverse experience with buprenorphine. The association of indirect exposure with interest in buprenorphine treatment suggests that counseling by peers with treatment experience might be a useful method to increase uptake.

Kevin L. Kraemer, MD, MSc

Reference: Fox AD, Shah PA, Sohler NL, et al. I Heard About it From a Friend: Assessing Interest in Buprenorphine Treatment. *Subst Abuse.* 2013 [Epub ahead of print]. doi: 10.1080/08897077.2013.804484.

Health Care Professionals' Attitudes Toward Patients with Substance Use Disorders Improve with Experience

This systematic review focused on studies assessing health care professionals' attitudes toward patients with substance use disorders (SUD) and their effect on health care delivery. The authors identified 28 studies conducted in Western countries published between 2000 and 2011. Study populations included nurses, professionals from addiction and mental health institutions, and physicians. The authors' general conclusions were:

- A high proportion of health care professionals had a negative attitude toward patients with SUD compared with other patient groups, such as those with diabetes or mental illness.
- Attitudes toward people with illicit drug use in particular were strongly negative and health care providers preferred for these patients to be cared for by addiction specialists.
- Many health care professionals reported poor knowledge of SUD and felt they lacked the education and skills to care for patients with these disorders. Training and experience in caring for populations with these disorders were associated with increasingly positive attitudes.
- Institutional support for health care providers also contributed to an increase in positive attitudes.
- Consequences of attitudes were seldom assessed. One study showed that perceived discrimination was associated with less treatment completion and another that the care provided to patients with SUD was suboptimal.

Comments: Some studies showed positive attitudes toward patients with SUD, but in general, negative attitudes among health care providers prevailed. Training and experience were associated with more positive attitudes. Addiction medicine training and experience should be encouraged in organizations and educational institutions to improve health care providers' confidence as well as treatment outcomes.

Nicolas Bertholet, MD, MSc

Reference: van Boekel LC, Brouwers EP, van Weeghel J, Garretsen HF. Stigma among health professionals toward patients with substance use disorders and its consequences for healthcare delivery: systematic review. *Drug Alcohol Depend.* 2013;131(1–2):23–35.

High Proportion of Patients Screened when Alcohol and Drug Questions are Integrated into Emergency Department Electronic Triage Forms

Although the prevalence is high, unhealthy alcohol and other drug use often goes unrecognized in emergency department (ED) patients. To screen a higher proportion of patients, investigators implemented three questions concerning past 12-month substance use in the electronic triage form of a level I trauma hospital ED, to be administered by nurses to every patient aged 18 or over: a multiple choice question on the number of heavy drinking days, and two yes/no questions for tobacco or other drug use. Any drug or heavy alcohol use triggered a brief intervention by a health education specialist.

- Over three years, 145,394 adults (96%) had screening documented. About 200 persons screened positive each week for either drug or at-risk alcohol use, accounting for 20–26% of patients.
- After an initial proportion of 89% screened, the proportion increased over the next 18 months to reach a plateau, remaining at over 96% for the remaining year and a half.
- About 40% of those who screened positive did not receive a brief intervention, because the health education specialists were not always available.

Comments: The proportion of patients screened after implementing systematic screening for substance use in ED electronic triage forms was high. Further information would have been useful regarding the small proportion of patients not screened, who were likely critically ill or otherwise unable to participate in screening. More importantly, the study does not indicate whether the validated screening questions were actually asked. It also points to a clear challenge—that of acting on positive screening results (i.e., with a brief intervention or treatment referral, where indicated).

Christine Maynié-François, MD, MSc † & Richard Saitz, MD, MPH

†Contributing Editorial Intern and Research Scholar, Clinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA.

Reference: Johnson JA, Woychek A, Vaughan D, Seale JP. Screening for at-risk alcohol use and drug use in an emergency department: integration of screening questions into electronic triage forms achieves high screening rates. *Ann Emerg Med.* 2013;62(3):262–266.

