New Dedicated Section: Prescription Drugs and Pain

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Alcohol, Other Drugs, and Health: Current Evidence

JULY–AUGUST 2016

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INTERVENTIONS & ASSESSMENTS

Extended-Release Naltrexone During Inpatient Detoxification: Opportunity for Linkage to Ongoing Care

Inpatient detoxification programs are often the first foray into treatment for many patients with opioid use disorder (OUD). However, linkage to and retention in aftercare programs continue to pose major barriers. One option to improve outcomes includes initiation of extended-release naltrexone (XR-NTX) during inpatient treatment (requiring an additional stay in the inpatient setting after completion of an opioid agonist detoxification) with linkage to office-based follow-up for ongoing XR-NTX treatment. Researchers examined follow-up rates of patients who received XR-NTX following detoxification and determined factors associated with receipt of a second injection during primary care follow-up.

- Mean age of the study sample was 32 (± 8) years of age; 90% were non-Latino Caucasian; 94% reported heroin as primary opioid of use.
- Of 62 patients who chose to receive an initial dose of XR-NTX during inpatient detoxification, 55% received a second injection during primary care follow-up, 32% received a third injection, and 23% received ≥4 injections.
- No demographic or clinical variables were associated with receipt of a second injection.

Comments: The data reported in this study come from a single site, lack a control group and information on substance use. Nonetheless, over half of patients who opted to stay an additional 10 days in inpatient treatment to receive XR-NTX followed up in primary care to receive a second injection. This model presents a unique opportunity to engage motivated patients with OUD in ongoing treatment.

Jeanette M. Tetrault, MD

Reference: Stein MD, Risi MM, Bailey GL, Anderson BJ. Linkage to primary care for persons first receiving injectable naltrexone during inpatient opioid detoxification. *J Subst Abuse Treat.* 2016;64:44–46.

Administering A Long-Acting Amphetamine to Individuals with Cocaine Use Disorder May Lead to Modest Reductions In Cocaine Use

No pharmacotherapies have been shown to reduce cocaine use among individuals with cocaine use disorder. Providing long-acting stimulants—analogous to opioid agonist treatment for opioid use disorder—is one potential approach. In this Dutch study, people with *DSM-IV* cocaine dependence and concurrent heroin dependence receiving heroin-based treatment were randomly assigned to receive sustained-release dexamfetamine (dextroamphetamine, 60 mg/day) or placebo over 12 weeks; the administration of both was directly supervised. The main outcome was self-reported cocaine use; secondary outcomes included craving, use of other substances, and criminality.

- Of 111 patients assessed, 73 were enrolled and randomized; 65 completed treatment. All 73 were included in the intention-to-treat analysis.

(continued page 2)

Free CME: ABAM-Approved MOC Activity!

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Alcohol, Other Drugs, and Health: Current Evidence **is a project of the Boston Medical Center produced in cooperation with the Boston University Schools of Medicine and Public Health. Initially supported by a grant from the National Institute on Alcohol Abuse and Alcoholism, the newsletter is currently supported by grant no. R25-DA013582 from the National Institute on Drug Abuse (NIDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDA or the National Institutes of Health.**

Administering A Long-Acting Amphetamine to Individuals with Cocaine Use Disorder May Lead to Modest Reductions In Cocaine Use (continued from page 1)

- Over the 84 days of treatment, the mean number of self-reported days of cocaine use was significantly lower in the dexamfetamine group (45 versus 61 days), compared with placebo.
- Patients receiving dexamfetamine were significantly more likely to have at least one cocaine-negative urine test in the last 4 weeks (21% versus 8%), compared with placebo.
- There were no significant differences in craving, use of other substances, or criminality.

Comments: Providing a sustained-release stimulant in a supervised fashion resulted in modest declines in cocaine use over a relatively brief period. It is not clear whether this would lead to improved clinical or psychosocial outcomes, and there is a potential for long-term harm, particularly cardiovascular complications among those with other risk factors. While this approach seems promising—particularly in settings where medication administration can be supervised—we need much more information before we can advocate prescribing long-acting stimulants to individuals with stimulant use disorder.

Darius A. Rastegar, MD

Reference: Nuijten M, Blanken P, van de Wetering B, et al. Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;6736:1–9.

