CLINICAL UPDATE

Update in Addiction Medicine for the Generalist

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Generalist physicians can play a critical role in identifying and treating patients with addictions to alcohol, nicotine, and/or other drugs of abuse. In the United States, nicotine dependence and unhealthy alcohol use are the first (18.1%) and third (3.5%) leading causes, respectively, of preventable deaths.[1] Primary care physicians have not traditionally treated substance use despite the harmful effects that addiction can cause in their patients. The objective of this paper is to present recent evidence on recognizing and treating addiction disorders that is relevant for generalist physicians. We conducted an electronic database (PubMed) search to systematically identify recent (January 1, 2003, to June 1, 2006), human subject, English language, peer-reviewed, research articles or publications that impact generalist care for patients with addiction disorders. The search strategy and consensus deliberations were used to identify important articles in the categories of screening strategies for patients with alcohol problems and use of specific pharmacotherapies for patients with alcohol, nicotine, and opioid dependence.

Alcohol Disorders

Anton RF, O'Malley SS, Ciraulo DA, Couper D, Donovan DM, Gastfriend DR et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence JAMA 2006;295(17):2003–2017

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Alcohol dependence affects approximately 8 million persons in the United States, contributing to substantial morbidity and mortality.[2–4] To date, however, most evidence regarding primary care interventions for unhealthy alcohol use has been in patients with hazardous or "at-risk" drinkers, not alcohol-dependent individuals.[5]

The Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study was designed to test interventions for alcohol-dependent persons, and this trial included medications and an intervention explicitly designed for nonspecialty settings, like primary care.[6,7] In this 9-arm controlled trial, alcohol-dependent persons (n=1,383) were assigned to combinations of the following: (a) a 9-visit primary care counseling intervention offered by medical professionals (typically nurses or physicians) termed Medical Management (MM), 8 arms; (b) daily oral naltrexone (an opioid receptor antagonist), 4 arms; (c) daily oral acamprosate (a putative glutamate modulator), 4 arms; and (d) up to 20 formal counseling sessions from alcohol treatment specialists termed the Combined Behavioral Intervention (CBI), 5 arms.[8,9] Participants were required to be abstinent for 4 to 21 days prior to entry, and candidates were excluded if they had drug abuse or psychiatric disorders requiring medication. Overall follow-up averaged 94% at the end of active treatment (16 weeks) and 82% at 1-year post-treatment (68 weeks), with no significant differences by trial arm.

Investigators assessed multiple trial outcomes, including percent days abstinent and return to heavy drinking. An overall "good clinical outcome" was defined as abstinence or moderate drinking—maximum of 11 (women) or 14 (men) drinks per week—with no more than 2 days on which more than 3 drinks (women) or 4 drinks (men) were consumed during the last 8 weeks of the 16-week trial period.

The percentages of good clinical outcomes at the end of treatment were 58% for MM/placebo, 74% for naltrexone/MM, 71% for CBI/MM, and 74% for naltrexone/CBI/MM. The odds ratios for good outcomes were significantly increased for the combination therapy groups compared with MM/placebo alone (all p<0.01). Relative to persons who received placebo

with medical management, the number needed to treat (NNT) to assure 1 additional good clinical outcome was 7 for CBI/MM, 6 for naltrexone/MM, and 7 for naltrexone/CBI/MM. One year after treatment, trial arm differences still favored the combination therapy groups, but results were no longer significant. The percentage of days abstinent (59–69%) remained higher than at baseline (24–25%).

Interpreting the trial arm comparisons was hindered by the complex study design. Broadly, this study showed that naltrexone and/or CBI in combination with MM were helpful treatments for alcohol dependent patients compared to MM alone. The applicability of COMBINE's findings in contemporary primary care practice remains unclear. While MM was explicitly designed to be offered by clinicians who are not addiction medicine specialists, the time required for the intervention (9 sessions, ranging from 20–45 minutes in length) and the currently available training materials (a 141-page manual) would seem difficult to incorporate in primary care practice.[6]

A separate finding in COMBINE highlights a more general challenge to the study of addiction treatment interventions. Consistent with recent trials on pharmaceutical interventions for alcohol problems, all trial arms achieved alcohol reductions exceeding the differences between trial arms.[10–12] Improvements independent of treatment assignment reflect the dominant impact of the contextual and motivational factors that propel patients to seek treatment and/or reduce drinking in the absence of treatment.[12] Primary care physicians may learn of such clinically important factors in the course of care. How and whether physicians should seek to assist patient recovery processes in light of these factors may prove difficult to study in the context of randomized controlled trials.

