Alcohol, Other Drugs, and Health: Current Evidence

JANUARY–FEBRUARY 2014

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INTERVENTIONS & ASSESSMENTS

Referral to Treatment for Substance Use Disorders Improves Depression Symptoms in Primary Care Patients

Substance use disorders (SUD) and depression commonly co-occur in primary care patients. Researchers assessed whether referral to SUD treatment improved depression symptoms among 2373 patients with co-occurring SUD and depression. The main outcome of depression improvement (defined as achieving a Patient Health Questionnaire 9 [PHQ-9] score of <10, or a ≥50% reduction in PHQ-9 score) was compared among participants who accessed (N=780), declined (N=315), or were not referred to (N=1278) SUD treatment.

- Depression improvement was observed in 40% of participants who accessed SUD treatment, in 25% who declined, and in 33% who were not referred.
- In analyses adjusted for the propensity to be referred to and access SUD treatment, participants who accessed SUD treatment were more likely to have depression improvement than those who declined referral (hazard ratio [HR], 1.82) and those who were not referred (HR, 1.13).
- Depression improvement was less likely when SUD treatment referral was delayed (HR, 0.97 for each 1-week delay).

Comments: These results support the need to initiate SUD treatment in primary care patients who have co-occurring SUD and depression. However, these patients were participants in a state-wide program for low-income uninsured patients with mental disorders who were cared for by an integrated team, including their PCP, a behavioral care manager, and a consulting psychiatrist. It is not clear if similar results could be achieved in a system without such fine integration.

Kevin L. Kraemer, MD, MSc

Reference: Chan YF, Huang H, Bradley K, Unützer J. Referral for substance abuse treatment and depression improvement among patients with co-occurring disorders seeking behavioral health services in primary care. *J Subst Abuse Treat.* 2014;46(2):106–112.

Little Evidence for Efficacy of Continuing Care in Treatment of Patients with Alcohol Use Disorders

The effectiveness of providing continuing care for people with substance use disorders has been best studied in the context of agonist treatment of opioid use disorders. In this systematic review, investigators examined randomized controlled trials of adults with primary alcohol use disorders receiving a continuing care intervention that followed inpatient or intensive outpatient treatment. Six high-quality randomized controlled trials with 12 or more weeks of follow-up were identified; one compared different interventions, but did not include a usual care control group.

- Three trials used telephone counseling; the remainder used a variety of counseling approaches, including cognitive behavioral therapy, relapse prevention, motivational therapy, couples therapy, and 12-step facilitation.
- None of the 3 studies that measured the proportion of patients with continuous abstinence found a difference between the intervention and usual care arms.
- Using a meta-analysis of 2 studies (one with outcomes at 2 points in time), the mean difference in drinking days was an 11% decrease among those who received continuing care.
- Three of 5 studies found a decrease in number of heavy drinking days or drinks per drinking episode.

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Little Evidence for Efficacy of Continuing Care in Treatment of Patients with Alcohol Use Disorders (continued from page 1)

Comments: As the authors note, this systematic review provides modest evidence that continuing care interventions have a beneficial effect on drinking outcomes in people with alcohol use disorders, but it also highlights the lack of evidence for best practices. The heterogeneity of the interventions, which included a variety of telephone and in-person counseling strategies, also precludes recommendations for the most efficacious or cost-effective interventions.

Hillary Kunins, MD, MPH, MS

Reference: Lenaerts E, Matheï C, Matthys F, et al. Continuing care for patients with alcohol use disorders: A systematic review. *Drug Alcohol Depend.* 2014;135:9–21.

Knowledge Gaps Persist in Assessment of the Efficacy of Alcohol Brief Interventions in Primary Care

In this study, researchers assessed the cumulative evidence of the effectiveness of brief alcohol interventions (BI) in primary care for reducing risky alcohol consumption and alcohol-related problems. They identified 24 systematic reviews reporting results of 56 randomized trials published between 2002 and 2012.

- The general consensus was that available evidence continues to support the use of BI in primary care. However, the majority of the evidence is for middle-aged men.
- Knowledge gaps concern women (and pregnant women), older and younger individuals, minority ethnic groups, people with alcohol dependence, and those living in transitional and developing countries.
- The optimum length, frequency, and content of BI are still unclear. There are unanswered questions on the ideal components of a successful intervention.

