Update in Addiction Medicine for the Primary Care Clinician

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INTRODUCTION

The United States Preventive Services Task Force recommends that primary care clinicians assume a major role in screening, identification, treatment, and referral to treatment of unhealthy alcohol and other drug (AOD) use—the spectrum from use that risks health consequences to AOD disorders (abuse and dependence)—in generalist settings.[1] In the United States, nicotine dependence, alcohol use, and drug use are the first, third, and ninth leading causes, respectively, of preventable deaths.[2] Despite the harmful effects of addiction and improved options for office-based treatments and referral, not all primary care clinicians routinely address AOD use in their patients.

The objectives of this paper are to identify and examine important recent advances in addiction medicine that have implications for primary care clinicians and that emphasize primary care clinicians' role in the identification, treatment and/or referral of patients with addictions. We conducted an electronic database (PubMed) search to systematically identify recent (June 1, 2006 to January 1, 2008) human subject, English language, peer-reviewed, research publications that are relevant to generalist care for patients with addiction disorders. We also surveyed the publications that were reviewed by a NIH-funded newsletter that, in an attempt to identify articles that address the health impact of alcohol and drugs, systematically reviews the core general medical, infectious disease, public health, and addiction subspecialty journals.[3] Similar to our prior review,[4] authors (A.G., D.F., R.S.) were provided a title listing of articles with addiction-related key words within the reference time frame, and then secondary searches and consensus deliberations were used to identify articles that may impact the care provided by primary care clinicians in the categories of 1) alcohol use and disorders and 2) opioid use and dependence. Articles were categorized as impacting primary care clinicians if they studied primary care settings or could impact such settings and had practice-changing findings or implications.

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ALCOHOL USE AND DISORDERS

Simplifying Alcohol Assessment: Two Questions to Identify Alcohol Use Disorders[5]

In this study,[5] the investigators developed a simple assessment for alcohol use disorders with data from the cases (1,522 injured patients seen in an emergency department) of a case-control study, the Missouri Injury Study (MIS). They validated the assessment with data from three cross-sectional samples: 1) the controls (1,124 non-injured adults responding to a telephone survey) from the MIS, 2) a primary care sample (n=623) from the Vital Signs Screening Project (VSSP), and 3) a nationally representative sample of U.S. adults (n=26,946) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

The investigators identified two criteria that were predictive of alcohol use disorders: 1) recurrent drinking in physically hazardous situations and 2) drinking more or for longer than intended. In the developmental sample, presence of either of the two criteria had a sensitivity of 96% and a specificity of 85% for a current alcohol use disorder. Among all subjects in the three validation samples, the presence of either of the two criteria had a sensitivity of 72% to 94% and a specificity of 80% to 95% for a current alcohol use disorder. Among screen-positive (>4 drinks in one day for women or >5 drinks in one day for men at least once over the past three months for MIS and VSSP; ≥5 or more drinks in a single day over the past 12 months for NESARC) subjects in the three validation samples, the presence of either of the two criteria had a sensitivity of 77% to 95% and a specificity of 62% to 86% for a current alcohol use disorder.

Although the two criteria—recurrent drinking in physically hazardous situations and drinking more or for longer than intended—demonstrated good sensitivity and specificity for alcohol use disorders in this retrospective secondary data analysis study, it is unclear how the relevant questions should be worded for use in primary care settings and how they would perform outside the context of an extensive research assessment. The investigators recommend the items be tested prospectively in practice settings. After development into an easy-to-use format with prospective validation, this approach could be a brief and efficient way to assess alcohol use disorders in primary care patients with an initial positive screen. Being able to quickly sort out the severity of unhealthy alcohol use in these settings could decrease at least one barrier to widespread dissemination of alcohol screening.

Brief Interventions Effective in Primary Care[6]

In numerous randomized trials, brief counseling interventions, including feedback, advice, and goal-setting done in an empathic manner, have efficacy for nondependent unhealthy alcohol use. But as with many efficacy trials, these studies have had numerous exclusions and the interventions have often been very carefully implemented or extensive, raising questions about reproducibility. Thus, effectiveness of alcohol brief intervention in real-world primary care settings is less clear. To assess the effectiveness of brief interventions, investigators performed a systematic review and meta-analysis of randomized trials done with patients presenting to primary care for reasons other than for alcohol treatment.[6] Interventions in these studies lasted from 7.5 to 60 minutes over 1 to 5 contacts. The researchers scored the trials on the presence or absence of features of efficacy and effectiveness trials. They identified 22 trials with 7619 subjects.

Brief intervention subjects drank (mean difference) 38 grams (about 3–4 standard drinks[7]) less per week than did control subjects at one year (95% CI, −54 to −23 grams). There was no significant difference in reductions between "effectiveness" and "efficacy" trials. In studies characterized as effectiveness trials, the difference in consumption was 28 g (95% CI, −48 to −9 grams); in efficacy studies, it was 51 grams (95% CI, −77 to −25 grams).

