Alcohol, Other Drugs, and Health: Current Evidence

NOVEMBER–DECEMBER 2017

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INTERVENTIONS & ASSESSMENTS

Early Initiation of Injectable Naltrexone After Low-Dose Naltrexone Titration May Lead to Improved Treatment Outcomes

Before starting long-acting injectable naltrexone (XR-naltrexone), a 7–10 day period of opioid abstinence is recommended for patients with opioid use disorder (OUD) to reduce the severity of precipitated withdrawal; this can be very difficult, especially for outpatients. Prior literature suggests that XR-naltrexone may be started earlier if preceded by low-dose oral naltrexone while managing withdrawal symptoms with non-opioid medication. Researchers randomly assigned 150 outpatient adults with OUD to either early oral naltrexone or standard buprenorphine-managed withdrawal. Patients in the early naltrexone group received buprenorphine on day 2 only, followed by ascending doses of oral naltrexone and non-opioid medications on days 3–7, and XR-naltrexone on day 8. Patients in the standard buprenorphine group received a 7-day buprenorphine taper, followed by 7 days of opioid abstinence, and XR-naltrexone on day 15. Primary outcomes were successful first and second XR-naltrexone injections.

- The buprenorphine group experienced a more rapid reduction in moderate-to-severe withdrawal symptoms compared with the early naltrexone group, but differences were not seen in the proportion of patients with at least mild withdrawal symptoms during the first week.
- 56% of participants in the early naltrexone group received a first XR-naltrexone injection, compared with 33% in the buprenorphine group.
- Half of the participants in the early naltrexone group received a second injection, compared with 27% in the buprenorphine group.
- People who used prescription opioids had 3.8 times greater odds of first naltrexone injection and 2.3 times greater odds of a second injection, compared with people who used heroin.

Comments: This study demonstrates that outpatients with OUD offered oral and then XR-naltrexone injection earlier during withdrawal managed medically with only one buprenorphine dose and other medications (day 8) are more likely to receive the injection than those offered buprenorphine followed by XR-naltrexone later (day 15). Generalizability of the findings may be limited because most participants (~4/5) did not inject opioids. Caution should be used in applying study findings to patients who use heroin, who were less successful in both treatment groups.

Jessica L. Taylor, MD† and Alexander Y. Walley, MD, MSc

† Contributing editorial intern and Assistant Professor of Medicine, Boston Medical Center

Reference: Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: A randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry*. 2017;174(5):459–467.

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Ongoing Opioid Use Is a Risk Factor for Early Disengagement From Buprenorphine Treatment

Opioid agonist treatment interruptions put patients at risk of return to opioid use and overdose. Rates of disengagement from buprenorphine treatment are highest within the first month of treatment. The authors of this study sought to characterize: 1) the incidence of treatment disengagement and attributes of patients with treatment disengagement within ≤1 month of treatment initiation of office-based opioid treatment (OBOT) with buprenorphine, and 2) the incidence and attributes of patients who re-engage in care at the same OBOT clinic within 2 years.

- Early disengagement occurred in 8% (104/1234) of patients.
- Urine drug screen positive for opioids within the first month was associated with increased odds of early disengagement (adjusted odds ratio [aOR], 2.01). Transferring from another buprenorphine prescriber was associated with decreased odds of very early disengagement (aOR, 0.09).
- Among the subset of patients with early disengagement, 12% (10/84) re-engaged with the OBOT program in the subsequent 2 years. No characteristics were significantly associated with reengagement.

Comments: In this exploratory analysis of data from one OBOT clinic, disengagement from buprenorphine treatment was rare and associated with ongoing opioid use within the first month of treatment, suggesting that patients with urine toxicology evidence of ongoing opioid use may benefit from added resources.

Jeanette M. Tetrault, MD

Reference: Hui D, Weinstein ZM, Cheng DM, et al. Very early disengagement and subsequent re-engagement in primary care Office Based Opioid Treatment (OBOT) with buprenorphine. *J Subst Abuse Treat*. 2017;79:12–19.