Comments: Evidence continues to support the use of BI in primary care, but the knowledge gaps are significant and concern the content of BI, the settings in which BI is delivered, and the populations who receive it. The authors aimed at reporting on BI effectiveness, but the translation of research results to real-world conditions continues to present a challenge. Questions also remain concerning whether and to what extent the effectiveness of BI is influenced by the means used to identify the target population (i.e., universal screening, targeted screening, or BI offered to help-seeking individuals).

Nicolas Bertholet, MD, MSc

Reference: O'Donnell A, Anderson P, Newbury-Birch D, et al. The impact of brief alcohol interventions in primary healthcare: a systematic review of reviews. *Alcohol Alcohol.* 2014;49(1):66–78.

Slow-Release Oral Morphine: Another Option for Opioid Agonist Therapy?

Methadone has long been the standard of care for opioid agonist therapy, but stigma and concerns about safety often limit its acceptability. This 22-week trial compared slow-release oral morphine (SROM) with methadone as a maintenance medication among 157 methadone-experienced adults at 14 outpatient addiction treatment centers. Under a prespecified 10% non-inferiority margin that assumed that heroin use would not differ between groups,

- The percentage of 6-monoacetylmorphine (6-MAM) positive urine samples in the SROM group (20%) was deemed non-inferior to the proportion under methadone treatment (15%), although this difference was statistically significant (p=0.0008).
- No difference was found in retention in treatment.
- A similar dose-response effect was observed in both groups.
- Incidence of adverse events was also similar between the two groups.

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Slow-Release Oral Morphine: Another Option for Opioid Agonist Therapy? (continued from page 2)

Comments: SROM has been approved for opioid agonist therapy in many European countries. Although the authors conclude that SROM is non-inferior to methadone in treating adults with an opioid use disorder, the 5% absolute rate difference in detectable heroin use represents a 20% relative risk difference. Other features of SROM also limit the likelihood of its approval for this indication in the US any time soon. Opioid treatment programs in the US would need to dispense anti-abuse formulations, especially for take-home dosing; such formulations are more expensive than methadone. Furthermore, the major detectable metabolite of heroin is morphine (6-MAM has a very short half-life), thus SROM would not be an optimal choice for long-term treatment of patients with heroin use disorders. SROM might be a useful option for selected patients in opioid treatment programs (e.g., those without primary heroin use), but until it is approved specifically for this purpose in the US, SROM cannot and should not be prescribed for this indication.

Peter D. Friedmann, MD

Reference: Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction*. 2013 [Epub ahead of print]. doi: 10.1111/add.12440.

Combined Motivational Interviewing/Cognitive Behavioral Therapy has Modest Effect on Treatment Outcomes for Patients with Alcohol Use Disorders and Depression

Alcohol use disorders (AUD) commonly co-occur with major depressive disorder (MDD). Integrated treatment approaches could improve care outcomes for these patients. This systematic review examined the effect of combined motivational interviewing/cognitive behavioral therapy (MI/CBT) on alcohol consumption and depressive symptoms in patients with AUD and MDD. Comprehensive literature searches through June 2013 identified 12 studies with a total of 1721 patients that compared MI/CBT with treatment as usual or another psychological treatment.

- Compared with controls, MI/CBT had a small clinical effect on both alcohol consumption (number needed to treat [NNT], 10) and depressive symptoms (NNT, 7).
- Subgroup analyses revealed similar effects on alcohol consumption and depressive symptoms, regardless of type of control, randomization, polysubstance use, age, or treatment setting.
- Patients who received a greater number of MI/CBT sessions experienced worse alcohol outcomes.
- Digital interventions (NNT, 8) showed larger effects than face-to-face interventions (NNT, 3) on depressive symptoms.

Comments: Combined MI/CBT produces modest reductions in alcohol consumption and depressive symptoms in patients with co-occurring AUD and MDD. However, antidepressant medications are commonly prescribed to such patients. Further studies are required to determine whether MI/CBT produces any additional effect over and above antidepressant medications in this population.

