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Alcohol, Other Drugs, and Health: Current Evidence

JANUARY–FEBRUARY 2016

INTERVENTIONS & ASSESSMENTS

Combined and Repeated Interventions May Reduce Self-Reported Drug Use in Primary Care Patients

Brief intervention among patients identified by screening as using drugs has had no effect in large randomized trials in primary care and emergency department settings. For drug use, investigators tested an intervention that combined a video doctor, clinician brief advice, a health education booklet, and two 20–30 minute telephone counseling sessions in a randomized trial of 334 adults identified by screening over 15,000 primary care patients in community health centers. Controls received cancer screening information. The sample was restricted to screened patients with Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) scores 4–26 (indicating risky or harmful use).

- The highest-scoring drug on the ASSIST was marijuana (52%), followed by cocaine (20%), amphetamines (12%), sedatives (9%), and opioids (7%).
- 78% completed 3-month follow-up.
- In a linear regression accounting for missing data and adjusting for baseline drug use and other factors, the intervention was associated with 2.2 fewer drug use days in the past month.
- There was no significant effect of the intervention among those reporting <5 days of use in the month prior to entering the study.

Comments: Study characteristics—this was an extensive intervention involving the clinician and masking of the study purpose—may explain why the intervention was associated with less drug use while brief interventions have lacked efficacy in the several thousand randomized patients in prior studies. Or it may be that self-report reflects what participants thought researchers wanted to hear. Furthermore, fewer than 2% of patients were eligible for the intervention based on ASSIST scores and the effects were small and limited to a subgroup. At this point, the bulk of the evidence does not support efficacy for drug screening and brief intervention.

Richard Saitz, MD, MPH

Reference: Gelberg L, Andersen RM, Afifi AA, et al. Project QUIT (Quit Using Drugs Intervention Trial): a randomized controlled trial of a primary care-based multi-component brief intervention to reduce risky drug use. *Addiction*. 2015;110:1777–1790.

Mixed Findings in Trial of Varenicline for Treatment of Alcohol Use Disorder

Varenicline, a partial agonist of the nicotinic acetylcholine receptor, is currently approved for smoking cessation and may reduce alcohol reinforcement and craving. In this double-blinded clinical trial, researchers randomized 160 people with alcohol dependence to varenicline 2 mg daily or placebo for 12 weeks. The primary outcome was proportion of self-reported heavy drinking days (> 5 standard drinks/day for men and > 4 drinks/day for women). Secondary outcomes included the full 10-item Alcohol Use Disorders Identification Test (AUDIT) and 3-item AUDIT-C (consumption) scores and phosphatidylethanol (PEth) levels.

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Mixed Findings in Trial of Varenicline for Treatment of Alcohol Use Disorder

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- 73% of the varenicline group and 81% of the placebo group completed the study.
- The proportion of heavy drinking days was about 81% at baseline for both groups and decreased to 51% in the varenicline group and 49% in the placebo group over the course of active treatment, but this difference was not significant.
- At the end of treatment, the AUDIT score was 2.8 points lower in the varenicline group compared with placebo, but there was no difference in AUDIT-C scores. The mean PEth level over the active treatment period was significantly lower in the varenicline group compared with placebo (although PEth levels returned to similar levels between groups by the end of treatment).
- PEth level correlated much better with self-reported alcohol use in the varenicline group (correlation coefficient range 0.51–0.68) than the placebo group (correlation coefficient 0.38–0.52).

Comments: Varenicline did not have an effect on the primary self-reported outcome measure but did have an effect on several secondary outcomes. In contrast to many prior studies of pharmacotherapy for alcohol dependence, subjects did not receive any type of psychosocial therapy, which may partially explain the modest response. Because PEth correlated much better with self-reported alcohol use in the varenicline group than the placebo group, it is possible that participants underreported alcohol use in the placebo group. It is interesting that the intervention may have had an effect on an objective marker, which is an important observation for interpreting other studies of alcohol interventions that largely rely on self-report.

Kevin L. Kraemer, MD, MSc

Reference: de Bejczy A, Löf E, Walther L, et al. Varenicline for treatment of alcohol dependence: a randomized, placebo-controlled trial. *Alcohol Clin Exp Res*. 2015;39(11):2189–2199.

Effectiveness of Alcohol Brief Intervention In a General Hospital: A Randomized Controlled Trial

While evidence demonstrates the utility of alcohol brief intervention (ABI) in primary care, its efficacy in a general hospital setting remains unclear. Researchers conducted a randomized controlled trial to determine the effectiveness of screening plus ABI compared with screening alone at 6 months among 124 people with hazardous drinking. A Fast Alcohol Screening Test (FAST)* score of 3–12 was used to identify eligible study participants who were admitted to a medical or orthopaedic ward of a general hospital in Glasgow, UK. ABI consisted of 1 motivational counselling session in which individuals set their own alcohol-reduction goals.

