Update in Addiction Medicine for the Generalist

Adam J. Gordon, MD, MPH[1], Hillary V. Kunins, MD, MPH, MS[2], Darius A. Rastegar, MD[3], Jeanette M. Tetrault, MD[4], and Alexander Y. Walley, MD, MSc[5]

[1]Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [2]Albert Einstein College of Medicine and Montefiore Medical Center, New York, NY, USA; [3]Johns Hopkins School of Medicine, Baltimore, MD, USA; [4]Yale University School of Medicine, New Haven, CT, USA; [5]Boston University School of Medicine, Boston, MA, USA.

KEY WORDS: review; substance-related disorders; primary health care; primary care; alcoholism and addictive behavior; drug abuse; smoking cessation.
J Gen Intern Med 26(1):77–82
DOI: 10.1007/s11606-010-1461-3

INTRODUCTION

Generalist clinicians routinely care for patients who misuse or are dependent on alcohol, nicotine, and other drugs of abuse.[1,2] These problems contribute to significant morbidity, health care utilization, cost, and preventable death.[3,4] The aim of this update is to identify and examine recent advances in addiction medicine that have practice implications for generalist physicians and their patients. To accomplish this, we independently selected articles in the field of addiction medicine, summarized and critically appraised, and examined the articles in the context of their implications for generalist practice using methodology we used in prior updates.[5,6] During an initial review, we identified articles through an electronic MedLine search (limited to human studies and in English) using search terms for alcohol, nicotine, and other drugs of abuse from January 2008 through January 2010. From the citations, the authors selected articles for more intensive review. After this initial review, we searched for other literature in web-based or journal resources (e.g., www.aodhealth.org, ACP Journal Club, table of contents of relevant journals). All authors then agreed collectively on the important articles regarding addiction medicine that have implications for practice for generalist clinicians.

PRESCRIPTION DRUG ABUSE

In treating chronic pain, physicians must balance the pain-relieving benefits of opioids with the risks of overdose and triggering addiction. Efforts to improve pain treatment since the 1990s have led to increases in opioid prescriptions. At the same time, there have been substantial increases in misuse and diversion of prescription opioids, opioid-related emergency department visits, and fatal opioid overdoses.

Received May 28, 2010
Revised June 30, 2010
Accepted July 6, 2010
Published online August 10, 2010

What Factors Increase the Overdose Risk of Prescribed Opioids?

Dunn KM and colleagues. Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of Internal Medicine.2010;152(2):85–92.[7]

Dunn and colleagues sought to estimate rates of fatal and non-fatal opioid overdose and determine whether these rates vary by prescribed opioid dose among patients receiving medically prescribed, long-term opioid therapy.[7] By linking pharmacy, electronic medical and state mortality records, investigators evaluated outcomes among 9,940 persons in a health maintenance organization who received three or more opioid prescriptions within 90 days for chronic non-cancer pain between 1997 and 2005. They estimated non-fatal and fatal overdose risk as a function of average daily opioid dose (morphine equivalents) received at the time of overdose. Over a mean follow-up time of 42 months, they identified 51 patients with opioid-related overdoses, 6 of whom died (mean follow-up time of 42 months). The rate of any opioid overdose was 0.15 per 100 person-years, and the rate of overdose mortality was 0.02 per 100 person-years. Overdose rates were found to be dose-related; compared with patients receiving 1 to 20 mg/day of opioids, patients receiving 100 mg/day or more had an 8.9 fold (95% CI: 4.0–19.7) increase in overdose risk. Overdose rates were also increased by two to three fold in patients who had a history of a substance abuse diagnosis, depression, or were receiving a concomitant sedative-hypnotic prescription.

Are Increases in Overdose Deaths Related to the Diversion of Prescription Drugs?