These findings suggest that brief counseling interventions in primary care settings lower alcohol consumption in those with nondependent unhealthy alcohol consumption. However, these effects are modest, and evidence for reduced consequences is not robust. This systematic review extends what we have known from other evidence reviews by specifically examining whether effects were similar in studies that assessed efficacy and effectiveness. Results were similar in both types of studies suggesting that brief counseling is effective in real world primary care settings.

However, the exclusion criteria for the original individual randomized trials (for example, alcohol dependence and psychiatric co-morbidity) limit the conclusions that can be drawn from this study. Nonetheless, the results do support practice guidelines that have recommended universal screening for unhealthy alcohol use in primary care settings and brief interventions for those who screen positive. Further research is needed in patient populations for whom the practice's benefits are less certain (e.g., medical inpatients, patients with dependence); research is also needed to determine how to go beyond decreasing consumption to decreasing consequences.

Intensive Referral to 12-Step Self-help Groups and 6-month Substance Use Disorder Outcomes[8]

Primary care clinicians commonly refer their patients with substance dependence to 12-step groups like Alcoholics Anonymous (AA) or Narcotics Anonymous (NA).[9] But making these referrals is often not simple; some patients may not be ready to take a step towards abstinence, and others have myriad ideological and practical barriers that prevent 12-step meeting attendance and participation. To examine whether intensive referral to AA or NA confers more benefit than standard, ad hoc referral, researchers randomized 345 veterans who entered a new substance abuse treatment episode (80% misused alcohol).[8] For the 181 patients assigned to intensive referral, treatment counselors provided a list of local AA/NA meetings preferred by other patients with directions to and times of those meetings and an introductory handout on 12-step groups. Counselors also arranged for an AA/NA volunteer to escort the patient to a meeting, confirmed with the patient in writing the meetings that they will attend, followed up on meeting attendance at the next session, and recommended in writing that the patient obtain a temporary sponsor. The 164 patients assigned to standard referral received only a schedule of local 12-step meetings and scripted encouragement to attend.

At six-month follow-up, intensive and standard referral groups did not differ on 12-step attendance overall, but intensive referral yielded more attendance among patients with less previous 12-step experience. The intensive group had more 12-step involvement (e.g., more likely to have participated actively in the meetings, had a spiritual awakening, or obtained a 12-step sponsor). The intensive group patients also improved more than the standard group on the Addiction Severity Index Alcohol Use (mean improvement 0.215) and Drug Use Composites scores (mean improvement 0.079). Twelve-step involvement mediated these effects. Finally, the intensive group patients were more likely to be abstinent from other drugs than the standard group (78% vs. 70%) and were more likely to be abstinence from alcohol, a difference of borderline significance (64% vs. 55%, p=0.06).

Although the referrals in this study were done by counselors among patients entering addiction treatment, the results have important implications for primary care clinicians. Internists' efforts to encourage substance-abusing patients to participate actively in AA/NA are likely worthwhile, especially for patients with less prior 12-step experience. Arranging for an AA/NA volunteer to escort the patient to a meeting and following up on participation appears to enhance successful facilitation of 12-step involvement. These findings are consistent with work from Project Match and others that suggest formalized 12-step facilitation is an effective relapse prevention strategy.[10–13] Furthermore, with modest effort and resources, the intensive referral implemented in this study could be reproduced in primary care settings, improving the management of substance dependence.

Topiramate for Treating Alcohol Dependence: A Randomized Controlled Trial[14]

Pharmacotherapy for alcohol dependence is approved by the FDA, but it is underutilized.

Topiramate may decrease alcohol consumption among alcohol-dependent persons by reducing dopamine release (and therefore alcohol's rewarding effects) via facilitation of GABA activity and inhibition of glutamate function, but has not been tested in a large controlled study. Investigators conducted a randomized trial of 371 alcohol-dependent men and women from 17 sites in the United States to determine if topiramate is more efficacious than placebo for reducing drinking.

Trial participants were alcohol-dependent adults (men who drank 35 or more drinks per week and women who drank 28 or more drinks per week; all participants scored 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT).[15,16] To be enrolled, participants had to express a desire to stop or reduce alcohol consumption and be free of comorbid conditions. After extensive screening, trial participants were randomized to receive topiramate or placebo for 14 weeks, and both participants and investigators were blinded to treatment assignment. Medication was titrated during the first six weeks in scheduled increments to achieve a minimum topiramate (or placebo equivalent) dose of up to 50 milligrams per day and a maximum of 300 milligrams per day. All participants received weekly brief manual-guided adherence enhancement counseling.