- At baseline, compared with usual care, the intervention group reported greater weekly alcohol use (270 g versus 220 g), although this difference was not significant.
- Although ABI was associated with a weekly reduction of 85 g alcohol (~6 US standard drinks) at 6-month follow-up compared with usual care, no significant difference was found between groups for absolute grams of alcohol per week (169 g versus 219 g).
- Lastly, ABI demonstrated a reduction in weekly heavy drinking episodes (approximately one half-day in a week), compared with treatment as usual.

* Four-item questionnaire with a sensitivity of 91% and specificity of 95% when compared with AUDIT in primary care. A score of > 3 indicates hazardous drinking; a score of > 12 indicates alcohol dependence.

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Effectiveness of Alcohol Brief Intervention In a General Hospital: A Randomized Controlled Trial

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Comments: This study demonstrates a minor reduction in self-reported weekly alcohol use and heavy drinking episodes among a small number of hospitalized patients with hazardous alcohol use who received ABI. While these results may raise the possibility that a single brief counselling session may benefit those individuals with hazardous drinking (but not an alcohol use disorder), the potential for social desirability bias and prior null studies should not be overlooked. Prior to recommending widespread adoption of this practice, further research on a much larger scale is required.

Seonaid Nolan, MD

Reference: McQueen JM, Howe TE, Ballinger C, Godwin J. Effectiveness of alcohol brief intervention in a general hospital: a randomized controlled trial. *J Stud Alcohol Drugs.* 2015;76(6): 838–844.

Adverse Effects Are Frequent and Mostly Persistent with High-Dose Baclofen

High-dose baclofen to treat alcohol use disorder (AUD) has been the subject of intense debate in France, and some physicians have prescribed as "compassionate use." The efficacy of high-dose baclofen for treating AUD is still unknown, especially when the treatment is introduced while patients are still drinking heavy amounts. Investigators conducted a retrospective case series of patients who received high-dose (> 90mg in a day) baclofen from a single general practitioner to establish the tolerability of the treatment. Baclofen was prescribed to patients with heavy drinking (> 60 g ethanol in a day for men, > 40 g for women). The dose was increased until the patients reached low-risk drinking (40 g ethanol in a day for men, ≤ 20 g for women,) or abstinence. Of 146 patients who received baclofen (75% met *DSM-IV* criteria for alcohol dependence), 116 (79%) were interviewed.

- 78% reported at least 1 adverse effect.
- The mean (SD) number of adverse effects per patient was 2.8 (2.7).
- 53% reported persistent adverse effects.
- The most frequent adverse effects were: somnolence (40%); insomnia (20%); asthenia, paresthesia, and respiratory disorders (17%); headaches (13%); sweating and nausea (10%); memory lapses, tinnitus, reduced libido, and hypomania (7%).
- The mean dose at which the first adverse effect appeared was 83 (57) mg in a day.

Comments: Despite important limitations that could lead to an underreporting of adverse effects and the impossibility by design to conclude whether or not they are attributable to baclofen (retrospective design, lack of control, risk of recall bias, interviews conducted by the prescribing physician in most cases), this study shows that high-dose baclofen's adverse effects are very frequent, persistent in most cases, and serious in some (e.g. hypomanic episodes). Given the frequency of adverse effects and their associated risks, evidence of efficacy is necessary to justify high-dose baclofen prescription for people with an alcohol use disorder who are drinking heavy amounts.

Nicolas Bertholet, MD, MSc

Reference: Rigal L, Legay Hoang L, Alexandre-Dubroeucq C, et al. Tolerability of high-dose baclofen in the treatment of patients with alcohol disorders: a retrospective study. *Alcohol Alcohol.* 2015;50(5):551–557.

Missed Opportunity: Suboptimal Addiction Treatment Interventions Among Patients Hospitalized for Infective Endocarditis

Patients hospitalized with infective endocarditis (IE)—which is often associated with injection drug use (IDU)—have high morbidity and mortality and hospital readmission is common. Acute management of patients with IE often focuses on treatment of the infection and associated complications. However, interventions, including initiation of and linkage to addiction treatment, are often lacking. The purpose of this study was to determine the addiction interventions delivered to inpatients, with IDU-associated IE, hospitalized during the hospitalization and at discharge with IDU-associated IE over a 10-year period at a single academic tertiary care hospital.

- 102 patients were admitted with IDU-associated IE; 86% had a social work consultation, 24% had an addiction medicine consultation, and 24% had a psychiatry consultation.
- 55% of discharge summaries mentioned addiction in the assessment and plan; 8% were referred for opioid agonist treatment (OAT) and none were prescribed naloxone for overdose prevention.
- 26% of the total sample died and 49% were readmitted (14% with recurrent IE); 28% of those readmitted had ongoing IDU.