Hall AJ and colleagues. Patterns of abuse among unintentional pharmaceutical overdose fatalities. Journal of the American Medical Association.2008;300(22):2613–20.[8]

Hall and colleagues sought to evaluate the risk characteristics of persons dying of unintentional prescription drug overdose in West Virginia in 2006.[8] They linked data from the state's medical examiner database, prescription drug monitor-

ing program, and opiate treatment programs to describe the type of substance use and concomitant behaviors. Among 295 people who died from an unintentional prescription drug poisoning, 78% had a history of substance abuse, 63% had taken a prescription drug not prescribed, 21% had 5 or more different prescribers over 12 months, 17% had a previous overdose, 16% had cocaine, heroin or methamphetamine also present, and 4% were enrolled in a methadone maintenance program. Prevalence of prescription drugs not prescribed was greatest among decedents aged 18 through 24 years and decreased across each successive age group. More than one substance was detected in 79% of deaths. The most common substance was opioids (93% of deaths); of these, only 44% had ever been prescribed these drugs. Methadone was the most common opioid (40%), followed by hydrocodone (23%) and oxycodone (21%). However, only 32% of decedents with methadone present at death had a prescription for it, whereas 85% with hydrocodone and 61% with oxycodone had prescriptions for hydrocodone and oxycodone, respectively. The authors concluded that the majority of prescription drug overdose deaths in West Virginia in 2006 were associated with nonmedical use and diversion of prescription drugs, primarily opioid analgesics.

What is the Arrhythmia Risk from Methadone?

Anchersen K and colleagues. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction.2009;104:993–999.[9]

Studies conducted by Hall and others have documented an increasing and disproportionate prevalence of methadone-related deaths, which has led to increasing focus on QT prolongation in methadone patients and the risk of torsades de pointes.[8,10] In this setting, recent expert panel recommendations for universal electrocardiography (ECG) screening and regular monitoring for corrected QT (QTc) prolongation for patients prescribed methadone[11] have been challenged as reaching beyond the evidence.[12] Anchersen determined the maximum mortality rate potentially attributable to QTc prolongation by linking the Norwegian Opioid Maintenance Treatment (OMT) registry and the national death certificate register.[9] They found 90 deaths occurring among 2,382 patients between 1997 and 2003, a rate of 1.3/100 patient-years. After review of each of these case records, four deaths were identified in which QTc prolongation could not be excluded as the cause of death. Thus, at most, 4% of methadone deaths could be potentially attributable to arrhythmias, resulting in a maximum mortality rate of 0.06 per 100 patient-years.

IMPLICATIONS FOR PRACTICE

Among patients treated with prescription opioids for chronic pain, having a substance use disorder, concomitant prescriptions for sedative-hypnotics, and higher doses of opioids increase the risk of overdose. However, most overdose deaths from prescription drugs involve diverted medications, particularly those involving methadone. Overdose victims commonly have a substance abuse history, mix multiple substances, and seek prescriptions from multiple prescribers. Methadone is disproportionately involved in overdoses, yet this is not explained by overdoses among patients receiving methadone maintenance for opioid dependence. Although methadone prolongs the QTc interval, other factors, such as prolonged and variable metabolism and mixing methadone with other sedating substances, likely explain the disproportionate number of deaths with methadone present compared to other opioids. Prescribers and patients should be educated about these overdose risk factors. Opioid prescribers should have a goal-directed approach, continuing or increasing opioid therapy only when there is demonstrated improvement in function or quality of life.[13] They should consider strategies to assess adherence and limit diversion, such as prescription monitoring programs, toxicology testing, and pill counts.