National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much: a clinician's guide. U.S. Department of Health & Human Services, Rockville, MD. 2005.

For patients who are not alcohol-dependent, evidence supports screening and counseling to reduce misuse in primary care settings, yet this recommendation is sporadically followed in everyday practice.[13,14] For this reason, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) recently issued revised guidelines designed to simplify integration of screening and intervention into primary care.[15] The guide contains evidence and consensus-based recommendations and its chief innovation is a simplified alcohol use screening algorithm. Persons who respond positively to a prescreening question (e.g., "Do you sometimes drink alcoholic beverages?") can be asked the following single question: "How many times in the past year have you had (>5 for men, >4 for women) drinks in a day?" This single-question approach, positive when any such episodes are reported in the prior 12 months, has reasonable sensitivity and specificity for detecting alcohol misuse.[16] Several investigators have examined single-item screening strategies.[17–21] For example, Taj found that a single question had a positive predictive value of 74% [95% confidence interval (CI), 66% to 83%], negative predictive value of 88% (95% CI, 80% to 94%), sensitivity of 62%, and specificity of 93% in detecting problem drinking.[21] Further research is warranted regarding the specific screening question from the Clinician's Guide, although the single question it recommends is similar to those previously studied. When responses to the screening questions are negative, only brief advice regarding safe use and annual rescreening are warranted. When positive, questions to distinguish at-risk use from abuse (interfering with the patient's life) or dependence (associated with tolerance, withdrawal, or preoccupation) are indicated.

The guide outlines and provides scripts for brief advice and assistance that clinicians can tailor to the patient's degree of alcohol use and motivation to change. Additional resources review the alcohol contents of standard drinks, more formal screening instruments, and referral options, as well as an abbreviated guide to pharmacologic treatment of alcohol dependence.

Nicotine Dependence

Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2004;(1):CD003041.

Despite a reduction in prevalence, smoking accounts for over 435,000 deaths annually.[22,23] Smoking is a well-known risk factor for developing coronary artery disease (CAD). However, the magnitude of the impact of smoking cessation in reducing overall and cardiovascular mortality in patients with CAD is not well known.

To estimate the magnitude of risk reduction when a patient with CAD stops smoking, investigators conducted a systematic review and meta-analysis.[24] The authors searched for studies in MEDLINE, EMBASE, Science Citation Index, Cochrane Controlled Trial Register, CINAHL, PsychLit, and Dissertation Abstracts through April 2003. In addition, searches were conducted of relevant conference proceedings, the UK National Research Register, references from retrieved articles, and experts in the field, and contact was made with the investigators from 61 cohort studies of cardiovascular risk. Finally, the authors attempted to identify any randomized clinical trials that collected but had not reported appropriate data.

Because widely accepted standards for assessing quality in observational research are lacking, the authors included those articles that had a minimum of 2-years follow-up (considered adequate time for smoking cessation to reduce risk) and employed 2 independent reviewers who assessed other aspects of quality (e.g., control of confounding, sample size, selection biases, operational definitions of smoking, smoking cessation, and index events).[25,26]

The 20 prospective cohort studies that were identified followed 12,603 patients with CAD (myocardial infarction, stable or unstable angina) for at least 2 years, conducted at least 2 assessments of smoking status, and provided cardiovascular outcomes and all-cause mortality. Eight studies included more than 500 subjects, predominantly males. While most studies had operational definitions of index cardiac events, few had biologic confirmation of smoking status. Six studies were assessed to have good control of confounding, whereas 9 had poor control. Losses to follow up were reported to be relatively small, although few studies were able to capture losses that occurred between the index cardiac event and study enrolment.