HEALTH OUTCOMES

Adverse Behavioral Effects of Prenatal Alcohol Exposure Still Present at 22 Years of Age

Prenatal alcohol exposure (PAE) can result in adverse behavioral and developmental effects, but it is not known how long they endure and whether there are long-term risks at a threshold below that of fetal alcohol syndrome (FAS). In this longitudinal study, researchers assessed women's prenatal alcohol use during each trimester. The birth sample (N=763) was followed up at regular intervals to the age of 22 when the sample completed the Adult Self-Report (ASR), which assesses aspects of adaptive functioning and problems.

- Median use decreased from 0.4 drinks/day during the first trimester to 0.08 drinks/day in the third trimester.
- Exposure to at least 1 drink/day decreased from 18% in the first trimester to 3.6% in the third.
- Any heavy episodic drinking (≥4 drinks/occasion) decreased from 34% in the first trimester to 5% in the third.
- Of the birth sample, 608 (80%) completed the 22-year assessment.
- PAE was significantly associated with more behavioral problems at 22 years of age in each of the ASR scales.
- PAE had a dose-response effect on Externalizing and Internalizing (mood, somatic complaints) scales and had a greater effect if present across pregnancy.

Comments: This long-term study shows adverse behavioral effects of PAE lasting into early adulthood in individuals without FAS. Although it cannot be ruled out, the study does not support a safe lower threshold for alcohol use during pregnancy. We should continue to advise abstinence from alcohol during pregnancy and be cognizant of behavioral and developmental problems among children with prenatal exposure.

Kevin L. Kraemer, MD, MSc

Reference: Day NL, Helsel A, Sonon K, Goldschmidt L. The association between prenatal alcohol exposure and behavior at 22 years of age. *Alcohol Clin Exp Res.* 2013;37(7):1171–1178.

Office-Based Buprenorphine Treatment Just as Effective for People with Opioid Dependence Who Use Cocaine as for Those Who Do Not

Previous research has found that people with opioid dependence who also use cocaine tend not to do as well on methadone maintenance treatment as those without concurrent cocaine use. The impact of cocaine use on outcomes in office-based buprenorphine treatment is less clear. Researchers followed a cohort of 87 participants who initiated buprenorphine treatment for opioid dependence in a community health center and interviewed them at 1, 3, and 6 months. The main outcome measures were retention in treatment and self-reported opioid use.

- Overall, 39% of participants reported using cocaine in the month prior to initiation of treatment. People with cocaine use were younger and more likely to use opioid analgesics.
- Cocaine use declined to 33% at 1 month, 19% at 3 months, and 12% at 6 months.
- Treatment retention at 6 months was not significantly different for people with cocaine use (59%), versus those without (51%) and self-reported opioid use was likewise not significantly different (~27% for both).

Comments: This study, although limited by short duration, small sample size, and reliance on self-report, suggests that concurrent cocaine use should not be a reason to deny a person access to office-based buprenorphine treatment for opioid dependence. It is interesting that treatment retention was somewhat better among people with cocaine use; this has been observed in at least one previous study. One concern is whether people who use cocaine are more likely to divert buprenorphine. It is possible that for some of these individuals, cocaine is the drug of choice and patients may use their access to buprenorphine to obtain cocaine; this should be studied further.

Darius A. Rastegar, MD

Reference: Cunningham CO, Giovanniello A, Kunins HV, et al. Buprenorphine treatment outcomes among opioid-dependent cocaine users and non-users. *Am J Addict.* 2013;22(4):352–357.