Peter D. Friedmann, MD

Reference: Riper H, Andersson G, Hunter SB, et al. Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: A meta-analysis. *Addiction*. 2013 [Epub ahead of print]. doi: 10.1111/add.12441.

HEALTH OUTCOMES

Alcohol Use Disorder in a Secret Service Agent: Commander James Bond, 007

James Bond is seen as a role model and his drinking is often portrayed in a glamorous light. UK investigators read all 12 original full-length James Bond novels and recorded his alcohol consumption. In total, 123.5 days were described; on 36 days there was no alcohol consumption due to hospitalization or incarceration.

- Bond abstained on 14% of days when he was able to drink.
- Average drinks per drinking day was 9 standard 12 g US drinks.
- Maximum consumption in one day was 33 drinks (in *From Russia With Love*, day 3).
- He had hangovers and drank while working, before driving; on one occasion this precipitated a crash-related hospitalization. Bond's period of peak consumption followed the death of his wife.
- He scored 3 on the CAGE alcoholism screening questionnaire, consistent with a moderate to severe alcohol use disorder (C: feels better drinking less; A: becomes annoyed when his drinking is challenged by his

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Alcohol Use Disorder in a Secret Service Agent: Commander James Bond, 007 (continued from page 3)

boss "M"; E: has an "eye opener" (reported in *Thunderball* and *Living Daylights*).

- The investigators hypothesize that he was unable to stir drinks as a result of an alcohol-related tremor that led him to prefer his drinks shaken, despite the fact that this is not the ideal preparation of vodka martinis.

Comments: The novels were read by only one investigator each; drinking was all by self-report and some was estimated (e.g., when the description was "serious drinking" or "a visit to a bar"); and results may not generalize beyond the British Secret Service. Nonetheless, it appears likely that this agent drinks excessively and has an alcohol use disorder, not ideal for a role model. Clinicians should have a high index of suspicion for unhealthy alcohol use in spies, others employed in high-stress jobs, and fictional characters.

Richard Saitz, MD, MPH

Reference: Johnson G, Guha IN, Davies P. Were James Bond's drinks shaken because of alcohol induced tremor? *BMJ*. 2013;347:f7255.

What is the Quality of Guidelines for Prescribing Opioids to Treat Chronic Pain?

High-quality guidelines may help clinicians prescribe opioids for chronic pain in a safe and effective manner. Researchers searched US and international guidelines and specialty society websites to assess English-language opioid prescribing guidelines published between January 2007 and July 2013. Guidelines were evaluated using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) and the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tools.

- Of the 1132 guidelines screened and 19 evaluated, 13 met selection criteria.*
- AGREE II quality ratings ranged from 3 to 6.2 (on a 1 to 7 scale) and were highest for the American Pain Society/American Academy of Pain Medicine (APS/AAPM) and the Canadian National Opioid Use Guideline Group (NOUGG) guidelines.
- AMSTAR ratings on quality of systematic review were poor-to-fair for 10 of the 13 guidelines. However, AMSTAR ratings were excellent-to-outstanding for the APS/AAPM guideline, good-to-excellent for the NOUGG guideline, and good for the VA/Department of Defense (VA/DOD) guideline.
- 10 of the 13 guidelines included relevant recommendations about mitigating risk. Recommendations included use of written treatment agreements, opioid risk assessment tools, urine drug testing, avoiding doses greater than 90 to 200 mg of morphine equivalents per day, acquiring extra training in order to prescribe methadone, attention to drug-drug (e.g., opioids and sedative-hypnotics) and drug-disease interactions (e.g., opioids and obstructive lung disease), and reducing doses by 25–50% when switching opioids.

*The 13 selected guidelines were from the APS/AAPM, the American College of Occupational and Environmental Medicine, the American Geriatrics Society, the American Society of Anesthesiologists, the American Society of Interventional Pain Physicians, the VA/DOD, the Colorado Division of Workers' Compensation, the Institute for Clinical Systems Improvement, the NOUGG, the Utah Department of Health, the University of Michigan Health System, the Work Loss Data Institute, and Fine and colleagues (expert panel).

Comments: Based on observational data and expert consensus for most recommendations, guidelines from the APS/AAPM and the NOUGG were judged to be acceptable in their current form by over 50% of the study appraisers. Unfortunately, the efficacy of implementing these guidelines in a practice setting is not known.