Inpatient Addiction Medicine Consult Service: Harnessing the Reachable Moment

Substance use disorders are common among hospitalized patients. The feasibility of initiating addiction treatment in the hospital and directly linking to outpatient treatment has been established, but barriers exist to operationalizing this practice. Inpatient Addiction Medicine consult services may facilitate linking patients to care. This study describes the initial experience of the Addiction Consult Service (ACS) at Boston Medical Center, which began providing services in 2015.

- In the first 26 weeks of the service, 367 consults were placed to the ACS, with 337 consults completed on 319 unique patients. A mean of 2.8 consults were requested for each weekday that the service was available.
- Of the 337 completed consults: 78% of patients had opioid use disorder (OUD), 37% alcohol use disorder (AUD), 28% cocaine use disorder, 9% benzodiazepine use disorder, 3% cannabinoid (including synthetic) use disorder, and <1% methamphetamine use disorder.
- Methadone was initiated in 70 inpatients and buprenorphine in 40 inpatients. Naltrexone was recommended 45 times (for OUD, AUD, or both).
- Of the patients initiated on methadone, 76% linked to an opioid treatment program, with 54%, 39%, and 29% retained at 30, 90, and 180 days, respectively. For buprenorphine initiates, 49% linked to ongoing buprenorphine, with 39%, 27%, and 18% retained at 30, 90, and 180 days, respectively. For naltrexone, 26% linked to ongoing naltrexone, all with AUD alone.

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Inpatient Addiction Medicine Consult Service: Harnessing the Reachable Moment (continued from page 2)

Comments: In this single-site descriptive study, implementation of an inpatient Addiction Consult Service was feasible and effective at linking patients to outpatient treatment. This was especially true for patients with OUD who were initiated on methadone. Additional strategies are needed to address outpatient addiction treatment retention among this population.

Jeanette M. Tetrault, MD

Reference: Trowbridge P, Weinstein ZM, Kerensky T, et al. Addiction consultation services – linking hospitalized patients to outpatient addiction treatment. *J Subst Abuse Treat*. 2017;79:1–5.

HEALTH OUTCOMES

Marijuana Use May Increase the Risk for Hypertension Mortality

Marijuana may be linked to cardiovascular disease, but evidence is scarce. Using data from the 2005 US National Health and Nutrition Examination Survey (NHANES) and 2011 mortality files of the National Center for Health Statistics, researchers estimated mortality rates and hazard ratios (HR) for hypertension, heart disease, and cerebrovascular deaths among people who use marijuana compared with those who do not.

- There were 1213 participants (aged ≥20) with 19,569 person-years of follow-up. Average age at entry was 38 years. Overall, 34% had neither marijuana nor cigarette use; 21% used marijuana only; 20% used marijuana and cigarettes; 16% used marijuana and were past smokers. Average duration of marijuana use was 12 years.
- In models adjusted for socio-demographic and medical characteristics (including smoking, alcohol use, and presence of hypertension and cardiovascular disease diagnoses), people with marijuana use had an increased risk of hypertension mortality (HR, 3.42), compared with those who did not. The HR for each year of marijuana use was 1.04.
- Hazard ratios for heart disease and cerebrovascular deaths were not significant.

Comments: This study suggests that marijuana use may increase the risk for hypertension mortality. These results should be replicated in a study assessing marijuana use over time, but raise concerns about the potential impact of recreational marijuana use on mortality from cardiovascular causes in an era of widespread legalization throughout the US.

Nicolas Bertholet, MD, MSc

Reference: Yankey BA, Rothenberg R, Strasser S, et al. Effect of marijuana use on cardiovascular and cerebrovascular mortality: A study using the National Health and Nutrition Examination Survey linked mortality file. *Eur J Prev Cardiol*. 2017;24(17):1833–1840.