Metabolic and Biochemical Effects of Alcohol Consumption

Researchers performed biochemical tests on serum from 8396 subjects (3750 men and 4646 women, aged 51 ± 13 years) who reported their alcohol consumption in the week preceding baseline blood collection. The analysis describes the cross-sectional relation between self-reported alcohol consumption and a variety of metabolic and biochemical factors. The study found:

- A linear increase in HDL-cholesterol and a linear decrease in insulin levels with increasing amounts of alcohol.
- For most other factors (including liver enzymes, triglycerides, blood glucose, and c-reactive protein levels) there was a "J-shaped" relation—lower values with light drinking and higher values with the consumption

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Metabolic and Biochemical Effects of Alcohol Consumption (continued from page 4)

of larger amounts of alcohol—as well as threshold values at which heavier drinking began to show adverse effects.
- The most favorable values varied by the measure: lowest triglycerides at about 1 to 2 drinks/day, lowest c-reactive protein levels at about 1 drink/day, lowest blood sugar and alkaline phosphatase values at 1 to 3 drinks/day.

Comments: A very high percentage of subjects in this study had lifetime alcohol dependence (32% of men and 16% of women), so the results of this study may not apply to the general population. The authors do not indicate whether there was a relationship between beverage of choice and dependence, nor do they report on the subjects' patterns of drinking. The markers of liver dysfunction related to alcohol consumption showed little change with consumption below 2 to 3 drinks/day, confirming these amounts as thresholds consistent with heavy alcohol use. The findings of this study tend to support the "J-shaped" curve usually seen in epidemiologic studies: better health outcomes from light-to-moderate alcohol consumption, but adverse health effects from heavier drinking.

R. Curtis Ellison, MD

Reference: Whitfield JB, Heath AC, Madden PA, et al. Metabolic and biochemical effects of low-to-moderate alcohol consumption. *Alcohol Clin Exp Res.* 2013;37(4):575–586.

HIV AND HCV

Brief Intervention Enhanced by Interactive Voice Response Reduces Heavy Drinking among People with HIV and Alcohol Dependence

Heavy alcohol use among HIV-infected patients is associated with worse HIV treatment outcomes and contributes to liver-related mortality. Researchers conducted a 3-arm randomized clinical trial among 258 primary care patients with HIV who reported ≥ 4 drinks at least once in the previous 30 days. The 3 arms were:

- Motivational Interview (MI)+HealthCall: A 20–25 minute MI followed by 60 days of daily patient self-monitoring and 1–3 minute phone calls to an automated telephone system that provided personalized feedback on alcohol use.
- MI-only: A 20–25 minute MI.
- Control: Feedback that drinking was more than recommended, pamphlet detailing alcohol reduction techniques, and a 30-minute HIV self-care video with no alcohol-related content.

All 3 groups received 5–10 minute counselor booster sessions at 30 and 60 days. The primary outcome was mean number of drinks per day.

- Of the sample, 48% had current alcohol dependence.
- The MI+HealthCall group completed a median 64% of self-monitoring calls.
- At 60 days, the mean number of drinks per day in the MI+HealthCall, MI-only, and Control groups was 3.58, 3.94, and 4.75, respectively. Among the alcohol-dependent subgroup, the mean number of drinks per day was 3.55, 5.12, and 6.07. Among the non-dependent subgroup, mean number of drinks per day ranged from 3.03 to 3.64 and no differences were significant.
- At 3, 6, and 12 months, the mean number of drinks per day was no longer significantly different in the overall sample or the dependent or non-dependent subgroups.

Comments: This trial is the first to suggest that a brief intervention appears to be effective, though only in the very short term, for people with HIV and alcohol dependence. Paradoxically, no benefit was observed in non-dependent drinkers. Enhancement of brief interventions with daily brief automated alcohol use assessment and feedback warrants study in more settings, populations, and for varying lengths of time.

Alexander Y. Walley, MD, MSc

Reference: Hasin DS, Aharonovich E, O'Leary A, et al. Reducing heavy drinking in HIV primary care: a randomized trial of brief intervention, with and without technological enhancement. *Addiction*. 2013;108(7):1230–1240.