Comments: Although this study reported on a retrospective medical record review at a single institution, it underscores the importance of addiction treatment as a component of hospital treatment and discharge planning. It is important to note that not all patients with IDU will be eligible for OAT or naloxone as some patients may inject non-opioid substances or may not meet criteria for an opioid use disorder. This study highlights hospitalization for addiction-related complications as an opportunity initiate and to link patients to addiction treatment services.

Jeanette M. Tetrault, MD

Reference: Rosenthal ES, Karchmer AW, Theisen-Toupal J, et al. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. *Am J Med.* 2015 [Epub ahead of print] doi: 10.1016/j.amjmed.2015.09.024.

HEALTH OUTCOMES

Nonfatal Opioid Overdose Rarely Results in Opioid Prescription Discontinuation

Opioids prescribed to treat chronic non-cancer pain have the potential to cause accidental overdose. Although nonfatal overdose represents an opportunity to stop opioids, reduce the dose, or address potential opioid use disorder (OUD) or unhealthy use, it is unknown how often these interventions occur. In this retrospective cohort study, researchers used a large national commercial insurance database to identify 2848 patients (mean age 44 years, 40% male) receiving chronic opioid therapy for non-cancer pain who had an index emergency department or inpatient claim for nonfatal opioid overdose. The primary outcome was daily opioid dosage (morphine equivalent dosage [MED]) following the index overdose. Secondary outcomes included repeat opioid overdose and doctor switches.

- Baseline opioid dosages (MED) were < 50 mg/day (low dose) in 33%, 50–100 mg/day (moderate dose) in 22%, and > 100 mg/day (high dose) in 46%.
- After the index overdose, 91% of patients received at least 1 opioid prescription over a median follow-up of 299 days; 69–71% of patients had an active opioid prescription 31–60 days after the index overdose and 1/3 were receiving high doses.
- Overall, mean opioid dosage decreased from the pre-overdose (152–164 mg) to post-overdose (111–131 mg) levels.
- The 2-year cumulative incidence of repeat overdose was 9% with low dosage, 15% with moderate dosage, and 17% with high dosage.
- 30% of patients switched to a new prescriber after the index overdose.

Comments: This interesting analysis indicates that the majority of patients with nonfatal opioid overdose continue to receive prescription opioids, often at high dosage, for their chronic non-cancer pain. Although the proportion of these patients with OUD or unhealthy use is not known, it is clear that much of the post-overdose prescribing was inappropriate and not guideline-concordant. Improved prescriber training, systems to identify patients at risk, and greater access to OUD treatment may help mitigate this important public health problem.

Kevin L. Kraemer, MD, MSc

Reference: Larochelle MR, Liebschutz JM, Zhang F, et al. Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. *Ann Intern Med*. 2016;164:1–9.

High-Dose Opioids, Depression Increase Risk for Overdose

This retrospective cohort study examined the complex interactions between opioid medications prescribed for chronic non-cancer pain (CNCP), mental health disorders, polypharmacy, and overdose risk. Researchers examined enrollment data for 206,869 patients 18–64 years with CNCP who filled ≥ 2 prescriptions for opioid analgesics 2009–2012. Medications, clinical conditions, and utilization were examined in 6-month intervals after the first opioid prescription up to a maximum of 42 months.

- Over 3.5 years, 1385 (0.67%) of the cohort experienced a drug overdose, for an incidence rate of 421 per 100,000 person-years. The highest rates of overdose were seen in women (64%) and patients with depression (55%), followed by those with large joint arthritis (53%) or back pain (52%), and those residing in the South (47%).
- Higher opioid dose conferred higher risk, but the highest risk for overdose was seen among patients with depression receiving high-dose opioids (> 100 mg morphine equivalent, adjusted odds ratio, 7.06).
- In each 6-month interval, 19–24% of the patients filled ≥ 1 antidepressant prescription; short-term (1–30 day) receipt of antidepressants conferred higher risk of overdose.
- In each 6-month interval, 15–25% filled ≥ 1 benzodiazepine prescription; longer duration of receipt of benzodiazepines conferred higher overdose risk.

Comments: This article suggests that short-term antidepressant receipt is associated with higher risk of overdose in patients with CNCP, even among those without depression. This finding might implicate overdose as a means of suicide among acutely depressed patients, or it might be an artifact of confounding by indication. Since antidepressants are commonly used as first-line agents for CNCP, short-term use (i.e., early discontinuation) might be a marker for opioid-seeking patients, or for CNCP patients whose pain is severe and unresponsive to non-opioid modalities. Either type of patient might seek higher opioid doses, including illicit opioids or self-escalations of prescribed opioids, both of which increase overdose risk. This study conversely suggests that longer-term antidepressant use might be protective against overdose. Long-term receipt of antidepressants could be a marker for more adherent patients or those whose pain responded to non-opioid modalities and can be controlled with lower, less risky opioid doses.