People Who Use Heroin Do Not Increase Use After Receipt of Naloxone Rescue Training

Equipping people who use opioids with naloxone rescue kits has emerged as a key strategy to reducing fatal opioid overdose. However, there is concern that this may lead to risk compensation - an increase in risky behaviors by reducing perceived negative consequences of opioid use. This prospective study examined whether self-reported drug use behavior and the Addiction Severity Index (ASI) drug score changed in response to opioid overdose education and naloxone training among people who use heroin who were receiving or not receiving methadone or buprenorphine treatment.

- Among people who use heroin who were not receiving opioid agonist treatment, daily heroin use and ASI drug score decreased at 1 and 3 months after receiving overdose education and naloxone training.
- No significant change in use of more than one drug use was detected.
- Among people treated with methadone or buprenorphine, no significant change in self-reported drug use at 1 and 3 months was detected.

Comments: This study provides reassurance that overdose prevention education and naloxone rescue kit distribution do not increase drug use. The pre-post design of this study is a limitation. Nevertheless, such information is helpful for providers treating patients with opioid use disorders, naloxone distribution programs. The findings may help to allay the fears about state initiatives that are facing resistance to supporting overdose prevention education and distributing naloxone rescue kits due to concerns of risk compensation.

Jessica Gray, MD† and Alexander Y. Walley, MD, MSc

† Contributing editorial intern and Addiction Medicine Fellow, Boston Medical Center/Boston University School of Medicine

Reference: Jones JD, Campbell A, Metz VE, Comer SD. No evidence of compensatory drug use risk behavior among

The State of Medical and Non-Medical Use of Prescription Opioids in the US

The National Survey on Drug Use and Health is conducted annually among US adolescents and adults and includes questions about prescription opioid use and non-medical use of prescription opioids (NMUPO). Researchers used data from interviews of 51,200 adults aged ≥18 in 2015 to investigate the prevalence of prescription opioid use and NMUPO, and associated demographic factors and motivations.

- Overall, 38% of respondents (representing an estimated 92 million US adults) reported taking an opioid in the past year; 4.7% reported NMUPO (12 million); 0.8% met criteria for an opioid use disorder (2 million).
- Among those who reported NMUPO, 60% reported taking an opioid without a prescription, 22% used them in greater amounts than directed, 15% more often than directed, and 13% longer than directed.
- Among those who reported NMUPO, the most common motivation was relief of physical pain (66%), followed by relaxing (11%), and getting high (11%). Among those with opioid use disorder, the most commonly reported motivations were relief of physical pain (49%), getting high (16%), being "hooked" (12%), and to relax (9%).

Comments: This survey shows that prescription opioid use and NMUPO are common in the US. The fact that relief of physical pain is the most frequently reported motivating factor for NMUPO is of interest and should be investigated further. The authors argue that this demonstrates the need for "evidence-based pain management," but it is far from clear that this will help. There is very little evidence to guide us and, so far, the notion that pain is something that must be "managed" aggressively has only contributed to this problem.

Darius A. Rastegar, MD

Reference: Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in US adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. 2017;167(5):293–301.

Strong Relationships with Parents Associated with Reductions in Heavy Episodic Drinking in Early Adulthood

Heavy episodic drinking (HED) is a leading cause of morbidity and mortality among US youth. The likelihood of HED increases throughout the high school years, stabilizes briefly, and then decreases as youth enter early adulthood. This report examined the relationship between a composite measure of parental relationship quality and the risk of HED among early adults, aged 18–25.

- Paternal relationship quality was negatively associated with HED for both sons and daughters aged 18–25 (odds ratio [OR], 0.73).
- Maternal relationship quality was negatively associated with HED among both sons and daughters through age 19 (OR, 0.50). The association weakened for daughters by age 20 (OR, 0.87, 95% CI: 0.72–1.04), but remained strong for sons until age 25.