Naltrexone Plus Buprenorphine for Cocaine Use In People with Opioid Dependence

Preclinical and small clinical studies suggest that the concurrent administration of buprenorphine (BUP) with naltrexone may reduce cocaine use. Using a complicated and perhaps counterintuitive combination of an antagonist (naltrexone) and a partial agonist (buprenorphine), both of which were delivered in a manner in which they were physiologically active, investigators provided extended-release injectable naltrexone (XR-NTX) and weekly cognitive behavioral therapy to 302 treatment-seeking adults with current DSM-IV cocaine dependence and current or past opioid dependence, then randomized them to placebo, 4 mg/day of BUP, or 16 mg/day of BUP for 8 weeks. Follow-up occurred 4 and 12 weeks after the treatment period.

- No between-group differences were detected for the primary outcome: urine drug screen (UDS)-corrected self-reported cocaine use days during the last 4 weeks of treatment.
- Longitudinal analyses during the evaluation period showed that the 16 mg BUP group had a greater proportion of negative UDS for cocaine compared with placebo (51% versus 46%, odds ratio 1.71; 95% CI 1.19 to ∞).
- No other secondary analyses showed benefits in terms of adherence or retention.

Comments: The study concludes that BUP plus XR-NTX deserves further "confirmatory" study as pharmacotherapy for cocaine use disorder. However, the null finding for the primary outcome, use of a single-sided test of significance, lack of adjustment for multiple analyses, and poor precision of the longitudinal effect estimate raise the likelihood that the one positive finding was by chance. The search for effective pharmacotherapy for cocaine use disorder continues.

Peter D. Friedmann, MD, MPH

Reference: Ling W, Hillhouse MP, Saxon AJ, et al. Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. *Addiction*. 2016;111(8):1416–1427.

HEALTH OUTCOMES

Cannabis Use Increases the Risk of Substance Use Disorder

In the context of the legalization of marijuana use in some US states (both for recreational and medical use) and of rising rates of use in the general population, it is important to assess the effect of cannabis use on mental health problems. Using data from the National Epidemiologic Survey on Alcohol and Related Conditions waves 1 and 2, researchers examined the prospective associations between cannabis use and substance use disorder (SUD) and mood and anxiety disorders 3 years later.

- In unadjusted analyses, cannabis use was associated with an increased prevalence and incidence of SUD and mood and anxiety disorders.
- In adjusted analyses,* cannabis use was associated with an increased prevalence and incidence of SUD, but not mood and anxiety disorders.
- Cannabis use was associated with alcohol use disorder (prevalence: odds ratio [OR], 2.5; incidence: OR, 2.7), cannabis use disorder (prevalence: OR, 12.4; incidence: OR, 9.5), other drug use disorder (prevalence: OR, 3.1; incidence: OR, 2.6), and nicotine dependence (prevalence: OR, 1.5; incidence: OR, 1.7).

* Adjusted for potential confounders from childhood (family history of SUD, parental loss, vulnerable family environment); early adolescence (low self-esteem, age of onset of anxiety disorders, social deviance); late adolescence (educational level, personality disorders, number of psychiatric disorders on axis I before age 18); adulthood (divorce, history of SUD, social deviance), in addition to age, sex, race/ethnicity.

Comments: The adjusted analyses indicate that associations between mood and anxiety disorders and cannabis use can be explained by differences in the distribution of confounders between people with cannabis use and those without. Even though the present study does not prove causation, the strong associations between cannabis use and SUD are biologically plausible and are of importance given the morbidity and mortality associated with SUD. Caution is needed when implementing policies legalizing recreational cannabis use.

Nicolas Bertholet, MD, MSc

Reference: Blanco C, Hasin DS, Wall MM, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. *JAMA Psychiatry*. 2016;73(4):388–395.

Advertising May Be Contributing to Increased E-Cigarette Consumption Among Youth

In the US, cigarette advertising has been prohibited on television since 1971, but advertising for e-cigarettes is unregulated. According to data cited in this study, youth exposure to e-cigarette ads increased by more than 250% from 2011 to 2013; past 30 day use of e-cigarettes by high school students increased from 1.5% to 13.4% in this same time period. Researchers used National Youth Tobacco Survey (N=22,007) data to examine the association between self-reported e-cigarette ad exposure and current use in middle school (n=10,419) and high school (n=11,399) students.

- Odds of past 30-day e-cigarette use were higher among students who reported frequent exposure to ads with adjusted odds ratios ranging from 1.54 to 2.91 depending on medium.
- Odds were greater for students that reported exposure "most of the time/always," suggesting a possible dose effect.