Kevin L. Kraemer, MD, MSc

Reference: Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med*. 2013 [Epub ahead of print]. doi: 10.7326/0003-4819-160-1-201401070-00732.

The Impact of Prenatal Exposure on Substance Use in Adolescence

A possible cause for alcohol and other drug use in adolescence is prenatal exposure. Researchers in Germany examined this association among adolescents aged 11 to 17 (N=5922), who self-reported their alcohol, tobacco, and other drug use. Prenatal exposure to alcohol was assessed using retrospective parental self-reports.

- Subjects had a mean age of 14 years; 21% reported drinking alcohol, 18% smoking tobacco, and 7% illicit drug use.
- Prenatal exposure to alcohol and tobacco were reported for 14% and 16% of subjects, respectively.
- In analyses adjusted for age, gender, ethnicity, socioeconomic status, quality of life within the family, school failure, presence of friends who smoke, current parental smoking, and maternal smoking during pregnancy, low to moderate prenatal exposure to alcohol was associated with an increased risk of alcohol and illicit drug use in adolescence, but not smoking.

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The Impact of Prenatal Exposure on Substance Use in Adolescence (continued from page 4)

- The association differed by ethnicity and gender: adverse effects of prenatal exposure were stronger among non-Germans and women and were not significant in males.

Comments: This study depends on the accuracy of retrospective assessment. The authors adjusted analyses for various potential confounders, but one possible explanation for the differing results by ethnicity may be unmeasured cultural and socio-economic determinants, in addition to differing genetic susceptibilities to prenatal alcohol exposure. Underreports of use—both during pregnancy and by the adolescent subjects—are possible and may have introduced bias. Nevertheless, these results are important since they are compatible with a fetal origin of substance use disorders due to intrauterine exposure to alcohol.

Nicolas Bertholet, MD, MSc

Reference: Pfinder M, Liebig S, Feldmann R. Adolescents' use of alcohol, tobacco and illicit drugs in relation to prenatal alcohol exposure: modifications by gender and ethnicity. *Alcohol Alcohol*. 2013 [Epub ahead of print]. PMID: 24217955.

People with Injection Drug Use Primarily Take Diverted Buprenorphine to Avoid Withdrawal

As opioid agonist treatment with buprenorphine has expanded, so too have concerns over diversion and illicit use. Participants in a Baltimore cohort of 2942 people with current and former injection drug use (IDU) were asked about their illicit use of buprenorphine.

- Overall, 74% of participants reported seeing buprenorphine sold on the street, 45% reported ever being prescribed it or taking it illicitly; 16% in the past 3 months and 11% in the prior 30 days.
- The majority (56%) of those who reported having ever taken buprenorphine stated that their usual source was a doctor; 23% reported obtaining it from the street, and 13% from a friend.
- Only 9% reported recently taking street-obtained buprenorphine; on multivariable analysis, this was associated with active heroin (odds ratio [OR], 6.6) and injection drug use (OR, 3.1).
- Among those who reported ever taking illicit buprenorphine, 72% of participants reported having taken it to manage withdrawal symptoms and over half of them reported doing so while waiting for treatment.

Comments: This study shows that people with IDU who take diverted buprenorphine primarily do so to prevent withdrawal symptoms. Moreover, it indicates that despite the increased availability of opioid agonist treatment with the introduction of sublingual buprenorphine, there is still an unmet need for treatment. The extent to which diverted buprenorphine is taken by other populations and for what reasons are concerns that were not addressed by this study.

Darius A. Rastegar, MD

Reference: Genberg BL, Gillespie M, Shuster CR, et al. Prevalence and correlates of street-obtained buprenorphine use among current and former injectors in Baltimore, Maryland. *Addict Behav*. 2013;38(12):2868–2873.