Incorrect Perceptions About Sexual Versus Injection Hepatitis C Transmission Risk among Couples May Contribute to Unsafe Injecting Practices

The majority of hepatitis C virus (HCV) transmissions occur via injection drug use (IDU). The risk of sexual transmission of HCV among HIV-uninfected heterosexual couples is believed to be very low. There is limited information about how people with IDU perceive the risk of HCV transmission via heterosexual sexual activity. This qualitative study examined how perceptions of risk among this population affected practices. Researchers conducted in-depth interviews with 37 adults who had used injection

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Incorrect Perceptions About Sexual Versus Injection Hepatitis C Transmission Risk among Couples May Contribute to Unsafe Injecting Practices (continued from page 5)

drugs within the past 30 days.

- Of the total sample, 15 (41%) were HCV-positive, 10 (27%) were female, 28 (76%) were Caucasian, and the mean age was 40 (range 23–57). Heroin was the primary drug of choice 25 (68%) followed by crack and heroin mix 12 (32%).
- The majority of participants who were, or had been, in long-term heterosexual relationships reported needle and syringe sharing with their regular sexual partner.
- Many participants believed that sexual transmission risk was equivalent to drug risk. This narrative of "risk equivalence" was frequently used to justify needle and syringe sharing practices among partners who were already having unprotected sex.

Comments: This study highlights a gap in knowledge about HCV transmission among people with IDU. The authors suggest that HCV prevention programs that "add on" safer sex messages may do more harm than good by perpetuating risk equivalence beliefs that foster dismissal of safer injecting practices among those practicing unprotected sex. While it is speculative whether more accurate messages about sexual transmission risk would impact injecting behaviors in couples, this study does provide an interesting new framework for understanding risk behaviors among people with IDU.

Judith Tsui, MD, MPH

Reference: Harris M, Rhodes T. Injecting practices in sexual partnerships: Hepatitis C transmission potentials in a "risk equivalence" framework. *Drug Alcohol Depend.* 2013; 132(3):617–623.

Trends in Hepatitis C Virus Treatment Uptake Among People Attending Australian Needle and Syringe Programs

Despite recommendations for hepatitis C (HCV) treatment among people with injection drug use (IDU), treatment initiation for this population remains low worldwide. This study examined trends in HCV treatment and correlates among people with IDU attending the Australian Needle and Syringe Programs between 1999 and 2011. This was a secondary data analysis of an annual self-report survey of people with IDU attending needle and syringe programs, which captures information about demographics, injection and sexual risk, history of HIV and HCV testing and treatment, as well as collection of a capillary blood sample. The study sample included 9748 subjects with self-reported and serologically confirmed HCV-antibody positivity.

- The proportion of participants currently receiving HCV treatment increased from 1.1% to 2.1%, and the proportion ever receiving treatment increased from 3.4% to 8.6%.
- Men were more likely than women to have received HCV treatment (7% versus 5%).
- Predictors of HCV treatment among men included homosexual identity and ≥ 45 years of age. Among women, predictors included homosexual identity and a history of imprisonment.

Comments: This study highlights the potential role for specialized HCV treatment approaches among people with IDU attending needle and syringe programs. Future research should explore barriers and correlates for HCV treatment uptake among people who are actively using injection drugs. Attention should be focused not only on those attending needle and syringe programs, but also those engaged in drug treatment in an effort to expand access to HCV treatment, especially as new and improved therapy options continue to emerge.

Jeanette M. Tetrault, MD

Reference: Iversen J, Grebely J, Topp L, et al. Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999–2011. *J Viral Hepat.* 2013 [Epub ahead of print]. doi: 10.111/jvh.12129.

RESOURCE ALERTS

Diagnostic and Statistical Manual of Mental Disorders: *DSM-5* Replaces *DSM-IV*

The previous edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) divided substance-related disorders into two categories: *substance abuse* and *substance dependence*. There were a number of problems with this system: the dividing line between *abuse* and *dependence* was not clear; *substance dependence* was often confused with *physical dependence*; and the term *abuse* has pejorative connotations. Published in May 2013, the *DSM-5* replaces these with a single term: *substance use disorder*. There are two major changes to the diagnostic criteria: 1) *Recurrent legal problems*, which was a criterion for substance abuse, has been removed. 2) A new criterion has been added: craving or strong desire/urge to use a substance.