Peter D. Friedmann, MD

Reference: Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treatment with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. *J Gen Intern Med*. 2015;30(8):1081–1096.

People Who Use Illicit Drugs Are More Likely to Leave the Hospital Against Medical Advice, But the Reasons and Solutions Are Not Clear

Leaving an acute care setting against medical advice (AMA) is associated with a number of negative health consequences. People with illicit drug use are at increased risk for AMA discharge, but the reasons are not clear. Researchers systematically assessed the literature on risk factors and predictors of AMA discharge as well as interventions to minimize this outcome.

- Overall, 17 studies published between 1977 and 2014 met their eligibility criteria; all but 1 were conducted in the US or Canada.
- The studies found a consistent association between illicit drug use and AMA discharge.
- One study of people with injection drug use and HIV in British Columbia reported that other factors associated with AMA discharge included recent injection drug use, aboriginal ancestry, and leaving on weekends and welfare check day. Factors that were negatively associated with AMA discharge included receipt of in-hospital methadone treatment, social support, and older age.
- One study reported that a community transitional care model of intravenous antibiotic therapy for deep tissue infections was associated with a lower rate of AMA discharges.

Comments: This review tells us that we do not know much about the reasons why people with illicit drug use leave the hospital AMA or what we can do about it. There are probably a number of factors involved, including mistrust of the health care system, inadequately treated symptoms, and lack of social support. We need to do more to understand this problem.

Darius A. Rastegar, MD

Reference: Ti L, Ti L. Leaving the hospital against medical advice among people who use illicit drugs: a systematic review. *Am J Pub Health*. 2015;105(12):e53–e59.

A New Report on Alcohol Consumption and Total Mortality Risk

This cohort study of 24,029 individuals from a nationally representative sample of US adults sought to determine any protection against mortality (n=7902) from light to "moderate" drinking. Risk ratios and 95% CIs were as follows:

- Using "occasional drinkers" (those consuming alcohol on at least 1 occasion, but always less than once in a week) as the referent group:

	Abstainers	Occasional drinkers	< 7 drinks/week	7 - < 14 drinks/week	14 - < 21 drinks/week	≥ 21 drinks/week
Corrected for age and sex	1.35 (1.26-1.44)	1.00	0.90 (0.83-0.97)	1.05 (0.95-1.17)	1.15 (0.99-1.34)	1.75 (1.49-2.05)
Adjusted	1.19 (1.11-1.27)	1.00	1.02 (0.94-1.11)	1.14 (1.02-1.28)	1.13 (0.93-1.35)	1.45 (1.16-1.81)

- Using abstainers as the referent group:

	Abstainers	Occasional drinkers	< 7 drinks/week	7 - < 14 drinks/week	14 - < 21 drinks/week	≥ 21 drinks/week
Corrected for age and sex	1.00	0.74 (0.69-0.80)	0.67 (0.63-0.71)	0.78 (0.72-0.86)	0.85 (0.74-0.99)	1.30 (1.12-1.51)
Adjusted	1.00	0.84 (0.79-0.90)	0.86 (0.81-0.92)	0.96 (0.87-1.07)	0.96 (0.81-1.13)	1.22 (0.99-1.51)

Comments: This study did not consider potential underreporting of alcohol intake, which could have led to inclusion of people with "light" consumption in the "occasional drinkers" referent group. More importantly, several factors that are actually mechanisms by which alcohol has been shown to reduce mortality (e.g., diabetes, coronary heart disease) were included and adjusted for as confounders. This would attenuate or even erase any true reduction in risk of mortality from moderate drinking. When analyses were adjusted for only age and sex, and when abstainers make up the referent group, consumers of 1-<21 drinks in a week show significant 15-30% reductions in the risk of mortality; these latter findings are very similar to those of most previous epidemiologic studies.

R. Curtis Ellison, MD

Reference: Goulden R. Moderate alcohol consumption is not associated with reduced all-cause mortality. *Am J Med*. 2016;129 (2):180–186.

Does Obesity Modify the Relation of Alcohol Consumption to Breast Cancer?

Most observational epidemiological studies have shown a slight increase in the risk of breast cancer for women who consume alcohol; there are a number of factors that affect this relationship. This study was based on a large cohort of Swedish women who were examined as part of the Women's Lifestyle and Health Study 1991–1992, then followed through 2009 for the development of breast cancer.

- Of the 45,000 women in the study, there were 1385 cases of breast cancer.
- After adjusting for confounding, the authors found no significant association between alcohol intake and risk of breast cancer.
- In sub-analyses, an increase in risk of breast cancer was found in women with a BMI ≤ 25, among whom there was a step-wise increase in the risk ratio for cancer: 1.0 (abstainers), 1.05 (0.1–5 g alcohol/day), 1.19 (5.1–15 g/day), 1.32 (> 15 g/day).