Effect of Alcohol Consumption on Risk of Skin Cancers: A Report from the Women's Health Initiative

Over the past 40 years there has been a rise in the incidence of skin cancer, particularly among women. The Women's Health Initiative's Observational Study collected data from more than 59,000 white, postmenopausal women relating alcohol consumption to the risk of malignant melanoma (MM) and non-melanoma skin cancer (NMSC). Over approximately 10 years of follow-up, there were 532 cases of MM and 9593 cases of NMSC. The key reported findings were:

- There was a higher hazard of MM and NMSC among women who consumed ≥7 drinks in a week, compared with abstainers.
- Lifetime alcohol consumption was positively associated with hazard of MM and risk of NMSC, with a significant increase in risk for MM related to consumption of white wine or liquor.

Comments: There were large decreases in the estimates of hazard ratios related to alcohol consumption when adjustments were made for sun exposure and other known confounders, although the primary findings remained significant. Further, the inclusion in the main analyses of subjects with these skin cancers prior to baseline could have introduced bias in the results. There are considerable observational epidemiologic data suggesting that alcohol consumption may relate to an increase in the risk of MM and NMSC. As mechanisms are not known, there is still concern that much of this association may relate to residual confounding by ultraviolet sun exposure, the most important environmental factor for these diseases.

R. Curtis Ellison, MD

Reference: Kubo JT, Henderson MT, Desai M, et al. Alcohol consumption and risk of melanoma and non-melanoma skin cancer in the Women's Health Initiative. *Cancer Causes Control*. 2014;25(1):1–10.

Estimations of Alcohol-Attributable and Alcohol-Preventable Mortality in Denmark

In an attempt to gauge the harmful and beneficial health effects of alcohol consumption, scientists studied data based on meta-analyses and the Danish National Survey to determine rates of alcohol-attributable and alcohol-preventable mortality in Denmark in 2010. They used estimates of the potentially harmful effects of alcohol use on more than 20 diseases, giving 100% values to "alcohol use disorders," although the specific causes of death are not known for this category. Key findings were as follows:

- The authors estimated that 5% of deaths among women and 9.5% of deaths among men were attributable to alcohol consumption.
- The majority of alcohol-attributable deaths were caused by high consumption.
- The authors estimated that between 2% and 3% of deaths were prevented by alcohol.

Comments: In these analyses, most of the attributions for harm are realistic, but the alcohol-preventable attributions for diabetes and ischemic heart disease appear to be low. Previous estimates of alcohol-attributable and alcohol-preventable effects have varied widely; differing assumptions about alcohol's effect on various diseases are apparently the prime reason for these disparities. There is no question that heavy alcohol consumption contributes to a large number of disease conditions. On the other hand, if the potential benefits of moderate alcohol consumption are underestimated, a net unfavorable result—as in the present study—is unavoidable.

R. Curtis Ellison, MD

Reference: Eliasen M, Becker U, Grønbæk M, et al. Alcohol-attributable and alcohol-preventable mortality in Denmark: an analysis of which intake levels contribute most to alcohol's harmful and beneficial effects. *Eur J Epidemiol.* 2013 [Epub ahead of print]. doi: 10.1007/s10654-013-9855-2.

HIV AND HCV

In HIV, Injection Drug Use, Independent of Hepatitis C Coinfection, is Associated with Increased Mortality and Worse HIV Treatment Response

Patients coinfected with HIV and hepatitis C (HCV) have more rapid HCV disease progression and may have worse response to HIV treatment. It is not clear whether this is due to HCV itself or injection drug use (IDU), because there is substantial overlap between IDU and HCV infection in most cohorts. Researchers investigated the association of IDU—as determined by records or interviews—with mortality and HIV treatment response (time to undetectable viral load and time to CD4 cell count recovery, defined as an increase of at least 100 cells/μl after starting ART) in patients with HIV and HCV coinfection who initiated HIV treatment. Among 1254 subjects, 88% had IDU documented as an HIV risk factor; the median follow-up time was 3.8 years (interquartile range of 2.1–6.2 years).

- Among patients with IDU, 67% had an undetectable HIV viral load at 12 months versus 88% among those without (adjusted hazard ratio [aHR], 0.78).
- CD4 cell count recovery at 12 months was 62% among patients with IDU versus 69% among those without (aHR, 0.82); the difference was not statistically significant (p=0.055).
- Mortality rates were 3.5 deaths per 100 person-years among people with IDU and 1 death per 100 person-years among those without (aHR, 2.15).