Comments: These findings suggest a link between viewing ads and using e-cigarettes. While this cross-sectional study cannot establish a causative effect, extensive previous investigations of traditional tobacco advertising raise alarms that unregulated e-cigarette ads may be targeting youth and influencing their behavior. These results suggest that efforts to reduce youth exposure to advertising are warranted.

Sharon Levy, MD

Reference: Singh T, Agaku IT, Arrazola RA, et al. Exposure to advertisements and electronic cigarette use among US middle and high school students. *Pediatrics*. 2016;137(5).

Increased Risk of Skin Cancer Related to Alcohol Intake

Skin cancer is common in areas of the world with extreme sun exposure and among individuals reporting excessive tanning; its association with alcohol consumption is not well understood. This study, based on combined data from 3 large US cohorts, examined the association between alcohol consumption and the risk of cutaneous squamous cell carcinoma (cSCC). The authors found:

- An increased risk of cSCC with alcohol intake. Among women, there was a steep increase in risk of cancer for lower levels of intake (< 5 g/day, slightly less than one half of a typical drink), with a gradual increase in risk thereafter; among men there was more of a gradual increase in risk with greater reported alcohol intake.
- A 22% increase in risk per typical drink in a day for invasive cSCC and 14% for in situ cSCC. In beverage-specific analyses, white wine consumption of ≥ 5 times in a week was associated with an increased risk of cSCC (relative risk, 1.31), but the increased risk was not found for other alcoholic beverages.
- The population-attributable risk associated with alcohol intake of < 20 g/day (about 1.5 typical drinks) was estimated as 3% of all cSCCs.

Comments: The results of the study are consistent with increases in risk associated with alcohol consumption for other types of skin cancer. Given that sun exposure is by far the primary risk factor for skin cancer, and consumers of alcohol tend to have a higher number of sunburns compared with abstainers, it is difficult to determine whether residual confounding by sun exposure is playing a role. While the authors recommend that physicians offer counseling to patients concerning the risks associated with alcohol consumption and cSCC, they should also focus on the much greater protection provided by avoiding exposure to ultraviolet radiation.

R. Curtis Ellison, MD

Reference: Siiskonen S, Han J, Li T, et al. Alcohol intake is associated with increased risk of squamous cell carcinoma of the skin: three US prospective cohort studies. *Nutr Cancer*. 2016;68(4):545–553.

HIV AND HCV

Among People with HIV, Those Who Inject Drugs Have an Increased Risk of End-Stage Liver and Renal Disease

With improvements in treatment, HIV-infected individuals are increasingly suffering from HIV-associated non-AIDS (HANA) related comorbidities. Researchers used data from a cohort of people living with HIV to investigate the association between injecting drugs and HANA comorbidities.

- Of the 5490 participants, 2028 (37%) were people who inject drugs (PWID).
- PWID had a higher risk of death before any HANA comorbidity diagnosis, compared with those who did not inject drugs.
- PWID also had a higher risk of end-stage renal or liver disease, compared with those who did not inject drugs.
- The risk of stroke, myocardial infarction, and non-AIDS defining cancers did not differ between PWID those who did not inject drugs.

Comments: It is important to note that the PWID in this study were those who had injection drug use as their risk factor for HIV infection and did not necessarily currently inject drugs; moreover, some of those who did not report injecting drugs at enrollment may have had used illicit substances or had a current substance use disorder over the course of the study period. The association between injecting drugs and end-stage liver disease is expected given the strong association between injecting behaviors and infection with hepatitis C virus. The finding that end-stage renal disease is also higher among PWID is novel and there is no obvious explanation; this needs to be investigated further.

Darius A. Rastegar, MD

Reference: Lesko CR, Moore RD, Tong W, Lau B. Association of injection drug use with incidence of HIV-associated non-AIDS-related morbidity by age, 1995–2014. *AIDS*. 2016;30(9):1447–1455.

Is Pre-Exposure Prophylaxis for HIV Transmission Cost-Effective in People Who Inject Drugs?

Daily oral pre-exposure prophylaxis (PrEP) can prevent transmission of HIV. However, PrEP is very expensive, currently about $10,000 per year per person. Researchers used a dynamic computer model to calculate the cost-effectiveness of PrEP for the high-risk group of all adult people who inject drugs (PWID) in the US. They modeled several intervention strategies: 1) PrEP alone; 2) PrEP + screen (HIV screening every 3 months and toxicity monitoring every 6 months); and 3) PrEP + screen + prompt antiretroviral therapy (ART; 50% prompt ART receipt versus 10% in strategies 1 and 2).