Comments: This was a very well-done study, but there remain some concerns, including the fact that the height and weight of subjects were self-reported, perhaps resulting in less accurate estimates of BMI. Further, there may have been residual confounding from other factors related to breast cancer that were not assessed. Given that both obesity and alcohol have been shown to modify estrogen levels, hormonal factors could explain these findings. The differences in effect according to BMI are interesting and add to our understanding of the association of alcohol with breast cancer, which remains limited.

R. Curtis Ellison, MD

Reference: Shin A, Sandin S, Lof M, et al. Alcohol consumption, body mass index and breast cancer risk by hormone receptor status: Women's Lifestyle and Health Study. *BMC Cancer*. 2015;15:881.

HIV AND HCV

Effect of HIV Antiretroviral Treatment (ART) as Prevention on HIV Viral Load and ART Resistance Among People Who Inject Drugs

Previous studies have confirmed that antiretroviral therapy (ART) among HIV-infected people who inject drugs (PWID) increases the likelihood of achieving non-detectable HIV viral load (VL); however, few have examined rates of ART resistance in this population. Using prospective data from a cohort of HIV-infected adult PWID engaged in HIV care, researchers examined changes in VL and rates of ART resistance 2006–2014 as part of a treatment-as-prevention (TasP) initiative.

- 819 HIV-infected PWID were included in the study; all had at least one VL observation during the study period. The mean age was 41 years, 276 (34%) patients were women, and 454 (55%) were Caucasian. Individuals included in the analysis did not differ from those excluded by age, gender, ancestry, or CD4+ cell count at baseline.
- Mean VL declined among all individuals from 3.6 to 1.5 log10 c/mL. The mean proportion of individuals with undetectable VL increased from 28% to 63%, and there was an increase in the proportion of individuals with ≥ 95% ART adherence (48% to 54%).
- Drug resistance incidence per 100 person-years declined from 6.2 to 1.8 per year.

Comments: This analysis confirms that exposure to ART as part of a TasP initiative increases non-detectable VL and decreases ART resistance in HIV-infected PWID. Future studies should attempt to define new strategies to retain this population in treatment, and further delineate other TasP factors which may promote improved HIV treatment outcomes.

Jenna L. Butner, MD† and Jeanette M. Tetrault, MD

† Contributing Editorial Intern and Clinical Instructor, General Internal Medicine, Yale University.

Reference: Milloy MJ, Wood E, Kerr T, et al. Increased prevalence of controlled viremia and decreased rates of HIV drug resistance among HIV-positive people who use illicit drugs during a community-wide Treatment-as-Prevention initiative. *Clin Infect Dis*. 2015 [Epub ahead of print]. doi: 10.1093/cid/civ929.

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American Journal of Drug & Alcohol Abuse
American Journal of Epidemiology
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American Journal of Preventive Medicine
American Journal of Psychiatry
American Journal of Public Health
American Journal on Addictions
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Journal of Viral Hepatitis
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Psychiatric Services
Substance Abuse
Substance Use & Misuse

Many others periodically reviewed (see www.aodhealth.org).

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Heavy Alcohol Use Is Associated with an Increased Risk of Cardiovascular Disease Among People with HIV

People living with HIV (PLWH) have a higher prevalence of cardiovascular disease (CVD) than those without, but little is known about the association between alcohol and CVD among PLWH. Researchers systematically reviewed the literature to investigate this.

- Overall, 13 studies met their eligibility criteria; 6 were cross-sectional, 3 were cohort, and 4 were nested case-control studies.
- The studies used a variety of measures of alcohol use. Three used dichotomous measures; of the remaining 10 that specified a level of consumption, only 3 provided incremental levels (number of drinks in a day or week).
- The studies focused on a variety of outcomes: 2 cardiomyopathy, 2 intracranial hemorrhage, 2 cerebral ischemic events, and 7 ischemic heart disease.
- Overall, heavy use or alcohol use disorder were associated with CVD (risk ratio [RR], 1.78). The 1 study that compared abstainers with people with "moderate" and heavy use* found a RR of 0.38 among those with "moderate" use when compared with abstainers.

* "Moderate" defined by study authors as average consumption of ≤4 standard drinks in a day for men and ≤3 for women. "Heavy" defined as >4 standard drinks in a day for men and >3 for women.

Comments: This review shows that we have limited evidence on the association between alcohol consumption and cardiovascular disease. The message for PLWH seems to be similar as for others: heavy alcohol use is not good for your health. Regarding "moderate" use, it is difficult to know whether the lower risk represents cause and effect or some other factor because people who drink "moderate" amounts often are healthy in many other ways. Furthermore, in PLWH, the carcinogenic effects of alcohol have not been extensively studied and PLWH often have conditions that make even "moderate" use potentially risky (e.g., hepatitis C infection).

Darius A. Rastegar, MD

Reference: Kelso NE, Sheps DS, Cook RL. The association between alcohol use and cardiovascular disease among people living with HIV: a systematic review. *Am J Drug Alcohol Abuse*. 2015;41(6):479–488.