The authors conducted a metaregression to help adjust for study heterogeneity; predictor variables included control of confounding variables, minimization of selection biases, and operational definitions for smoking status, smoking cessation,

and outcome events. Among those who quit smoking, the relative risk (RR) of mortality was reduced 36% compared with those who continued to smoke [1,044/5,659 vs 1,884/6,944; crude RR 0.64, 95% CI 0.58 to 0.71]. While these results were dominated by 3 large studies that included patients with bypass Surgery, the results did not differ significantly when limited to trials of patients who were enrolled following myocardial infarction. In addition, the risk of nonfatal myocardial infarctions was reduced by 32% for those who quit smoking (263/2,467 vs 516/3,662; crude RR 0.68, 95% CI 0.57 to 0.82). The authors conducted a sensitivity analysis of those studies that had an initial sample size of at least 500 smokers at baseline, at least 85% follow-up, and adequate or good control of confounding. The main findings were similar in these 6 studies. The risk reduction associated with quitting smoking was similar across index cardiac events, age, sex, country, and time period.

These findings highlight the benefit of smoking cessation for patients with CAD. The 36% risk reduction in all-cause mortality is similar to benefits seen with treating hypercholesterolemia and hypertension.[27–30] While these findings were not demonstrated in randomized trials, the authors attempted to reduce bias in this meta-analysis by creating rigorous eligibility criteria for the studies, and conducting a sensitivity analysis using the highest quality studies. However, there are still potential limitations to the generalizability of the meta-analysis. First, patients who cease smoking following a cardiac event may differ from those who do not. Unmeasured confounders could account for the mortality benefit seen in patients who quit smoking. Secondly, because most studies relied on subject self-report, it is possible that studies were not able to accurately classify the subject's smoking status at follow-up. Nonetheless, the high prevalence of nicotine dependence among patients with CAD, the impact of smoking cessation on mortality, and the effectiveness of smoking cessation interventions all support clinician efforts to aggressively treat nicotine dependence in patients with known CAD. Physicians should address smoking cessation using guideline-consistent strategies in all patients who smoke and consider the added benefit in those patients with established CAD, especially those who appear motivated following a significant cardiac event.[31]

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296(1):47–55.

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296(1):56–63.

Buproprion and nicotine replacement therapies are the mainstay of pharmacotherapy for smoking cessation. Previous research has shown that current smoking cessation treatments are not widely disseminated to the general population of smokers.[32] A new agent, varenicline, is an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist that stimulates the release of dopamine to reduce craving and withdrawal, while simultaneously blocking nicotine's reinforcing effects. Two industry-funded, randomized, double-blinded trials evaluated varenicline against bupropion SR and placebo in adults who were motivated to stop smoking.[33,34] Randomization was stratified by center. In the first trial, the 1,025 subjects who met inclusion criteria (age 18–75, smoked >10 cigarettes per day, had <3 months of smoking abstinence in the past year, and were motivated to quit) received varenicline, 0.5 mg/day for days 1–3, 0.5 mg twice per day for days 4–7, then 1 mg twice per day through week 12 (n=352), or SR bupropion 50 mg/day for days 1–3, then 150 mg twice per day through week 12 (n=329), or placebo (n=344). The second trial[26] had a similar design and enrolled 1,027 subjects.

The primary endpoint for both trials was continuous abstinence for the final 4 weeks of treatment, defined as the proportion of participants who reported no smoking or use of any nicotine-containing products, confirmed by exhaled carbon monoxide. Secondary endpoints included continuous abstinence rates from week 9 through week 24 and through week 52. The 52-week study completion rates in the first study were 60.5% for varenicline, 56% for bupropion SR, and 54% for placebo, and 70% for varenicline, 65% for bupropion SR, and 60% for placebo in the second study.

In the first trial, the investigators found that subjects receiving varenicline (44.0%) were most likely to achieve the primary abstinence endpoint compared with placebo subjects (17.0%) (p<0.001; NNT, 3.7) and SR buproprion subjects (29.5%, p<0.001, NNT, 6.9). Subjects receiving varenicline (29.5%) were also more likely to achieve secondary abstinence endpoints compared with placebo subjects (10.5%, p<0.001, NNT, 5.2) and SR bupropion subjects (20.7%, p=0.007, NNT, 11.4) at 24-week follow-up. However, varenicline was superior only to placebo (21.9 vs 8.4%, p<0.001, NNT, 7.4) for the primary endpoint at 52 weeks and not to SR buproprion (16.1%, p=0.06). In the second study, varenicline was superior to SR bupropion at 52-week follow-up (30.5 vs 23.4%, p=0.05, NNT, 14.1). Minor adverse events, including nausea and abnormal dreams, were more common in the varenicline group in both trials, but did not cause patients to discontinue therapy.