In analysis, the researchers employed a conservative approach that assumed all dropouts to have relapsed to baseline drinking behaviors. With this consideration, topiramate recipients showed a greater reduction in the percent of drinking days than placebo recipients (from a mean of 82% to 44% vs. 82% to 52%, p=0.002), a greater increase in abstinent days than placebo recipients (from a mean of 9.7% to 37.6% vs. 9.4% to 29.1%, p=0.002), and a greater reduction in liver enzymes. Using a less conservative approach that considered dropouts as missing rather than relapsed, topiramate recipients showed even greater reductions in percent of drinking days than placebo recipients (from a mean of 82% to 20% versus 82% to 42%, p<0.001). With both analytic approaches, topiramate recipients achieved at least 28 days of both continuous abstinence and continuous non-heavy drinking faster than placebo recipients.

These results suggest that topiramate is a promising treatment for alcohol dependence for those seeking help with their drinking. The conservative analytic approach suggests that broadening the use of topiramate to treat alcohol dependence among adults who desire to reduce their alcohol consumption is warranted. Unfortunately, the side effects of topiramate (including depression, insomnia, difficulty with memory, somnolence, paresthesia, psychomotor slowing, dizziness, and nausea) may limit widespread acceptance as pharmacotherapy for alcohol dependence. Furthermore, because this randomized controlled trial had strict eligibility criteria to ensure that safety and efficacy could be measured, the generalizability of these findings to patients with other comorbid illnesses, such as other substance disorders or psychiatric disease, may be limited. In summary, this study, along with additional analyses that showed improvement in physical health and quality of life of patients on topiramate,[17] indicates that topiramate may be another pharmacotherapy available to physicians to treat alcohol dependence. Although the study is convincing regarding topiramate's positive effects on alcohol dependence, it is not FDA-approved for this indication. But with four approved drugs available (counting both injectable and oral naltrexone), prescription of pharmacotherapy represents an obvious means for primary care clinicians to become involved in the management of patients with alcohol dependence that is similar to how physicians address other chronic conditions like hypertension, diabetes and asthma.

OPIOID USE AND DEPENDENCE

Systemic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction[18]

Researchers systematically reviewed the literature to determine the prevalence and efficacy of opioid treatment for chronic back pain. They also examined the risk for substance use disorders and prescription medication misuse among patients perpetually treated with opioids.

Across 11 studies, the prevalence of opioid prescribing for chronic back pain ranged widely, from 3% to 66%. Regarding efficacy, in a meta-analysis of data from five studies, pain decreased (though non-significantly) with opioid treatment. Opioids had more efficacy than non-opioids or placebo in four of six short-term (less than four months) treatment studies. In four studies, the prevalence of a current substance use disorder in patients receiving opioids for chronic back pain also ranged widely (3–43%). These studies generally were of poor quality. In the highest quality study, the prevalence was 23%. It is notable that this prevalence (23%) was the same as in a comparison group of patients with chronic back pain who had not received opioid treatment. Across five studies, the prevalence of substance use disorders in patients receiving opioids for chronic back pain was 5% to 24%. These studies generally did not consider whether inadequate pain relief led to a misdiagnosis of substance misuse (known as pseudoaddiction[19]).

Although the quality of studies to date is limited and efficacy testing for chronic back pain has not been extensive, this collection of evidence suggests that opioids are a reasonable short-term treatment option. Nonetheless, the evidence for their efficacy is scanty, and long-term benefits are unknown. Furthermore, while the prevalence of a substance use disorder may or may not be higher than in other patients, these disorders are common particularly in people with chronic pain. It is critical to know whether such disorders are present when prescribing opioids for chronic pain so that they can be addressed.

Prescription Opioid Use, Misuse, and Diversion Among Street Drug Users in New York City[20]

To determine the patterns of prescription opioid use, misuse, and diversion among 586 drug users in New York City, researchers conducted detailed interviews. Among their findings, 72% of subjects used methadone and 65% sold it. Methadone was used and sold by more individuals than were long-acting preparations of oxycodone, hydrocodone/acetaminophen, or oxycodone/acetaminophen. More than half (58%) of prescription drug users reported that they used the opioids they obtained from physicians' offices to treat pain, prevent withdrawal, or to obtain euphoria. For example,

among the subjects who reported obtaining long-acting preparations of oxycodone from physicians, 83% reported using the medication primarily to treat pain, 50% primarily to prevent opioid withdrawal symptoms, and 38% primarily to experience euphoria. Of note, this study found that prescription drug users reported they were less likely to obtain prescription opioids for euphoria than for pain, and when they obtained prescription opioids for euphoria, they usually did so from dealers instead of physicians.

The primary limitations of this study as they relate to primary care are that the patients were not selected from clinical sites, but they did report on what they did with medications obtained from physicians. In addition, prescription drug use patterns are likely to vary geographically limiting the generalizability of these findings.