Comments: HIV-HCV coinfected patients with past or current IDU have worse response to HIV treatment and increased mortality compared to those without IDU. Therefore, IDU status, independent of HCV infection, should be accounted for when studying people with HIV-HCV coinfection.

Alexander Y. Walley, MD, MSc

Reference: Cescon A, Chan K, Raboud JM, et al. Significant differences in clinical outcomes between HIV-hepatitis C virus coinfected individuals with and without injection drug use history. *AIDS*. 2014:28;121–127.

Alcohol Consumption Does Not Affect HIV Surrogate Markers in Treated or Untreated HIV-Infected Individuals

Alcohol use is common in HIV-infected individuals, but clinical data on the effects of alcohol consumption on virologic outcomes among this population have been conflicting. Researchers investigated the association between alcohol consumption and HIV surrogate markers of disease progression among two groups of individuals enrolled in the Swiss HIV cohort study: treatment naïve individuals who remained off antiretroviral treatment (ART, N=2982), and individuals recently initiating ART (N=2085). Data were collected over a 7-year period. Outcomes included log-transformed CD4 counts in both groups, and virologic failure (defined as failure to achieve virologic suppression or viral rebound after suppression after treatment initiation), or ART interruption (defined

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Alcohol Consumption Does Not Affect HIV Surrogate Markers in Treated or Untreated HIV-Infected Individuals (continued from page 6)

as discontinuation of ART for greater than 7 days without medical indication) in recent ART-initiates.

- Alcohol consumption was not associated with change in CD4 count over time in either group.
- Among recent ART-initiates, virologic failure occurred in 241 (8%) of participants and was not associated with alcohol consumption.
- ART interruption occurred in 449 (15%) individuals. Heavy alcohol use (defined as average daily consumption of >40 g for women and >60 g for men) was more commonly associated with ART interruption compared with abstainers or people with light alcohol use (hazard ratio [HR], 2.24) and remained significant even after adjusting for nonadherence.

Comments: This study confirms other reports suggesting that alcohol consumption does not affect HIV biomarkers in HIV-infected individuals. However, heavier consumption was associated with ART interruption, which could have detrimental effects on HIV outcomes.

Jeanette M. Tetrault, MD

Reference: Conen A, Wang Q, Glass TR, et al. Association of alcohol consumption and HIV surrogate markers in participants of the Swiss HIV cohort study. *J Acquir Immune Defic Syndr*. 2013;64(5):472–478.

Hepatitis C Infection and Mortality Among HIV-Infected Patients with Alcohol Problems

Hepatitis C infection (HCV) is associated with an increased risk of cirrhosis and liver cancer, particularly among individuals who are coinfected with HIV. To investigate the association between HCV and mortality, researchers analyzed a cohort of 397 adults with HIV infection and alcohol problems, defined as 2 or more positive answers on the CAGE, or a physician diagnosis of alcohol dependence.

- Participants with HCV were older and more likely to report prior injection drug use, current heroin/cocaine use, and recent homelessness.
- The annual overall mortality among those with HCV was higher than those without (4.68% versus 1.65%). Liver-related mortality was also higher (1.64% versus 0.36%).
- On multivariable analysis, HCV and lower CD4 cell count were the only factors associated with higher all-cause mortality (hazard ratio [HR], 2.55 and 2.97, respectively) and liver-related mortality (HR, 3.24 and 2.79, respectively). Cocaine/heroin use was associated with higher liver-related mortality (HR, 2.29). In contrast, recent heavy alcohol use was not associated with all-cause or liver-related mortality.
- Mortality among those with prior HCV (antibody positive, HCV RNA negative) was not higher than those with no prior HCV (antibody negative).

Comments: Among individuals with HIV and alcohol problems, those with HCV have a higher mortality than those without HCV, but liver disease accounts for less than half of the difference. It is possible that there is an unmeasured factor influencing these results, but that seems unlikely since those who cleared the infection did not have higher mortality. This suggests that HCV increases mortality by mechanisms other than liver damage and reinforces the need for expanded treatment of HCV.

Darius A. Rastegar, MD

Reference: Fuster D, Cheng DM, Quinn EK, et al. Chronic hepatitis C virus infection is associated with all-cause and liver-related mortality in a cohort of HIV-infected patients with alcohol problems. *Addiction*. 2013;109:62–70.