Comments: Parents may feel powerless to influence their children's risk behaviors once they become legally recognized as adults and responsible for their own actions and decisions. This article is an important reminder of the influence that parents continue to have on their children into adulthood and suggests that fostering strong positive relationships between parents and young adult children may offer substantial health benefits.

Sharon Levy, MD, MPH

Reference: Madkour AS, Clum G, Miles TT, et al. Parental influences on heavy episodic drinking development in the transition to early adulthood. *J Adolsec Health*. 2017;61(2):147–154.

HIV AND HCV

Criminalization of Drug Use Hampers HIV Prevention and Treatment

People who inject drugs (PWID) are at risk for acquiring HIV infection. Criminalization of drug use may reduce HIV transmission by discouraging use in general. On the other hand, it may encourage risky use and create barriers to accessing preventive services and treatment. Researchers completed a systematic review of the literature from 2006 to 2014 exploring this topic.

- 106 articles met inclusion criteria: 49 cross-sectional, 29 longitudinal, 22 qualitative, 4 mathematical modeling, and 2 mixed methods studies. Study locations included North America (40%), Asia (25%), Eastern Europe (11%), South America (9%), Middle East (8%), Western Europe (5%), and Oceania (1%).
- The studies reported on a variety of indicators of criminalization, including street-level policing (37%), incarceration (36%), drug paraphernalia laws (12%), national drug strategies (10%), and prohibitions or restrictions on opioid agonist treatment, needle exchange, or other HIV prevention interventions (9%).

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Criminalization of Drug Use Hampers HIV Prevention and Treatment (continued from page 4)

- Among the included studies, 80% suggested that criminalization of drug use has negative effects on HIV prevention and treatment, 9% found no association, 5% both null and negative effects, and 1% beneficial and negative effects.

Comments: The preponderance of the evidence suggests that criminalization of drug use has a negative effect on HIV prevention and treatment. This has to be added to the tremendous financial and social costs of criminalization. In order to best address the problem of HIV infection among PWID, we need to move away from punitive policies.

Darius A. Rastegar, MD

Reference: DeBeck K, Cheng T, Montaner JS, et al. HIV and criminalisation of drug use among people who inject drugs: a systematic review. *Lancet HIV*. 2017;4:e357–e374.

PRESCRIPTION DRUGS & PAIN

Limited Evidence to Support Cannabis Use for Chronic Pain

Although legal and illicit cannabis is frequently used for chronic pain control, the strength of scientific evidence for this practice is uncertain. Researchers examined 2 systematic reviews, 27 randomized controlled trials, and 3 observational studies to assess the impact of cannabis on chronic pain. Eleven systematic reviews and 32 observational studies were identified to assess adverse effects.

- For chronic neuropathic pain, 11 studies indicated that "a higher proportion of intervention patients had clinically significant pain relief up to several months later." A meta-analysis of 9 of these studies indicated patients receiving cannabis were more likely to report 30% or better neuropathic pain improvement than control patients (risk ratio [RR], 1.43).
- For chronic pain due to multiple sclerosis (9 studies), cancer (3 studies), and other causes (5 studies), there was insufficient evidence to show a benefit of cannabis.
- For adverse effects, there was moderate evidence to suggest an increased risk of motor vehicle accidents and limited evidence to suggest increased mental health adverse effects from cannabis use.

Comments: This well-done systematic review indicates that cannabis may be effective for chronic neuropathic pain. Conclusions about its efficacy for other types of chronic pain could not be drawn, illustrating the inadequate evidence base for cannabis as a treatment for chronic pain. Most identified studies included few or highly selected participants, were short duration, and used variable cannabinoid dose. Higher quality studies are needed and will either need to use standardized plant-based cannabis or study specific doses of cannabinoids. For this to happen in the US, federal barriers to cannabis-related research will need to be relaxed.

Kevin L. Kraemer, MD, MSc

Reference: Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med*. 2017;167 (5):319–331.

