Alcohol, Other Drugs, and Health: Current Evidence

APRIL 2008

TABLE OF CONTENTS

INTERVENTIONS & ASSESSMENTS

Baclofen for Alcohol Dependence in Patients with Cirrhosis, 1

Bupropion Added to Nicotine Replacement for Patients in Alcohol Treatment, 1

Effect of Opioid Dependence Medications on Cardiac QT Intervals, 2

A Brief Screen for Classifying Pain Severity in Patients with Opioid Dependence, 3

HEALTH OUTCOMES

Death Before, During, and After Opioid Maintenance Treatment, 3

Relapse Risk in People with Remitted Alcohol Dependence, 4

Similar Outcomes from Observed and Unobserved Dosing of Buprenorphine-Naloxone, 4

Persistent Hepatitis C Reinfection in Injection Drug Users Who Have Cleared the Virus, 5

JOURNAL ALERT

Supplement to *Pediatrics* Examines the Developmental Nature of Underage Drinking, 5

Interventions and Assessments

Baclofen for Alcohol Dependence in Patients with Cirrhosis

Some of the medications used to treat alcohol dependence are potentially hepatotoxic. Therefore, efficacious and safe alternatives to treat alcohol dependence in people with cirrhosis are desirable.

Researchers in this study assessed the safety and efficacy of baclofen, a muscle relaxant, in a 12-week randomized, placebo-controlled trial of 84 patients with cirrhosis and alcohol dependence who underwent detoxification. The medication was given by a family member who also checked adherence, side effects, and alcohol use. All patients received counseling.

- Baclofen patients were more likely than placebo patients to be abstinent (71% versus 29%).
- Baclofen patients also had greater improvements in liver-related blood tests (international normalized ratio, gamma-glutamyltransferase, alanine aminotransferase, albumin, and bilirubin).
- Side effects were similar in both groups, and none led patients to discontinue the medication.

Comments: Some medications used to treat alcohol dependence are potentially hepatotoxic. Such toxicity, however, is not caused by acamprosate and generally not a concern with naltrexone at standard doses. Nonetheless, having another medication to treat alcohol dependence, particularly one that is not hepatotoxic, is useful. The effect of baclofen on abstinence in this study was impressive, although the sample was small and the study was short. If these results are confirmed in future studies, baclofen would be a welcome treatment option for alcohol dependence.

Richard Saitz, MD, MPH

Reference: Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet.* 2007;370 (9603):1915–1922.

Bupropion Added to Nicotine Replacement for Patients in Alcohol Treatment

The effectiveness of bupropion, an antidepressant approved for smoking cessation in the general population, has not been studied in people being treated for alcoholism. Therefore, researchers conducted this double-blind, placebo-controlled study of 58 patients who were beginning alcoholism treatment, smoked ≥20 cigarettes per day, were willing to quit smoking, and did not have a psychiatric condition or a contraindication to bupropion.

Subjects were randomized to receive either bupropion SR (150 mg twice per day) or placebo. Both groups received nicotine patches, were asked to attend 1 hour of smoking cessation counseling, and were instructed to start taking their pills 8 days before their planned quit day.

- Thirty-three percent of the bupropion group and 11% of the placebo group discontinued their medication by week 4.
- At each follow-up, both the bupropion and placebo groups showed a significant reduction in smoking. At week 4, 30% and 18%, respectively, reported abstinence from smoking in

(continued on page 2)

Alcohol, Other Drugs, and Health: Current Evidence is a project of the Boston Medical Center, supported by the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, and produced in cooperation with the Boston University Schools of Medicine and Public Health.

Editorial Board

Editor
Richard Saitz, MD, MPH, FASAM, FACP
Professor of Medicine & Epidemiology
Boston University Schools of Medicine & Public Health

Co-Editor
David A. Fiellin, MD
Associate Professor of Medicine
Yale University School of Medicine

Associate Editors
Julia H. Arnsten, MD, MPH
Associate Professor of Medicine, Epidemiology, & Psychiatry
Albert Einstein College of Medicine

R. Curtis Ellison, MD
Professor of Medicine & Public Health
Boston University School of Medicine

Peter D. Friedmann, MD, MPH
Associate Professor of Medicine & Community Health
Warren Alpert Medical School of Brown University

Marc N. Gourevitch, MD, MPH
Dr. Adolph & Margaret Berger Professor of Medicine
New York University School of Medicine

Kevin L. Kraemer, MD, MSc
Associate Professor of Medicine & Health Policy & Management
University of Pittsburgh Schools of Medicine & Public Health

Jeffrey H. Samet, MD, MA, MPH
Professor of Medicine & Social & Behavioral Sciences
Boston University Schools of Medicine & Public Health

Alexander Y. Walley, MD, MSc
Instructor of Medicine
Boston University School of Medicine

Managing Editor
Donna M. Vaillancourt
Boston Medical Center

Bupropion Added to Nicotine Replacement (continued from page 1)

the past 7 days; at 6 months, the proportions were 17% and 29%, respectively.