ADDICTION SCREENING AND BRIEF INTERVENTIONS

Cost Effectiveness of Screening for Addictions

Solberg LI and colleagues. Primary care intervention to reduce alcohol misuse: ranking its health impact and cost-effectiveness. American Journal of Preventive Medicine.2008;34(2):143–152.[14]

The US Preventive Services Tasks Force (USPSTF) recommends screening and behavioral counseling interventions in primary care to reduce alcohol misuse. Screening, Brief Intervention, and Referrals and/to Treatment (SBIRT) is a strategy that has been tested in emergency room and primary care settings with proven efficacy, yet is incorporated into practice less than 9% of the time.[15] To measure the clinically preventable burden (CPB) and cost-effectiveness of screening and brief interventions (SBI) compared with other recommended preventive services, Solberg and colleagues conducted a systematic review of randomized controlled trials and cost-effectiveness studies.[14] CPB was calculated as the product of effectiveness and the alcohol-attributable fraction of mortality and morbidity (measured in quality-adjusted life years [QALYs]). Cost effectiveness was estimated from both the societal perspective and the health system perspective. Calculated CPB was 176,000 QALYs saved over the lifetime of a birth cohort of 4,000,000 individuals. Screening and brief counseling were cost-saving from the societal perspective and had a cost-effectiveness ratio of $1,755/QALY saved. SBI is one of the top five ranking preventive services, comparable to screening for colorectal cancer, hypertension, visual problems, and for influenza and pneumococcal vaccination.

Screening for Addictions in Primary Care

Smith PC and colleagues. Primary care validation of a single-question alcohol screening test. Journal General Internal Medicine.2009;24(7):783–8.[16]

Unhealthy alcohol use is under-diagnosed in primary care settings.[17] High performing screening instruments, such as the Alcohol Use Disorders Identification Test (AUDIT) and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), are lengthy and can be difficult to administer in primary care environments.[18–20] Several prior studies have

examined the performance characteristics of abbreviated and single-item alcohol screening questionnaires, but none have examined the single-item screening test recommended by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in primary care settings.[21–24] Smith and colleagues validated, in an urban safety net primary care clinic, the performance of the single screening question, "How many times in the past year have you had X or more drinks in a day?" where X is 5 for men and 4 for women, and a response of ≥1 is considered positive.[16] They defined unhealthy alcohol use as the presence of an alcohol use disorder (either Alcohol Abuse or Dependence[25]) or risky consumption, as determined using a validated 30-day calendar method.[26,27] Among 286 patients, the single-question screen was 82% sensitive (95%, CI=73%–89%) and 79% specific (CI=73%–84%) for the detection of unhealthy alcohol use. It was more sensitive (88%, CI=73%–95 %) but less specific (67%, CI=61%–72%) for the detection of a current alcohol use disorder. Test characteristics were similar to that of a commonly used three-item screen (first three items of the AUDIT) and were affected very little by subject demographic characteristics. They concluded that the single screening question recommended by the NIAAA accurately identified unhealthy alcohol use in this sample of primary care patients. One potential limitation of this study was that the high prevalence of alcohol problems in this urban safety-net population (44%) may have been a marker for greater disease severity and/or selection bias, thus leading to greater sensitivity than would be observed in a lower risk population.

Application of SBIRT for Drug Use

Madras BK and colleagues. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: comparison at intake and 6 months later. Drug and Alcohol Dependence.2009;99:280–295.[28]

Components of SBIRT have been studied extensively for unhealthy alcohol use with evidence of efficacy, effectiveness, and cost-effectiveness.[29–33] However, research regarding the efficacy and effectiveness of SBIRT components for alcohol dependence and illicit drug use have been limited. In the last decade, an alcohol-focused SBIRT service program was initiated by the Substance Abuse and Mental Health Services Administration (SAMHSA) in a wide variety of medical settings (and diverse patient populations) in six states (http://www.sbirt.samhsa.gov). As part of this initiative, patients were screened and offered score-based progressive levels of intervention (brief intervention, brief treatment, referral to specialty treatment). Through a secondary analysis, Madras and colleagues examined illicit drug use at baseline and 6-month follow-up in a randomly selected sample of the nearly 60,000 patients who screened positive for drug use at baseline and received an SBIRT intervention.[28] Among those reporting baseline illicit drug use, rates of drug use at 6-month follow-up (4 of 6 sites) were 68% lower ($p<0.001$) and heavy alcohol use was 39% lower ($p<0.001$) than at baseline, with comparable findings across sites, gender, race/ethnic, and age subgroups. However, improvements in alcohol and illicit drug use from baseline were self-reported, assessed only in a sample of patients screening positive at baseline, and included subjects who all received an intervention, either brief intervention or more intensive treatment. Therefore, the true efficacy of brief intervention for illicit drug use needs further investigation.