The *DSM-5* defines a *substance use disorder* as the presence of at least 2 of 11 criteria, which are clustered in four groups:

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Diagnostic and Statistical Manual of Mental Disorders: *DSM-5* Replaces *DSM-IV* (continued from page 6)

****Criteria not displayed due to intellectual property and copyright regulations, but can be found for free online: http://www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics"****

The *DSM-5* suggests using the number of criteria met as a general measure of severity, from *mild* (2–3 criteria) to *moderate* (4–5 criteria) and *severe* (6 or more criteria).

Defining substance use disorders on a single continuum makes sense, but will likely create confusion in the short term and the DSM provides no guidance on how to use these criteria to decide on who needs formal treatment.

Finally, new to *DSM-5* are cannabis and caffeine withdrawal, and the criteria for tobacco use disorder are now the same as for all other substance use disorders.

Darius A. Rastegar, MD

References: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Arlington, VA: American Psychiatric Association; 2013.
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.

U.S. Preventive Services Task Force Updates Recommendations for Hepatitis C Virus (HCV) Screening

The USPSTF has broadened its recommendations for HCV screening to include 1-time testing for all persons born between 1945 and 1965, stating that this population has the highest incidence of infection and that the testing carries a moderate benefit and low risk.

The Task Force continues to recommend screening populations at high risk (e.g., those with injection drug use).

The full statement is available for free in the *Annals of Internal Medicine*: http://annals.org/article.aspx?articleid=1700383.

FEATURE ARTICLE: ETHICAL CONDUCT OF ALCOHOL AND OTHER DRUG RESEARCH

Guidelines for Protecting Prisoner Subjects in Addiction Research

Mary-Tara Roth, RN, MSN, MPH. Director, Clinical Research Resources Office, Clinical and Translational Science Institute, Boston University School of Medicine/Boston Medical Center, Boston, MA, USA

Special rules and regulations apply to research involving prisoners who participate in studies that follow US Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP) regulations on the protection of human subjects.[1] This includes any research study that is supported by federal funds. Addiction researchers should be aware of these rules because, by the nature of the subject population and the study topics, addiction research has the potential to involve prisoners, in part because addiction and related problems, such as hepatitis and HIV, affect prisoners at a higher rate than the general population. Some of this research may directly target prison populations, while subjects in other studies may become incarcerated over the course of the study. In either case, it is essential that researchers and their teams understand what the rules are, when they apply, and how to comply with them. It is also important that researchers anticipate that prisoners may be crucial to addiction prospective or epidemiologic studies to make those studies more valid, since people with addictions may be more likely to be incarcerated.

This article will provide an overview of the historical context and regulations pertaining to prisoner subjects and provide information about regulatory processes that researchers need to know to ensure the ethical conduct of addiction research that involves prisoners.

Vulnerable Subjects and the Development of Regulations

Although the Nuremberg Code was developed in response to the unethical experiments conducted on people held in concentration camps during the Second World War,

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Guidelines for Protecting Prisoner Subjects in Addiction Research (continued from page 7)

researchers were slow to connect the atrocities inflicted on that population with research on prison inmates in the United States. It took another egregious example of unethical research in a vulnerable (though not prisoner) population to set in motion public awareness in the US that research on humans needed more guidance and oversight.

The modern regulations guiding human subjects research were formed in the early 1970s in response to public outcry at the Tuskegee Syphilis Study, which followed 399 men in Macon County, Alabama for forty years to study the long-term effects of syphilis.[2] The participants were not adequately informed of the purpose of the study, nor were they offered treatment when a cure for syphilis was discovered. The Tuskegee scandal set in motion important changes, such as the establishment of standards for outside review and informed consent, but it is important to note that examples of unethical research appeared in reputable medical journals and was sponsored or conducted by the US government in the years prior to Tuskegee.[3, 4] The common denominators in many of these studies were the inclusion of subjects who were not fully informed as to the purpose and risks of the research, as well as those who were particularly vulnerable: the poor and the disenfranchised, people with mental disabilities, children, prison inmates, and terminal hospital patients. Research on captive populations, including but not limited to prisoners, was common. In fact, prior to the early 1970s, more than 90 percent of pharmaceutical research was conducted using prisoners as subjects.[4, 5]