- However, there was no significant difference in smoking abstinence between the groups.

Comments: People with alcohol or other drug use disorders have a high prevalence of smoking and much difficulty quitting. Although this study did not show a benefit of bupropion, it does suggest that using nicotine replacement with patients in treatment for alcoholism could help them quit smoking.

Julia H. Arnsten, MD, MPH

Reference: Grant K, Kelly S, Smith L, et al. Bupropion and nicotine patch as smoking cessation aids in alcoholics. *Alcohol.* 2007;41(5):381–391.

Effect of Opioid Dependence Medications on Cardiac QT Intervals

Levomethadyl (LAAM), methadone, and buprenorphine are effective treatments for opioid dependence. Although all 3 have been shown to block hERG*-channel activity, which can prolong the corrected QT interval (QTc), only LAAM (no longer available in the US) and methadone have been associated with reports of severe cardiac arrhythmias including *torsades de pointes* ventricular tachycardia.

A recent study compared the effect of all 3 medications on the QTc. Researchers obtained 12-lead electrocardiograms (ECGs) at baseline and every 4 weeks in 154 patients randomized to receive 1 of the 3 medications, at efficacious doses, for 17 weeks. A QTc over 470 milliseconds in men or 490 milliseconds in women was considered prolonged, and an increase of >60 milliseconds above baseline in any patient was considered important.

Primary findings were as follows:

- Baseline QTc was similar in the 3 groups.
- During treatment, QTc was prolonged in 28% of subjects in the LAAM group and in 23% of subjects in the methadone group, but in no subjects in the buprenorphine group.
- In the LAMM group, 21% of patients had an increase in QTc >60 milliseconds above baseline compared with 12% in the methadone group and 2% in the buprenorphine group.

Comments: Although physiologic data suggest all 3 medications could prolong the QTc, results of this clinical study indicate that buprenorphine is less likely than LAAM or methadone to do so. (The study has limitations in that buprenorphine was administered thrice weekly instead of once daily, as is standard practice; the period of treatment was short compared with standard usage; and the study had no placebo arm due to ethical concerns.) Physicians caring for patients receiving methadone, but not buprenorphine, should consider checking a baseline ECG and monitoring QTc intervals periodically, although the frequency of monitoring is not clear.

David A. Fiellin, MD

*human ether-a-go-go–related gene

Reference: Wedam EF, Bigelow GE, Johnson RE, et al. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med.* 2007;167(22):2469-2475.

A Brief Screen for Classifying Pain Severity in Patients with Opioid Dependence

Pain is prevalent among people with opioid dependence, and its association with psychosocial stressors (e.g., depression) may threaten clinical gains achieved through substance abuse treatment. A rationale exists, therefore, for screening treatment-seeking patients with opioid dependence for potentially destabilizing pain.

Researchers in this study examined the effectiveness of a streamlined pain screening instrument among people with opioid dependence who sought inpatient opioid detoxification in Massachusetts. Following admission, 110 adults completed a brief questionnaire, including the Brief Pain Inventory–Short Form, to assess physical pain during the last week.

- Ninety-one percent of patients reported some pain during the previous week. Forty-three percent reported chronic pain (lasting ≥6 months), and 70% of those with chronic pain rated their pain as "severe" (≥7 on a scale of 1 to 10).
- Patients with severe chronic pain, versus patients with less severe or no pain, had worse depressive symptoms and were more likely to be receiving occupational disability benefits.

Comments: Severe chronic pain was common among people with opioid dependence seeking inpatient detoxification and was associated with conditions (depressive symptoms, disability) that complicate recovery from drug dependence.

Limitations of this study include the high-acuity patient population (seeking inpatient treatment) and lack of detail about the timing of pain assessment, sequencing of screening steps, and potential for opioid withdrawal symptoms to be reported as pain. Nonetheless, this study suggests that assessing pain severity among patients in opioid dependence treatment could help clinicians identify which of their patients might benefit from pain-related intervention. Additional research is needed to define the impact of simple pain screening algorithms on clinical outcomes among people in treatment for opioid dependence.