(continued page 5)

Is Pre-Exposure Prophylaxis for HIV Transmission Cost-Effective in People Who Inject Drugs?

(continued from page 4)

The model assumed 25% of eligible uninfected PWID would enroll in a PrEP program. Estimates for model parameters (e.g., prevalence, efficacy of treatments, costs) came from the published literature and expert opinion. Outcomes were calculated over a 20-year and lifetime time horizon.

- Main results (adapted from Table 2):

Strategy	Total HIV Infections Averted	Total Cost, US $ (trillions)	Total QALYs* (billions)	Incremental Cost-Effectiveness Ratio ($/QALY)
No PrEP	-	32.528	6.4340	-
PrEP only	21,800	32.568	6.4341	Dominated**
PrEP + screen	23,700	32.571	6.4341	Dominated
PrEP + screen + ART	26,700	32.572	6.4342	253,000

* QALYs: Quality-adjusted life-years
** Dominated: Strategy is more costly and less effective than an alternative

- Sensitivity analyses indicated that the incremental cost-effectiveness ratio of PrEP strategies decreased substantially with decreased PrEP cost and increased PrEP efficacy (e.g., approaching $50,000 per QALY when PrEP cost decreased 65% and efficacy increased to 90%).

Comments: Compared with no PrEP, PrEP strategies targeted at PWID prevented HIV transmission in this population. The PrEP with frequent screening and prompt ART strategy was the most cost-effective, but was very expensive at $253,000 per additional QALY. Medication prices will need to drop significantly to improve the value of PrEP programs for PWID. When PrEP can be delivered, providers should ensure that frequent screening and prompt ART for converters are included in the program.

Kevin L. Kraemer, MD, MSc

Reference: Bernard CL, Brandeau ML, Humphreys K, et al. Cost-effectiveness of HIV preexposure prophylaxis for people who inject drugs in the United States. *Ann Intern Med*. 2016;165(1):10–19.

PRESCRIPTION DRUGS & PAIN

Chronic Pain Associated with Substance Use, Self-Medication in Primary Care

Chronic pain is among the most common chief complaints in primary care and many patients treated for substance use disorder report it. This cross-sectional secondary analysis of baseline data from a randomized brief counseling trial included 589 adults in a hospital primary care practice who screened positive for illicit drug use or non-medical use of prescription drugs (NMUPD) based on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) for past 3 month use (scores range 0–39).

- 50% reported severe chronic pain, 24% moderate, and 13% mild, based on scores on the validated Graded Chronic Pain Scale (scores: none [0], mild [1–3], moderate [4–6] and severe [7–10]). Similar proportions of those with high-risk drug use (ASSIST ≥ 27) and lower to moderate-risk drug use (ASSIST 2–26) had severe pain. Three-quarters reported pain-related dysfunction.
- Those with severe pain were more likely to be older, Latino, less educated, less healthy, unemployed, more depressed or anxious, and have lower overall health status. They were less likely to report alcohol use and more likely to have had a hospitalization and emergency department visit in the prior 3 months.
- Of the 121 with NMUPD, 81% reported substance use to treat pain.
- Of the 576 who reported marijuana, cocaine, or heroin use in the prior 3 months, 51% reported use to treat pain.

(continued page 6)

Chronic Pain Associated with Substance Use, Self-Medication in Primary Care (continued from page 5)

- Of the 57 who had high-risk alcohol use (ASSIST ≥ 27), 79% drank to treat pain, compared with only 38% of the 265 with any unhealthy alcohol use in the prior 3 months.

Comments: This study affirms the well-described associations among substance use, chronic pain, mental health problems, poor health, and socioeconomic vulnerability. Notably, the association between substance use and chronic pain held true regardless of severity of use, which suggests that "self-medication" for pain contributes to continued substance use and return to use even among those with mild substance use problems. Empirical research is needed to demonstrate the study's implication that the assessment and management of chronic pain might improve the impact of treatments to reduce substance use in primary care settings.

Peter D. Friedmann, MD, MPH

Reference: Alford DP, German JS, Samet JH, et al. Primary care patients with drug use report chronic pain and self-medicate with alcohol and other drugs. *J Gen Intern Med*. 2016;31(5):486–491.