FEATURE ARTICLE: ETHICAL CONDUCT OF ALCOHOL AND OTHER DRUG RESEARCH

Issues for Consideration in the Inclusion of Pregnant Women in Addiction Treatment Trials

Sylvia Baedorf Kassis, MPH, Instructor, Master of Science in Clinical Investigation (MSCI) Program, Boston University School of Medicine, Division of Graduate Medical Sciences, Boston, MA, USA

According to the 2010 National Survey on Drug Use and Health, an estimated 4.4% of pregnant women reported illicit drug use in the past 30 days, including heroin and the harmful use of prescription opioid analgesic medications.[1,2] Given the prevalence of substance use in this population, as well as the potential benefits and unknown consequences of intervention for both the pregnant mother and fetus, clinicians require a solid evidence base for how best to treat pregnant women with unhealthy substance use.

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Issues for Consideration in the Inclusion of Pregnant Women in Addiction Treatment Trials

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The Belmont Principle of Justice dictates that the burdens and benefits of research be distributed fairly and equally,[3] yet the current regulatory framework and a pervasive fear of legal liability discourage the inclusion of pregnant women in clinical trials testing pharmacologic treatments because of the potential risk to the fetus. In recent years, research ethics thought leaders have begun calling for medical researchers and pharmaceutical manufacturers to reconsider the exclusion of pregnant women from clinical research and challenging Institutional Review Boards (IRBs) to approve their responsible inclusion.[4] For researchers interested in studying treatments for addiction in pregnancy, understanding the regulations and developing a thoughtful, well-justified study protocol are essential.

Historical Context

Current regulations regarding the inclusion of pregnant women in research studies have been influenced by several factors. According to Levine, the US Supreme Court's 1973 decision in *Roe v. Wade* to legalize abortion led to an ongoing ethical controversy surrounding a woman's right to choose as balanced against the potential rights of a fetus.[3] Further, the devastating consequences of treating pregnant women with thalidomide, diethylstilbestrol, and the Dalkon Shield adversely affected research among this population, in spite of the fact that none of those consequences were the result of pregnant women's participation in research.[4] In fact, these tragedies were largely the unfortunate result of too little available research data to inform the use of medications in pregnancy. Nevertheless, the effect of these events was a move to categorize pregnant women as a vulnerable population requiring special protections. While the resulting research regulations provide important safeguards to women and fetuses, they also place serious restrictions on the systematic collection of data, thus limiting the evidence-based practice of medicine in this group.

The Regulations

The inclusion of pregnant women and fetuses in clinical research is covered under 45 CFR 46.204 of Subpart B of the Code of Federal Regulations,[5] which states that pregnant women and their fetuses can be included only if the study meets 10 criteria concerning preclinical study data availability, the risk profile, potential benefits, informed consent provisions, pregnant minors, and pregnancy termination (see Table). However, ambiguity in the wording of some of these criteria can present significant challenges to IRBs and impede approval of the research, particularly in evaluating whether the research risk to the fetus is greater than minimal when there is little to no benefit to either woman or fetus. IRBs are left to grapple with just how much risk is acceptable. Even in cases of potential benefit to the fetus and/or pregnant woman, as in addiction treatment studies, the frequently narrow interpretation of the regulations either encourages the removal of pregnant women from the study design or altogether discourages research aimed at studying this population. Despite general agreement that pregnant women should have access to sound information and advice upon which to base medical decisions for themselves and their fetuses, due largely to concern over legal liability IRBs tend to be highly conservative regarding the review and approval of research involving women who are, or could become, pregnant.[4]

***Table**: 45 CFR 46.204, Subpart B: Pregnant women or fetuses may be involved in research if ALL of the following conditions are met:*

Criteria:
a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
c. Any risk is the least possible for achieving the objectives of the research;
d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions;
e. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
f. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
g. For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of the Protections for Children Involved as Subjects (Subpart D);
h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; AND
j. Individuals engaged in the research will have no part in determining the viability of a neonate.