Marc N. Gourevitch, MD, MPH

Reference: Potter JS, Shiffman SJ, Weiss RD. Chronic pain severity in opioid-dependent patients. *Am J Drug Alcohol Abuse.* 2008;34(1):101–107.

Health Outcomes

Death Before, During, and After Opioid Maintenance Treatment

To what extent does opioid maintenance therapy (OMT) reduce mortality in patients with dependence? To answer this question, Norwegian researchers linked data from a national death registry to a national database of people who were on a waiting list for OMT, receiving OMT (predominantly methadone), or discontinued OMT. Researchers then compared the risk of death during treatment with the risk before and after treatment among 3789 patients. In some cases, data from the death registry were confirmed with death certificates and autopsy results.

- Over 7 years, 213 patients died.
- Seventy-nine percent of deaths in the waiting-list group, 27% of deaths in the treatment group, and 61% of deaths in the discontinued-treatment group were attributed to overdose.
- Mortality risk (from overdose and other causes) was significantly lower in patients receiving treatment than in patients on the waiting list (relative risk [RR], 0.5; death rates of 1.4 versus 2.4 per 100 person years, respectively).
- Risk was highest among men who discontinued treatment (RR, 1.8 compared with men on the waiting list).

Comments: With impressive methodological rigor, these investigators provide further strong evidence that OMT lowers the risk of death. Because of the increasing cases of overdose death attributed to physician-prescribed methadone for pain and the potential negative public backlash towards this treatment, these data may play an important role in policy efforts that support the continued use of OMT to reduce mortality risk in people with opioid dependence.

Jeffrey A. Samet, MD, MA, MPH

Reference: Clausen T, Anchersen K, Waal H. Mortality prior to, during, and after opioid maintenance treatment (OMT): a national prospective cross-registry study. *Drug Alcohol Depend.* 2008;94(1-3):151-157.

Relapse Risk in People with Remitted Alcohol Dependence

The rate of relapse among people in remission from alcohol dependence has not been extensively studied. To examine this, researchers assessed alcohol use and alcohol use disorder symptoms over 3 years among 1772 adults who had participated in a national alcohol survey and were in remission from alcohol dependence at baseline.

- At the baseline interview, 25% of subjects drank risky amounts,* 38% drank lower-risk amounts,** and 37% abstained.
- During follow-up, 51% of subjects who drank risky amounts, 27% of subjects who drank lower-risk amounts, and 7% of subjects who abstained reported a recurrence of alcohol use disorder symptoms; 10%, 4%, and 3%, respectively, met criteria for a recurrence of alcohol dependence.
- Recurrence of alcohol use disorder symptoms or alcohol dependence was more likely in younger subjects. It was less likely among patients with a longer duration of remission at baseline.
- In adjusted analyses, subjects who drank risky or lower-risk amounts were more likely than subjects who abstained to report at follow-up recurrent alcohol use disorder symptoms (odds ratios [ORs], 14.6 and 5.8, respectively) and alcohol dependence (ORs, 7.0 and 3.0, respectively).

Comments: This study shows that relapse is common among people in remission from alcohol dependence and much more likely if they are drinking risky amounts. The results support the need to carefully monitor and support abstinence in people with remitted alcohol dependence.

Kevin L. Kraemer, MD, MSc

*Subjects who drank risky amounts had no current symptoms of alcohol abuse or dependence and drank >14 drinks per week (>7 for women) or >4 drinks on any day (>3 for women).
**Subjects who drank lower-risk amounts had no current symptoms of alcohol abuse or dependence and did not meet criteria for risky drinking.

Reference: Dawson DA, Goldstein RB, Grant BF. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: a 3-year follow-up. *Alcohol Clin Exp Res.* 2007;31(12):2036–2045.

Similar Outcomes from Observed and Unobserved Dosing of Buprenorphine-Naloxone

Few studies have compared the effects of observed dosing of opioid maintenance treatment (medication dispensed daily in a clinic) with the effects of unobserved dosing (medication dispensed weekly and taken at home). This Australian study randomized 119 people who used heroin and were seeking maintenance treatment to receive either observed dosing or unobserved dosing of buprenorphine-naloxone for 3 months. All subjects met weekly with a nurse case-manager.