A Multicomponent Primary-care Intervention Can Improve Guideline-concordant Opioid Prescribing

Prevention of unsafe opioid prescribing is a national priority. Researchers cluster-randomized 53 clinicians in 4 primary care practices to a multicomponent intervention (electronic registry, academic detailing, nurse care management, electronic decision tools) or control (electronic decision tools only). Eligible clinicians had ≥4 patients receiving chronic opioid therapy. Over a 12-month period, the researchers assessed the primary outcomes of guideline-concordant care (e.g., signed agreement and at least 1 urine drug test) and early refills (defined as ≥2 early refills), and the secondary outcomes of opioid discontinuation and/or 10% reduction in opioid dose.

- Patients in the intervention group (n=586) were more likely than controls (n=399) to receive guideline-concordant care (adjusted odds ratio [aOR], 6.0), but no less likely than controls to have ≥2 early refills (aOR, 1.1).
- Intervention group patients were more likely than controls to have opioid discontinuation (aOR, 1.5) or opioid dose reduction (aOR, 1.6).
- All 4 primary care practices made efforts to continue the intervention once the research study ended.

Comments: This well-designed trial demonstrates that a primary care-based multicomponent intervention can increase guideline-concordant opioid therapy, opioid discontinuation, and dose reduction. It is not clear whether instances of opioid discontinuation or dose reduction were in response to opioid misuse identified via increased monitoring. Although one-fifth of patients in

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A Multicomponent Primary-care Intervention Can Improve Guideline-concordant Opioid Prescribing (continued from page 5)

both groups received ≥2 early refills, the researchers cautioned that early refills do not necessarily reflect opioid misuse because actual fill date was not known and other legitimate reasons for an early refill exist. Further research will be required to determine whether similar interventions decrease opioid-related adverse outcomes while maintaining patient pain control and function.

Kevin L. Kraemer, MD, MSc

Reference: Liebschutz JM, Xuan Z, Shanahan CW, et al. Improving adherence to long-term opioid therapy guidelines to reduce opioid misuse in primary care: a cluster-randomized clinical trial. *JAMA Intern Med*. 2017;177(9):1265–1272.

US Adults With Mental Health Disorders Receive More Prescription Opioids

Given the current US opioid epidemic, identification of specific populations that receive prescription opioids is of strategic importance for risk-mitigation efforts. Using self-report and administrative or pharmacy database linkages from the Medical Expenditure Panel Survey (a nationally representative sample of non-institutionalized US adults), this cross-sectional study sought to derive national estimates of prescription opioid receipt among people with mental health (mood or anxiety) disorders and examine factors associated with their use.

- Of the almost 52,000 survey participants, 14% had a mental health disorder.
- Prescription opioid receipt (defined as >2 filled opioid prescriptions in a calendar year) was more prevalent among adults with a mental health disorder compared with those without (19% versus 5%, respectively).
- Even after adjusting for socio-demographics, health status, and use of selected health services, adults with a mental health disorder were more than twice as likely as those without to receive prescription opioids (odds ratio, 2.08).
- Based on these findings, national estimates approximate that of the 38.6 million US adults with a mental health disorder, 7.2 million receive prescription opioids.
- Furthermore, 51% of all opioid prescriptions distributed in the US are provided to adults with a mental health condition (60 million of 115 million prescriptions).

Comments: Mental health disorders are a risk factor for non-medical use of prescription opioids. The higher prevalence of prescription opioid receipt among adults with a mental health disorder suggests that this population is critical to consider when addressing the issue of opioid use from a health system or policy perspective. Future studies should focus on identifying patient and provider factors related to higher opioid prescribing rates among this group and developing interventions to mitigate risk.

Seonaid Nolan, MD

Reference: Davis MA, Lin LA, Liu H, Sites BD. Prescription opioid use among adults with mental health disorders. *J Am Board Fam Med*. 2017;30(4):507–517.

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