After the atrocities of Tuskegee became public, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission) was formed in 1974 and the office of the Secretary of Health, Education, and Welfare issued "Basic Regulations Governing the Protection of Human Subjects Involved in Research".[6] In 1978, the Commission issued the Belmont Report, which articulates three basic tenets of the conduct of research on human subjects: Respect for Persons (informed consent), Beneficence (maximizing benefits and minimizing harms for individual subjects), and Justice (fair selection of subjects). These became the philosophical underpinnings of the current regulations on the protection of human subjects. The basic set of protections is known as Subpart A, and in 1991 it was formally adopted by 15 federal agencies as the Common Rule. The Common Rule ensures that research conducted or supported by federal funds has the following attributes: independent review, informed consent, minimization of harm, and protection of privacy and confidentiality.[7,8]

There are 3 subparts to the regulations that provide added protections for specific groups of vulnerable subjects. Subpart C was issued in 1978 and specifies protections for prisoner subjects in federally supported or conducted biomedical and sociobehavioral research. Although it was considered, a complete ban on prisoner research was not the outcome of the Commission's recommendations, but the resulting regulations placed strict conditions on this research.[9]

Prisoners as Vulnerable Subjects

An internal 1943 memo[10] between two doctors from the National Research Council justified using prisoners versus members of the general population for research "testing chemical and chemotherapeutic prophylaxis of gonorrhea," citing that prisoners are subject to the necessary sexual isolation and that medical facilities already exist within the prison systems, supporting an increased feasibility and lower cost of studies within this population. This argument essentially sums up the appeal of including prisoners in medical research studies: convenience. Prisoners are not going anywhere, and are intensively supervised, on strict schedules, and—compared with a general population outside of prison—do not have many other activities such as family and job responsibilities competing for their time.

This convenience, however, is an outcome of prisoners' limited rights and choices, important factors that may make the conduct of research involving captive populations ethically untenable. The first tenet of the Nuremburg Code is clear: "The voluntary consent of the human subject is absolutely essential."[11] The document goes on to state that the person "should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion."[12] All of the above are issues that prisoners may face during incarceration.

One might question whether any prisoner is "so situated to be able to exercise free power of choice" and provide valid informed consent. When freedom and choice are so limited, is a prisoner able to refuse to take part in research? And even if the prisoner is assured that his or her participation is voluntary, might the subject believe that he or she actually has no choice but to take part? Prisoners have an increased likelihood of being susceptible to coercion (or at least the perception of coercion) that can impact voluntariness. They may also be vulnerable to undue inducements if the perceived benefits of taking part in the research—such as higher payments (compared usual prison wages), or better facilities or care within the prison system—compel prisoner subjects to participate when doing so is not in their best interest.

In addition to the more obvious issues related to prisoners' (continued page 9)

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participation in research studies, there other important aspects that increase the vulnerability of this population as well as the potential for exploitation. For example, compared with the general population, prisoners generally have greater healthcare issues and less access to acceptable care, a higher prevalence of psychiatric conditions, and lower education level, which could result in a diminished ability to read and/or understand research consent forms.[12] Furthermore, prisoners who have addictions are at risk for consequences when incarcerated if it is found that they are using or have used or sold drugs. In this instance, confidentiality becomes even more critical and may be a risk too great to take for research participation.