No Clear Opioid Dose Threshold for Opioid Overdose Death Risk

Higher-dose opioid therapy for chronic pain is associated with opioid overdose, but prescribing guidelines that recommend dosing limits are based on sparse data and arbitrary dosing categorizations. Researchers used a nested case-control methodology with Veterans Administration and National Death Index data to examine the association of prescribed opioid dosage as a continuous measure in relation to risk of unintentional opioid overdose death to determine a threshold for opioid prescribing limits.

- Among 399 patients prescribed opioid therapy and who died of overdose, 221 opioid overdose death cases were compared with 221 controls matched with cases on age, sex, race/ethnicity, prescribing date range, mental health and substance use diagnosis, medical co-morbidity, and benzodiazepine prescription.
- The average prescribed daily opioid dosage was 98.1 morphine-equivalent mg (MEM) for opioid overdose death cases and 47.7 MEM for controls.
- In a receiver operating characteristic (ROC) analysis, "dosage was a moderately good 'predictor' of opioid overdose death," but almost 30% of cases were prescribed ≤ 30 MEM.
- A dose threshold below the 100 MEM would potentially protect 31% of cases and affect 11% of controls, while a dose threshold of 50 MEM would potentially protect 66% of cases and affect 29% of controls.

Comments: This study confirms the relationship between prescribed opioid dose and the risk of opioid overdose death, but was not able to discern a clear dose threshold distinguishing overdose cases from controls. Perhaps because opioid overdose deaths frequently involve multiple substances, there is no prescribed dose threshold that eliminates overdose risk or can be used to guide prescribing policy on dose limits.

Joseph Merrill, MD, MPH

Reference: Bohnert AS, Logan JE, Ganoczy D, Dowell D. A detailed exploration into the association of prescribed opioid dosage and overdose deaths among patients with chronic pain. *Med Care*. 2016;54(5):435–441.

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The major journals regularly reviewed for the newsletter include:

Addiction
Addiction Science & Clinical Practice
Addictive Behaviors
AIDS
Alcohol
Alcohol & Alcoholism
Alcoholism: Clinical & Experimental Research
American Journal of Drug & Alcohol Abuse
American Journal of Epidemiology
American Journal of Medicine
American Journal of Preventive Medicine
American Journal of Psychiatry
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Annals of Internal Medicine
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Journal of Addiction Medicine
Journal of Addictive Diseases
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Journal of Behavioral Health Services & Research
Journal of General Internal Medicine
Journal of Hepatology
Journal of Infectious Diseases
Journal of Studies on Alcohol
Journal of Substance Abuse Treatment
Journal of the American Medical Association
Journal of Viral Hepatitis
Lancet
New England Journal of Medicine
Preventive Medicine
Psychiatric Services
Substance Abuse
Substance Use & Misuse

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

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Risky Drinking Is Associated with Poorly Controlled Chronic Pain Among Patients Receiving Long-Term Opioids

While alcohol use is common among patients prescribed opioids for pain, the relationship between patients' alcohol use patterns and pain is not known. Researchers categorized a cohort of 1424 Australian patients receiving ≥6 weeks of opioid medication for non-cancer pain as drinking risky amounts in the past 12 months occasionally (≥5 drinks on a single occasion, but not regularly), regularly (≥5 drinks weekly), or not at all (≤4 drinks per occasion).

- 24% of the patients drank risky amounts occasionally or regularly.
- 16% used alcohol to treat pain symptoms.
- 3% had an overdose in the past 12 months; alcohol was involved in 18%.
- Those drinking risky amounts occasionally or regularly reported higher pain interference.
- Those regularly drinking risky amounts also had greater pain severity.

Comments: This study suggests that unhealthy alcohol use is important among patients receiving opioids for chronic pain. Risky drinking is associated with worse pain and overdose. Although lower-level drinking was better than risky use, we cannot draw conclusions about effects of such levels of use on pain. The effectiveness of long-term opioid treatment, which is limited for chronic pain, may be limited further among patients with risky drinking, contributing towards tipping the risk-benefit balance towards not prescribing opioids when such co-occurring risks exist.

Zoe Weinstein, MD† and Alexander Y. Walley, MD, MSc

† Contributing Editorial Intern and Addiction Medicine Fellow, Boston University/Boston Medical Center

Reference: Larance B, Campbell G, Peacock A, et al. Pain, alcohol use disorders and risky patterns of drinking among people with chronic non-cancer pain receiving long-term opioid therapy. *Drug Alcohol Depend*. 2016;162:79–87.