- At 3 months, retention in treatment was similar among the groups (61% of the observed dosing group versus 57% of the unobserved dosing group).
- Reduction in days of heroin use from baseline to 3 months was also similar (reduction of 22 days for the observed dosing group versus 18.5 days for the unobserved dosing group).
- Cost was significantly higher for the observed dosing group ($1858 versus $1445).*

Comments: This paper has implications for primary care and office-based providers who routinely prescribe buprenorphine-naloxone. An editorialist notes that opioid treatment providers often believe that observed dosing (i.e., "more intensive treatment") leads to better outcomes. Conversely, this study's investigators hypothesized that attendance for observed dosing would serve as a deterrent to treatment retention and lead to worse outcomes. The overall findings suggest that neither assertion is universal and that unobserved dosing is, on average, more cost effective.

From a clinical perspective, however, the results beg this question: will certain patients (e.g., those with more severe and disabling disorders) do better in a more structured program and others (e.g., those able to work) benefit from fewer constraints? Ideology aside, the availability of both office-based buprenorphine-naloxone and structured opioid treatment programs remains necessary in order to meet the individual treatment needs of patients with opioid dependence.

Peter D. Friedmann, MD, MPH

*US dollars converted from Australian dollars

Reference: Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. *Addiction.* 2007;102(12):1899–1907.

Persistent Hepatitis C Reinfection in Injection Drug Users Who Have Cleared the Virus

Previous retrospective studies of injection drug users who resolved their hepatitis C infection (HCV) have reported high rates of acute reinfection. But the rate of clinically relevant persistent reinfection (i.e., more than one consecutive positive test for HCV RNA in people with resolved HCV) has not been measured prospectively.

To determine this rate, researchers in this study prospectively examined 224 people with hepatitis C infection, a history of injection drug use, and serial hepatitis C viral loads.

- Of 224 subjects followed for 1391 person-years, 38 resolved their infection.
- Of these 38 subjects, 29 resolved their infection spontaneously, and 9 resolved their infection after receiving HCV treatment.
- Fourteen of the spontaneous resolvers and 2 of the treatment-associated resolvers continued to inject drugs during follow-up.
- Only 1 of the 38 subjects with a resolved infection (a subject who had spontaneous resolution, continued to inject drugs, and also had HIV) had persistent hepatitis C reinfection.

Comments: Persistent reinfection with hepatitis C in people who have resolved the infection, even in those with ongoing injection drug use, appears to be less common than suggested by previously published reports. However, determining a more certain rate of hepatitis C reinfection among injection drug users will require larger studies.

Alexander Y. Walley, MD, MSc

Reference: Currie SL, Ryan JC, Tracy D, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. *Drug Alcohol Depend.* 2008:93:(1-2):148–154.

Supplement to *Pediatrics* Examines the Developmental Nature of Underage Drinking

A supplement to *Pediatrics* is dedicated to the biological, behavioral, and environmental changes that foster the use of alcohol by underage youth. Recent research indicates that binge drinking is associated with the development of alcohol dependence later in life, and that the risk of alcohol dependence is related to how early drinking starts. Additional results reported include:

- patterns of onset, prevalence, and the course of alcohol use
- the relationship between early developmental processes and problem drinking
- pathways toward and away from underage drinking
- an examination of developmental processes in 10-15 year olds
- changes that typically occur in late adolescence and their impact on drinking
- evidence-based interventions for teens with alcohol use disorders

Comments: Addressing alcohol use in young people is important to reduce harm for youth and to prevent harm among adults. This issue highlights robust research findings, but also points to the need for additional research to identify more effective preventive interventions.

Richard Saitz MD, MPH

Reference: Underage drinking: understanding and reducing risk in the context of human development. *Pediatrics* 2008; 121 (Supplement).

Visit
www.aodhealth.org
to view the newsletter online, to sign up for a free subscription, and to access additional features including downloadable PowerPoint presentations, free CME credits, and much more!

The major journals regularly reviewed for the newsletter include the following:

Addiction
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
American Journal of Public Health
American Journal on Addictions
Annals of Internal Medicine
Archives of General Psychiatry
Archives of Internal Medicine
British Medical Journal
Drug & Alcohol Dependence
Epidemiology
Journal of Addiction Medicine
Journal of Addictive Diseases
Journal of AIDS
Journal of Behavioral Health Services & Research
Journal of General Internal Medicine
Journal of Studies on Alcohol
Journal of Substance Abuse Treatment
Journal of the American Medical Association
Lancet
New England Journal of Medicine
Preventive Medicine
Psychiatric Services
Substance Abuse
Substance Use & Misuse
Many others periodically reviewed
(see www..aodhealth.org)

Contact Information:

Alcohol, Other Drugs, and Health: Current Evidence
Boston University School of Medicine/Boston Medical Center
801 Massachusetts Avenue, 2nd floor
Boston, MA 02118
aodhce@bu.edu