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Issues for Consideration in the Inclusion of Pregnant Women in Addiction Treatment Trials

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More Recent Considerations

A general increase in the understanding of the complex physiologic changes of pregnancy—including metabolism, body weight, plasma volume, and hormone levels—has exposed the clear limitations of applying data from other populations to pregnant women. As such, this population needs safe and effective treatment with adequate pharmacokinetic details to identify the appropriate therapeutic dose of medications across each of the trimesters of pregnancy and to quantify the risks of exposure of the fetus.[6] In addition, reticence to treat pregnant women because of concern over limited fetal safety data has its own risks, as is often seen in under- or untreated asthma, depression, diabetes, and cancer.[6]

Consequently, in recent years there has been a backlash against conservative regulatory interpretations and a call for pregnant women to be thought of as complex rather than vulnerable research subjects so that issues relevant to all aspects of women's health can be appropriately studied. "Complex" means that there are special considerations to take into account in studying them; not that they should be protected from inclusion in research.[4] The ethical imperative is that the responsible inclusion of pregnant women in research is to the benefit of the subjects. But given the highly protectionist regulatory environment, how can researchers move forward with gathering evidence that could benefit this population?

Toward the Responsible Inclusion of Pregnant Women in Addiction Research

While there are clearly agents that should not be studied in pregnancy because of their known toxic or teratogenic effects, substance use disorders pose such a high risk to pregnancy outcomes that research on addiction treatments can often be readily justified. For example, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study, is a randomized controlled trial of the impact of methadone versus buprenorphine treatment during pregnancy on maternal outcomes and on the occurrence of neonatal abstinence syndrome.[7] In a discussion of the study at an NIH workshop on the inclusion of pregnant women in clinical research, Jones noted that that the ethics approval process had not been particularly challenging, and credited her IRB's experience with two similar protocols for the favorable review.[4] Despite the reported ease of the MOTHER study's approval, however, if a researcher is interested in pursuing such an area of investigation, it is often in the best interest of the study to start a conversation with the local IRB early in the protocol development process. Such proactive behavior enables the IRB to pre-emptively review the relevant regulations and guidance documents and allows researchers to feel out the regulatory climate at their institution so that potential issues can be addressed in advance. Since the decision to enroll pregnant women in a specific trial must be based on a careful risk/benefit assessment, consideration of the following aspects, in collaboration with local IRB professionals, can support researchers' efforts to include pregnant women in their studies:

- Prior studies:
  - Have any similar studies been approved by the local IRB? If so, how did investigators address any ethical concerns in order to allow the study to proceed?
- What are the current standards of care and limits of knowledge for the condition under study in pregnant women? Justify the inclusion of pregnant women:
  - Why must this population be studied?
  - How does the topic under investigation affect pregnant women?
  - What are the risks to the pregnant woman and the fetus, and how will they be minimized?
- Argue why it would be unethical to exclude pregnant women from the research study.
- Develop a thoughtful recruitment strategy:
  - Is it possible to include a pre-screen of medical records to approach only those who have a high probability of being eligible in order to minimize distress due to exclusion?[4]
- Address issues of informed consent:
  - What information do pregnant women need about the known and unknown risks, as well as the potential benefits, of the agent under investigation in order to give truly informed consent?
- For multi-center studies, consider the comprehensive care environment and culture at each of the sites:
  - What is the experience of the sites with pregnant women who have opioid dependence?
- Monitoring:
  - What outcome measures will be monitored throughout the pregnancy?
  - Will there be any long-term follow-up of the child?
- Should a pharmacokinetic component be added to the study?

Greater detail on the aforementioned considerations can be found in the report of the United States Office of Research on Women's Health 2010 scientific forum: "Issues in Clinical Research: Enrolling Pregnant Women,"[4] and Health Canada's 2012 "Draft Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex."[8]

Conclusion

While current federal research regulations and the fear of legal liability can impede the enrollment of pregnant

(continued page 10)

Issues for Consideration in the Inclusion of Pregnant Women in Addiction Treatment Trials (continued from page 9)

women in clinical trials, there has been a recent movement encouraging the responsible inclusion of this population. Researchers interested in studying pregnant women in trials of treatments for substance use disorders should consider the regulatory environment at their institution and craft a thoughtful justification for why this population must be studied.

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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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