Because these were the first published trials of varenicline's efficacy for quitting smoking, important questions remain unanswered about how effective varenicline will be in routine clinical practice. These 2 studies were also not designed primarily to test varenicline's efficacy for maintenance of abstinence, although other studies have addressed this question, using higher varenicline doses.[35] Finally, it is currently unknown whether nicotine replacement therapy will be effective when used with varenicline, whether postmarketing surveillance will reveal rare but serious complications, whether there will be important drug interactions with varenicline, or whether insurance plans will cover varenicline.

Opioid Dependence

Turner BJ, Laine C, Lin YT, Lynch K. Barriers and facilitators to primary care or human immunodeficiency virus clinics providing methadone or buprenorphine for the management of opioid dependence. Arch Intern Med 2005;165(15):1769–1776.

Dependence upon heroin and prescription opioid analgesics is an important public health problem.[2,36–38] Historically, effective treatment for opioid dependence has been limited to methadone provided in specialty substance abuse programs. The Drug Addiction Treatment Act of 2000 and the approval of buprenorphine in 2002 have, for the first time, allowed physicians to prescribe medication for the treatment of opioid dependence in primary care settings.

This study examined factors associated with interest in delivering buprenorphine and methadone treatment by primary care and HIV specialty clinics.[39] In a survey of 261 clinics that serve Medicaid patients, 41% of which provided HIV care, medical directors were questioned about knowledge and attitudes towards opioid dependence treatment, and potential facilitators and barriers to providing this treatment. Analyses compared willingness to provide buprenorphine versus methadone and examined the associations of clinic characteristics and attitudes with interest in offering these treatments. Clinics were more interested in providing buprenorphine than methadone (60 vs 33% $p<0.001$), partly because of the perceived lower abuse potential and stigma. Nearly half of respondents had at least 1 negative opinion about patients with opioid dependence. Interest in providing buprenorphine was greater in clinics offering HIV services, treating more patients with chronic pain, or those affiliated with methadone programs. Fifty-seven percent of medical directors reported a high level of concern about adequate reimbursement for treating opioid dependency. Greater than 60% cited the availability of Continuing Medical Education credits and telephone access to addiction medicine expertise as important in enhancing their interest in providing this care.

This study highlights important barriers to adopting buprenorphine treatment in primary care and HIV specialty practices. Information concerning methadone is less relevant given the continued regulatory barriers to providing this treatment outside methadone clinics. The stigma of opioid dependence and its treatment remains a major obstacle to disseminating medication-assisted treatment in medical clinics, although perhaps less so for buprenorphine. Access to substance abuse treatment continues to present major challenges, especially for patients relying on public funding mechanisms that separate medical and specialty addiction treatment services. HIV clinics appear to be appropriate sites for developing buprenorphine programs (http://www.bhives.org). Access to physicians with experience treating opioid dependence (http://www.pcssmentor.org) may be an important factor in the willingness of physicians and clinics to provide office-based treatment.

Mainstreaming Addiction Care Into Practice

Institute of Medicine. Improving the quality of healthcare for mental and substance-use conditions: the quality chasm series. The National Academies Press, Washington, D.C. 2005.

The move to address patients' alcohol and drug use by generalist physicians should be advanced by the current attention to improving the quality of medical care. A recently published Institute of Medicine (IOM) report developed an agenda for change of the health care system's approach to the treatment and prevention of these conditions.[40] The IOM's underlying theme is that only by addressing substance use and mental health problems can patients achieve optimal benefit.

The IOM report advocates coordinated care among primary care, mental health, and substance-use treatment providers. Specifically, coordination models can be straightforward (i.e., formal agreements among mental, substance-use, and primary health care providers) to incrementally more complex arrangements (i.e., case management among systems, co-location of services, to clinically integrated practices).[40] Evidence suggests that the more complex arrangements have stronger evidence for yielding improved patient outcomes. Other recommendations addressed to all clinicians including primary care physicians include the need to screen all mental health patients for alcohol and drug use problems given the high comorbidity of these conditions. The report also stressed maintaining a patient-centered approach to the care of individuals with alcohol and drug problems. That means providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide clinical decisions.[41] The increasing attention to the impact of substance use disorders on patients' medical outcomes should drive efforts to engage generalists in identifying and treating these disorders.

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