Marijuana Use Is Associated with Greater Odds of Condomless Sex Among Black Men Who Have Sex With Men

Black men who have sex with men (BMSM) are at particularly high risk contracting HIV. Few studies have investigated the association between marijuana use and HIV risk behavior. The authors assessed marijuana and other substance use* over the past 12 months via self-report among 202 BMSM recruited from community health centers. They used logistic regression to determine the relationship between marijuana use in general or as a drug used to enhance sexual experience (sex drug) and the odds of engaging in high-risk sex (condomless or group sex).

- At baseline, 36% reported condomless sex; 22% reported group sex.
- 40% reported general marijuana use and 21% reported using it as a sex drug. The most commonly used other substances were cocaine/crack (13%), heroin (3%), and psychedelics (6%).
- After adjusting for age, education, number of sex partners, and other substance use, marijuana use in general was associated with group sex, and marijuana use as a sex drug was associated with both condomless sex and group sex. However, after adjusting for the same covariates plus use of other substances as a sex drug, the only significant relationship was between marijuana used as a sex drug and condomless sex (adjusted odds ratio, 2.86).

* Cocaine/crack, heroin, psychedelics, opioid analgesics, anti-anxiety medication, methamphetamines, poppers, other inhalants, antidepressants, erectile dysfunction drugs.

Comments: This is one of the first studies to investigate marijuana's role in HIV risk behavior and it reinforces prior findings that risky marijuana use can be a surrogate for other risky substance use. The results support inclusion of marijuana-related content in HIV risk-reduction interventions. This study used self-report over a relatively long time period; a prospective study with a shorter look-back period might improve reporting accuracy. The authors do not explain whether other substance use was limited to non-medical use, or could include use as directed by a medical provider (e.g., of antidepressants, opioids, anxiolytics, erectile dysfunction medications). Also, they note that their regression models did not include alcohol use, which could have confounded the relationship between marijuana use and condomless sex.

Jessica S. Merlin, MD, MBA

Reference: Morgan E, Skaathun B, Michaels S, et al. Marijuana use as a sex-drug is associated with HIV risk among black MSM and their network. *AIDS Behav*. 2015 [Epub ahead of print]. doi: 10.1007/s10461-015-1195-7.

FEATURE ARTICLE: ETHICAL CONDUCT OF ALCOHOL AND OTHER DRUG RESEARCH

Quality Improvement in Addiction Medicine: When Is It Research?

By Mary-Tara Roth, RN, MSN, MPH
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Patients with substance use disorder (SUD) can benefit from research advances,[1] but there is often a delay between the establishment of evidence of benefit and the implementation of an improved practice.[2,3] These advances can lead to novel therapies and treatments as well as changes at a programmatic level, such as improving processes to increase the number of patients who can be treated and retained in treatment. Once new treatments and practices are implemented, important questions remain: Are they beneficial, in *this* program, within *this* patient population? Have the changes led to the desired and expected outcomes? Are there any undesirable associated outcomes? Further, implementation of certain practices may need to be adjusted to conform to a specific treatment program or population. Thus, evidence-based new treatments, programs, and practices should be assessed to ensure that they deliver the expected benefits. This process of implementation and assessment of evidence-based practices to improve health care and delivery of care is known as *Quality Improvement* (QI).

Since QI involves the initiation and assessment of a change, and because results may be applicable to settings outside the local organization (and even published), it is common for those performing these initiatives to be concerned as to whether their QI projects also qualify as human subjects research. It can be difficult to illuminate the gray space between QI and research,[4,5,6] as evidenced by a well-publicized and controversial Office of Human Research Protections (OHRP) ruling that a multicenter project involving implementation of a simple 5-item checklist to ensure proper infection control when inserting a central venous line met the regulatory definition of human subjects research.[7,8,9,10] This article will review the distinctions between QI and research, including differentiating factors, and what steps must be taken to ensure that a project is carried out ethically and in compliance with applicable regulations.

The Quality Improvement/Research Distinction

The difference between QI and research is not mundane, and it is significant for both ethical and practical reasons. From an ethical and regulatory perspective, QI that is also considered to be research involving human participants must follow the Department of Health and Human Services (DHHS) Human Subjects Protection regulations under the OHRP.[11,12] This means that it must receive prospective approval from an Institutional Review Board (IRB) prior to starting, and obtain informed consent from the study participants (or obtain approval for a waiver of consent, which applies in some cases of minimal-risk research). Practically speaking, if one goal of the project is to publish the results, it is also important to know that the International Committee of Medical Journal Editors (ICMJE) requires research involving human subjects to describe IRB review and consent.[13] So, if a QI project is also considered to be research and it hasn't met these requirements, it cannot be published in journals following ICMJE standards.

What is Quality Improvement?