Additional Protections Pertaining to Research on Prisoner Subjects: Subpart C

In 1978, the federal government passed strict regulations limiting prisoner experimentation to 4 categories of research, commonly referred to as Subpart C (45 CFR 46.306(a)(2)(i)-(iv)),[1] which was amended in 2003 to allow for a waiver of the applicability of certain requirements for some types of epidemiologic research.[13] Thus, applicable research involving prisoners may address:

- The causes and effects of incarceration and criminal behavior. The research must present no greater than minimal risk or inconvenience.
- Prisons as institutions. The research must present no greater than minimal risk.
- Health conditions that particularly affect prisoners. The Secretary must consult with experts as well as publish the intent to approve the research in the Federal Register.
- Practices that are likely to improve the health or wellbeing of individual subjects. If there is a control group involved, the Secretary must consult with experts and publish the intent to approve the research in the Federal Register.
- Epidemiologic research on diseases where prisoners are included in the population of interest, but are not the sole study group.

Under Subpart C, the Institutional Review Board (IRB) that approves research involving prisoners must be comprised of at least one member who is a prisoner or prisoner representative. Also, the majority of the board must not have association with the prison(s) involved, apart from their membership on the board.[1]

The IRB has additional responsibilities when it reviews prisoner research. It must determine that the study falls within one of the permissible categories for prisoner research, that the advantages (such as living situation, pay, food, medical care) for the participant are not so great that they affect the participant's ability to weigh benefits and risks, that the risks are commensurate with those that would be accepted by volunteers who are not prisoners, that subject selection is fair, that there is assurance that a prisoner's participation in research will not affect his or her parole, and that there is provision for follow-up care after the conclusion of the study, where applicable.

The institution responsible for the conduct of the research must certify to the Secretary that the IRB has approved the research under these requirements. To accomplish this, after IRB review and approval, the institution must send to OHRP a certification letter that provides all the relevant information regarding the IRB approval of the research under Subpart C. The requirements for this letter are detailed in OHRP guidance *Prisoner Research Certification*. Once OHRP receives the certification letter, it will review the research proposal and determine whether it meets one of the categories of permissible research (or a waiver for epidemiological research). Then, when applicable, the OHRP will publish a notice of intent to approve the research in the Federal Register. Research involving prisoners as subjects cannot begin until the OHRP issues its approval in writing to the institution on behalf of the Secretary.

As previously noted, addiction research carries a risk of enrolling subjects who may become incarcerated at some point during their participation in a study. In these cases, the regulatory safeguards pertaining to prisoners in research apply. If the research was not already reviewed and approved under Subpart C, the PI should immediately notify the IRB that a subject has become a prisoner. All research interactions, including obtaining private identifiable data on the subject, must be suspended until the research is reviewed and approved under Subpart C. If it is in the best interest of the prisoner subject to remain in the study while incarcerated, however, the IRB chairperson may determine that the participant can continue until Subpart C requirements are satisfied. Once the IRB is informed that a research subject has become a prisoner, it will meet as soon as possible to re-review the protocol under Subpart C requirements, as long as the PI wants the subject to continue in the research.

Understanding the regulations that govern research involving prisoners is essential for addiction researchers who are likely at some point to involve prisoners in their studies. The regulations provide additional provisions to ensure the protection of prisoners as subjects and the ethical conduct of research.

(continued page 10)

Guidelines for Protecting Prisoner Subjects in Addiction Research
(continued from page 9)