A Comparison of Overdose Risk Behaviors and Knowledge Among Patients Receiving Opioid Medications for Opioid Use Disorder and Pain

Individuals receiving opioids for chronic pain may be at risk for opioid overdose (OOD), but the need for overdose education remains unknown. Investigators sought to identify risk factors and determine the risk awareness for OOD among US veterans, receiving medical care within the Veterans Administration, treated with opioids for chronic pain (n=38) and compared them with those treated with methadone or buprenorphine for opioid use disorder (OUD, n=52). Participants completed a questionnaire assessing OOD risk factors, knowledge, and self-estimate of overdose risk.

- The median total daily morphine equivalent (ME) dose prescribed was 35 ME among those receiving treatment for chronic pain and 430 ME for those with OUD.
- Patients receiving treatment for chronic pain demonstrated multiple OOD risk factors, but fewer than those with OUD (5.9 versus 8.5).
- Knowledge of OOD risk factors was also lower among patients receiving treatment for chronic pain compared with those with OUD.
- 70% of all study participants, irrespective of group, believed their OOD risk was below that of the average American adult.

Comments: Though limited by its small sample size and single-site recruitment, this study suggests that patients prescribed opioids for chronic pain have multiple opioid overdose risk factors and underestimate their risk for overdose. Given the recent rise in overdoses, findings from this study indicate that education for overdose prevention may need to be broadened to include patients prescribed opioids for chronic pain who are at increased risk for overdose. Future research should focus on better characterizing specific opioid overdose risk factors and risk awareness among patients prescribed opioids for chronic pain.

Seonaid Nolan, MD

Reference: Wilder CM, Miller SC, Tiffany E, et al. Risk factors for opioid overdoses and awareness of overdose risk among veterans prescribed chronic opioids for addiction or pain. *J Addict Dis*. 2016;35(1):42–51.

Benzodiazepine Prescription Associated with Early Opioid Refills in Patients Receiving Long-Term Opioid Therapy

Benzodiazepines are often prescribed to patients receiving opioids for chronic pain. Although concurrent receipt of benzodiazepines and opioids is associated with increased risk of adverse outcomes such as fatal and nonfatal opioid overdose, less is known about the association of benzodiazepines with aberrant drug-related behavior in this patient population. In this study, researchers retrospectively evaluated the medical records of 847 primary care patients receiving long-term opioid therapy (3+ prescriptions 21+ days apart within 6 months) who had at least 1 urine drug screen over 1 year. The aberrant drug-related behavior outcomes were ≥ 2 early opioid refills (prescription for same opioid within 7–25 days of the prior prescription) and positive urine cocaine screen.

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Benzodiazepine Prescription Associated with Early Opioid Refills in Patients Receiving Long-Term Opioid Therapy (continued from page 7)

- 196 (23%) patients received ≥ 1 benzodiazepine prescriptions. Patients receiving benzodiazepines were more likely to be white, female, and to have headache, depression, and anxiety.
- 183 (22%) patients had ≥ 2 early opioid refills and 93 (11%) had ≥ 1 positive urine cocaine screens. Eighty percent of early opioid refills lacked prescriber documentation of the reason for early refill.
- In adjusted analyses, receipt of a benzodiazepine prescription was associated with increased risk of early opioid refills (hazard ratio, 1.54) but not associated with a positive urine cocaine screen (odds ratio, 1.07).

Comments: The increased risk of receiving early opioid refills may indicate addictive behavior, severe pain, or lower pain tolerance among patients receiving a benzodiazepine prescription. However, the reason for early opioid refills cannot be discerned from this study. The results add to the growing literature on the increased risks of concurrent receipt of benzodiazepine and opioid medications. For their patients receiving opioid therapy for chronic pain, providers should consider alternative therapies to benzodiazepines.

Kevin L. Kraemer, MD, MSc

Reference: Park TW, Saitz R, Nelson KP, et al. The association between benzodiazepine prescription and aberrant drug-related behaviors in primary care patients receiving opioids for chronic pain. *Subst Abuse*. 2016 [Epub ahead of print]. doi: 10.1080/08897077.2016.1179242.

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.

Disclosure Statement
Boston University School of Medicine asks all individuals involved in the development and presentation of Continuing Medical Education/Continuing Education (CME/CE) activities to disclose all relationships with commercial interests. This information is disclosed to activity participants. Boston University School of Medicine has procedures to resolve apparent conflicts of interest. In addition, faculty members are asked to disclose when any unapproved use of pharmaceuticals and devices is being discussed.

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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.

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