This study highlights a growing problem: abuse of and dependence on prescription opioids. Practicing physicians confronted with decisions about prescribing opioid medications need to weigh perceived benefits with potential adverse effects. In this study, methadone was the most commonly diverted prescription opioid, and many individuals used these medications to avoid opioid withdrawal or to treat pain; both findings are informative. Patients were less likely to use physician-obtained medications for euphoria than for other indications. Other work has shown that patient factors such as panic disorder, social phobia and agoraphobia, low self-rated health status, and other substance misuse among those with non-medical use of prescription opioids should alert clinicians to screen for prescription opioid abuse and dependence.[21] Regardless, this study highlights that physicians should prescribe opioids with caution and consider offering office-based treatment or specialty treatment referral when indicated.

Mortality Prior to, During and after Opioid Maintenance Treatment (OMT): A National Prospective Cross-Registry Study[22]

Opioid dependence is associated with significant morbidity and mortality.[23] Overdose is among the leading causes of death. This study, conducted in Norway, sought to determine the extent to which opioid agonist treatment reduced mortality in patients with opioid dependence. Researchers linked data collected over a seven-year period from a national death registry to a national database of people who were on a waiting list for opioid agonist treatment, receiving opioid agonist treatment (predominantly methadone), or who had discontinued opioid agonist treatment. Over the course of the study, 213 of 3789 patients died, 113 (53%) from overdose. Overdose mortality rates per 100 person years were 1.9 (95% CI, 1.6–2.1) for those on the waiting list for treatment, 0.4 (95% CI, 0–0.8) during opioid agonist treatment, and 2.1 (95% CI, 1.7–2.5) after treatment was discontinued. Overall mortality (relative risk [RR] 0.5; $p<0.001$) and overdose mortality (RR 0.2; $p<0.001$) were lower in patients receiving opioid agonist treatment than in patients on the waiting list. Among those who discontinued treatment, total mortality risk was higher among men (compared with men on the waiting list) (RR, 1.8; $p<0.02$), but not among women.

The primary limitation of this study relates to the regulations regarding entry into opioid agonist treatment in Norway, which are more stringent than those in the United States. The Norwegian regulations restrict this treatment to individuals who are at least 25 years of age and can demonstrate several years of opioid dependence. Patients with medical and psychiatric co-morbidity are given priority access to these services.

This investigation adds to the ample evidence that opioid agonist treatment reduces mortality in opioid-dependent patients. In the arena of pain treatment, cases of overdose death that appear to be attributed to physician-prescribed methadone have increased the potential for negative public and regulatory backlash against methadone.[24,25] Therefore, these results may play an important role in contemporary policy discussions about opioid agonist treatment for opioid dependence. Furthermore, primary care clinicians can use this information to decide to provide or advocate for access to initial and maintenance opioid agonist treatment (e.g. with buprenorphine) for their patients with opioid dependence.

Treating Homeless Opioid Dependent Patients with Buprenorphine in an Office-based Setting[26]

Buprenorphine treatment outcomes are generally evaluated in resource-rich settings (e.g., with research staff) or among patients with some social support. The effectiveness of this treatment in everyday practice settings and among indigent patients remains unclear. Two studies explored more generalizable approaches to buprenorphine treatment for opioid dependence. In one study, a Boston group compared the effectiveness of buprenorphine in patients treated at a clinic for the homeless (n=44) and in-house patients treated in a general primary care setting (n=41). A nurse care manager was actively engaged in patients' care at both sites. Although homeless patients were more likely than housed patients to have comorbidity, treatment outcomes were similar between the two groups. Twenty-one percent of homeless patients and 22% of housed patients "failed treatment" (were lost to follow-up during induction phase or discharged due to disruptive behavior or ongoing alcohol or other drug use while not adhering to intensified substance abuse treatment). Both groups had median treatment retention of nine months and equally low rates of illicit opioid use at 12 months. Homelessness resolved for 36% and employment rates increased in both groups.[26]

This study supports the premise that buprenorphine opioid agonist therapy can be applied to diverse patients in typical healthcare environments. These findings are corroborated by other investigators who examined 99 patients receiving buprenorphine treatment in 1) a hospital-based primary care center with an on-site pharmacy but no on-site addiction counselor or 2) a neighborhood health center with an on-site addiction counselor but no on-site pharmacy.[27] At six months, 54% of patients were abstinent from illicit opioids (determined by urine toxicology, self-reported drug use, and general clinical assessment). Clinical outcomes did not differ across the two treatment settings.

The findings of both feasibility studies support the effectiveness of extending office-based buprenorphine treatment into less specialized, low-intensity settings and to patients with only marginal social support. The results imply that these interventions can be delivered in real world primary care settings. Implementation and application of evidence based

addiction treatment, such as buprenorphine, into typical clinical settings may reduce addiction- and non-addiction-related morbidity and improve the quality of care provided to patients with addictions.

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