References

1. US Department of Health and Human Services: Code of Federal Regulations no. 45 CFR 46. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.
2. Levine RJ. *Ethics and Regulation of Clinical Research*, 2nd ed. New Haven: Yale University Press; 1988.
3. Beecher HK. Ethics and Clinical Research. *N Eng J Med.* 1966;274:1354–1360.
4. Advisory Committee on Human Radiation Experiments. Final report of the advisory committee on human radiation experiments. Washington DC: US Government Printing Office; 1996.
5. US Department of Energy: Human Radiation Experiments: The Department of Energy Roadmap to the Story and the Records. Available at http://www.agriculturedefensecoalition.org/sites/default/files/file/nuclear/14H_2010_U.S._Department_of_Energy_Human_Radiation_Experiments_Roadmap_Story_Records_Website_SEPT_5_2010.pdf.
6. Porter J, Koski, G. Regulations for the Protection of Humans in Research in the United States. In: Ezekiel E, Grady CG, Crouch RA, et al., eds. *Oxford Textbook of Clinical Research Ethics.* York: Oxford University Press; 2008:156–167.
7. Kalmbach KC, Lyons PM Jr. Ethical and legal standards for research in prisons. *Behav Sci Law*, 2003;21(5):671–686.
8. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: Research Involving Prisoners: Report and Recommendations no. (OS) 76–131. Available at http://www.bioethics.gov/.
9. Bonham V, Moreno J. Research with Captive Populations: Prisoners, Students, and Soldiers. In: Ezekiel E, Grady CG, Crouch RA, et al., eds. *Oxford Textbook of Clinical Research Ethics.* York: Oxford University Press; 2008:386–396.
10. Letter from National Science Council on using prisoners. Available at http://bioethics.gov/sites/default/files/NARA-II_0000176.PDF.
11. Shuster E. Fifty Years Later: The significance of the Nuremberg Code. *N Engl J Med*. 1997;337:1436–1440.
12. Brewer-Smyth K. Ethical, regulatory, and investigator considerations in prison research. *ANS Adv Nurs Sci*. 2008;31(2):119-127.
13. US Federal Register vol. 68, no. 119:36929–36931. Available at http://www.gpo.gov/fdsys/pkg/FR-2003-06-20/html/03-15580.htm.

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

Continuing Medical Education (CME) Accreditation Statements

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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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Course Faculty

Richard Saitz, MD, MPH, FASAM, FACP
Course Director
Professor of Medicine and Epidemiology
Boston University Schools of Medicine and Public Health
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

David A. Fiellin, MD
Professor of Medicine
Yale University School of Medicine
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

Nicolas Bertholet, MD, MSc
Department of Medicine and Public Health
Lausanne University, Switzerland
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

R. Curtis Ellison, MD
Professor of Medicine and Public Health
Boston University School of Medicine
Faculty member is the Director of the Institute on Lifestyle and Health, which receives various donations from individuals and companies in the alcohol beverage industry, given as "unrestricted educational gifts." Funds are not given for specific research projects and donors have no prior information on, or input into, the surveillance being carried out or critiques published by the Institute or the Section. Faculty member does not discuss unlabeled/investigational uses of a commercial product.

Peter D. Friedmann, MD, MPH
Professor of Medicine and Community Health
Warren Alpert Medical School of Brown University
Faculty member receives grant/research support from Alkermes, Inc. and is a stockholder in Becton-Dickenson, Pfizer, and Siemens. Faculty member does not discuss unlabeled/investigational uses of a commercial product.

Kevin L. Kraemer, MD, MSc
Associate Professor of Medicine and Health Policy and Management
University of Pittsburgh Schools of Medicine and Public Health
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

Hillary Kunins, MD, MPH, MS
New York City Department of Health and Mental Hygiene, and
Professor of Clinical Medicine, Psychiatry & Behavioral Sciences
Albert Einstein College of Medicine
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product .

Darius A. Rastegar, MD
Associate Professor of Medicine
Johns Hopkins School of Medicine
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

Jeffrey H. Samet, MD, MA, MPH
Professor of Medicine and Community Health Sciences
Boston University Schools of Medicine and Public Health
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

Jeanette M. Tetrault, MD
Assistant Professor of Medicine (General Medicine)
Yale University School of Medicine
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

Alexander Y. Walley, MD, MSc
Assistant Professor of Medicine
Boston University School of Medicine
Faculty member has nothing to disclose in regards to commercial support and does not discuss unlabeled/investigational uses of a commercial product.

Katherine Calver, MA
Managing Editor
Alcohol, Other Drugs, and Health: Current Evidence
Boston Medical Center
Ms. Calver has nothing to disclose in regards to commercial support.

Jody Walker, MS
Boston University School of Medicine
CME Program Manager
Ms. Walker has nothing to disclose in regards to commercial support.

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