A recent expert working-group defined QI in health care as "systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings."[14] Interventions that are known to be efficacious are put in place to benefit the patients who receive them. This is unlike research, where interventions tested are not necessarily known to have benefits (this is what the research is testing), and although the participant may have some prospect of direct benefit from participation, the main goal of research is not to benefit the research participants, but to attain new knowledge and to generalize it to help future patients.

Multiple reports have underscored the importance of QI within a health care system.[15,16] Unlike research, QI is a necessary part of the provision of good medical care,[5,14,17] and part of the hospital's ethical duty to provide patients with the best care. Some claim that institutions have a "moral imperative" to perform QI,[18] and ongoing QI efforts are expected by certifying agencies such as the Joint Commission on Accreditation of Healthcare Organizations and the National Committee for Quality Assurance.[17]

What is Research?

One key to understanding whether a QI project is also research is to determine if the project meets the definition of research, under the DHHS Protection of Human Subjects Regulations (45 CFR 46).[19] In order to determine whether a project is considered to be research in need of IRB approval, one must first ask: Is it research? If so, does it involve human subjects?

The DHHS Protection of Human Subjects regulations define research as: "[…] a systematic investigation […] designed to contribute to generalizable knowledge […]" (45 CFR 46.102 [d]).[11] Both parts of this regulatory definition must be in place for a given

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activity to be considered research. First, research involves systematic processes (such as data collection based on pre-defined data-points). Second, the main purpose, or the *intent* of the investigation (what it is designed to do), is to generalize that knowledge. Most QI projects involve techniques and processes that satisfy the first part of this definition, such as systematic implementation/ intervention, data collection, and analysis. Thus, this part of the regulatory definition of research is usually not helpful in making a distinction between QI and research.

The second part of the regulatory definition of research can be more instructive. True QI-only projects have as their goal to improve systems of care for current patients at the local institution. The changes are made to benefit these patients; they are not put in place with the objective of testing them to determine whether they might benefit patients elsewhere. Although some argue that the intent (i.e., designing the project this way) to generalize the knowledge from a project should not be the primary criterion to distinguish QI and research,[20] without a change in the current regulatory requirements, individuals doing QI and research will have to make judgments based on the best interpretation of the available and applicable regulations and guidance on human subjects research. It should be noted that true QI-only projects may not be designed to contribute to generalizable knowledge, but can contribute nonetheless. The key is what the project is *designed* to do.

Further Clarification of Generalizable Knowledge

Intent at the onset and extent of what is known (intent to sustain improvements)

To clarify whether a project is QI-only or QI plus research, it is helpful to appraise the intent of a project, as well as the extent of what is known about the intervention. In regards to *intent*, if a project is put in place to improve care for current patients, there must be some agreement by those with the authority to mandate changes within the organization that the changes are a) being made to improve care; b) feasible (though this is in part what might be assessed in the QI efforts); and c) sustainable, assuming that there are positive results from the QI efforts.[17] For example, suppose a medical resident undertakes a project as QI and initiates an intervention and data collection to improve physician adherence to state guidelines for prescribing opioids for chronic pain and assessing for risk of opioid use disorder and aberrant behaviors. Once that project is done, and the medical resident moves on to a new rotation, will that effort continue to be in place? If not, and if the intervention was not something that was vetted and authorized by those with the authority to make sustained changes, then one must question whether the primary intent of implementing the change was really to improve care at the local level.

Another aspect to consider is the *extent* of what is known about the intervention or improvement. The implementation of a new health practice to improve care should be supported by sufficient evidence that it will be successful. Implementing a new health practice that has little available evidence to support its success should be considered to be research and implemented only after obtaining the necessary approval from the IRB.

Does publishing mean that the findings are generalized?

Often the first question people ask when considering whether they should submit their project to the IRB is whether they plan to publish the results in a scientific journal. After all, publishing is a way of generalizing research results. OHRP Frequently Asked Questions (FAQ) guidance[21] notes that publishing "an account of a quality improvement project does not necessarily mean that the project fits the definition of research; people seek to publish descriptions of nonresearch activities for a variety of reasons, if they believe others may be interested in learning about those activities […]" In fact, some experts advocate that publishing QI is essential as it provides documentation of evidence, allows scrutiny, and facilitates dissemination of improvements.[22] However, when planning to publish a QI activity, one should be careful to ensure that the manuscript is clear about the intent of the project. It should not be described as research, and results of the QI project should not be generalized beyond the local setting.

Further illuminating the gray area

Lynn et al[14] advise that if a QI effort is "designed to produce both local improvement and new, enduring knowledge," (p. 671) then it should be considered an "overlap project" with human subjects research. They list five characteristics of QI that overlaps with human subjects research:

1. Testing of issues that go beyond current knowledge
2. Random allocation of patients to enhance confidence in differences (rather than for equitable allocation of a scarce resource)
3. Deliberately delayed or ineffective feedback of data from monitoring the implementation to avoided bias in data interpretation
4. Involvement of researchers who have no ongoing commitment to improve care at the local level
5. Funding by parties outside the clinical setting

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Reinhardt and Ray[5] list 4 additional criteria that can be used to determine whether a project is QI-only, QI plus research, or research only. Meeting one of these criteria means that the project should be considered research, requiring prospective submission to the IRB:

1. Intervention: Is the intervention an accepted practice that is a new implementation within an organization, or is it a new, untried practice, or one with a little evidence to support its effectiveness and safety?
2. Risk: Is there absence of risk beyond the standard of practice or is there presence of any risk beyond the standard of practice?
3. Audience: Is the primary audience the organization or is it the scientific community and consumers?
4. Data source: Does the project include data from one single organization or does it include data from multiple organizations?

And what about randomization? Does randomization push the project into a research realm? Lynn et al[14] touch on this topic in their list, detailed above. Programs with limited resources may need to demonstrate that QI initiatives are cost-effective before implementing on a program/institution-wide scale. In this case, the QI effort could be introduced on a limited basis, possibly through random assignment (individual or group level) of the improvement. In this way, feasibility and effectiveness can be assessed by comparing outcomes of groups who received and did not receive the improvement to determine if the improvement should be implemented throughout the organization. Lynn et al make a distinction between randomization to enhance confidence in differences between groups and randomization for equitable allocation of scarce resources, with the former more likely to be considered in the research realm. Individuals initiating QI efforts should follow their institutional policies but can inform their thinking using the guidance criteria described above from Lynn et al and Reinhardt and Roy.[5]

Oversight

Any QI project that contains a research component will need to be submitted to the IRB and approved prior to starting. As noted earlier, the Protection of Human Subjects regulations (45 CFR 46 subpart A)[19] provide some flexibility and allow for waiver of consent as well as exemption determination for some categories of minimal-risk research. Compliance with Human Subjects Protection regulations is an important step in assuring the rights and safety of research participants.

Although QI projects that are not also research do not have to be submitted to the IRB, this does not mean that they can be conducted without adherence to appropriate best practice standards to ensure that the patients are protected and that the results can be counted on to inform the local practice. That is, QI projects must adhere to quality, safety, and ethical standards similar to research, even though the review and oversight pathways will likely function differently at different institutions. Lynn et al[14] suggest requirements derived from Emmanuel et al, "What makes research ethical?"[23] A QI project must have scientific value, scientific validity, fair participant selection, favorable risk-benefit ratio, respect for participants, informed consent, and independent review. Although similar to ethical standards guiding human subjects research, some differ in how they are implemented. For example, the authors do not suggest that the independent review be conducted by the IRB. In QI, review will be integrated into the same procedures that ensure accountability for clinical care. Also, consent will be different from what is required for research. According to Lynn et al, consent for QI should be integrated within the consent for clinical care, and patients should understand that their consent to care is also consent to participate in minimal-risk QI activities. On the other hand, it should be noted that multiple authors support the systematic ethical oversight of QI projects—akin to but separate from the IRB.[17] Individuals involved in QI efforts should check the applicable policies of their institutions.

Conclusion

It is important for those involved in carrying out QI within addiction medicine to know that there is often an overlap of QI and research, and that the primary intent of the project can determine whether the project is considered to be research or not. Some QI projects also involve research and will require submission and oversight from an IRB. However, all QI projects should be carried out in an ethical manner.

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Continuing Medical Education (CME) Accreditation Statements

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Boston University School of Medicine and Boston Medical Center. Boston University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. Boston University School of Medicine designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Target Audience
The target audience is generalist clinicians, many of whom have received limited training on detecting and treating substance abuse.

Educational Needs Addressed
Primary-care clinicians often miss the diagnosis of alcohol or drug problems and cannot stay abreast of the current substance-abuse literature in the context of a busy practice. Because of the effects of alcohol and drugs on adherence to care plans and physician-patient relationships, patients with alcohol or drug problems may receive suboptimal treatment for other conditions. Further, physicians sometimes perceive alcohol or drug dependence as less treatable than other medical conditions, and thus delegate responsibilities for screening and intervention to others. At the root of the screening and treatment gap is the inadequate provision of substance-abuse education in medical schools and mental-health fields. The newsletter addresses this not only by research dissemination but by providing free downloadable teaching tools for use by educators.

Educational Objectives
At the conclusion of this program, participants will be able to state the latest research findings on alcohol, illicit drugs, and health; incorporate the latest research findings on alcohol, illicit drugs, and health into their clinical practices, when appropriate; and recognize the importance of addressing alcohol and drug problems in primary care settings. In sum, the purpose of the newsletter is to raise the status of alcohol and drug problems in both academic and clinical culture to promote evidence-based screening and treatment and ultimately improve patient care.

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