IMPLICATIONS FOR PRACTICE

Generalist physicians must select among numerous recommended preventive medicine measures for their patients during brief visits. Solberg's study should encourage primary care physicians to prioritize SBIRT over other, less effective preventive interventions. Smith's study provides evidence that clinicians can screen for alcohol use disorders using the single-item alcohol screening question recommended by NIAAA. Moreover, the question detects alcohol use disorders, binge drinking, and risky drinking. Binge drinking is episodic, but deleterious to health, and risky drinking is a prevalent problem in primary care settings. Madras' evaluation of a large-scale SBIRT program implementation concluded that combined screening and intervention for alcohol and illicit drug use is feasible across a range of health care sites and diverse patient populations, though the true efficacy needs further investigation.

Applications of SBIRT-type interventions to populations other than at-risk drinkers have yielded mixed results, but remain an important area for ongoing investigation. A recent study of a counseling intervention among inpatients with prescription drug misuse showed a reduction in drug misuse at 3 months, but these improvements were no longer evident at 12 months.[34,35] A meta-analysis of 11 trials investigating brief intervention for hospitalized heavy drinkers had inconclusive results.[36] Finally, a study of brief intervention for dependent drinkers versus non-dependent drinkers enrolled in a clinical trial suggested that dependent drinkers decreased drinks per day similar to non-dependent drinkers 6 months following intervention.[37] Although promising, these studies do not provide definitive conclusions on the use of SBIRT for illicit drug use, prescription drug misuse, inpatient populations, or dependent drinkers. Further studies with controlled designs and standardized interventions are needed to assess the efficacy of SBIRT to these populations and settings.

Evidence for Interventions Associated with Co-Morbid Improvements in Health

Stewart SH and colleagues. Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. Addiction.2008;103:1622–28.[38]

Heavy alcohol consumption and alcohol use disorders are associated with a variety of health conditions, including hypertension. Stewart and colleagues evaluated blood pressure changes occurring during treatment for alcohol dependence among 1,383 subjects participating in the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study, a large multi-center treatment study for alcohol dependence.[38,39] Over the 16-week treatment period, the authors assessed the relationship between percentage of drinking days (PDD) and systolic and diastolic blood pressure. Systolic blood pressure decreased by an average of 12 mmHg

and diastolic blood pressure decreased by an average of 8 mmHg; however, these reductions were only evident in people who were above the median blood pressure at baseline and occurred during the first month of treatment.

Nordback I and colleagues. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology. 2009;136(3):848–55.[40]

Alcohol-associated pancreatitis often recurs in patients who continue to consume alcohol. In this randomized clinical trial, Nordback and colleagues evaluated whether the recurrence of alcohol-associated acute pancreatitis can be reduced through a counseling intervention.[40] They examined 120 patients admitted to a university hospital for an initial episode of alcohol-associated acute pancreatitis and randomized them either to a 30-min, nurse-led pre-discharge intervention with repeated (6-month intervals) outpatient interventions or an initial, pre-discharge intervention only. They found that repeated interventions, each consisting of 30 min of counseling, appear to be better than a single intervention at hospital discharge in reducing the development of recurrent acute pancreatitis during a 2-year period.

IMPLICATIONS FOR PRACTICE

While alcohol can be deleterious to health, there has been scant but emerging literature indicating that interventions for alcohol may improve the effects of alcohol-related co-morbidities. Both the Stewart and Nordback studies suggest that a counseling intervention for alcohol use can have a positive impact on co-morbid health conditions. However, future research should focus on determining the appropriate intervention intensity (i.e., length and frequency of counseling) to produce improvements in outcomes of alcohol-related diseases commonly encountered in the clinical setting and whether alcohol counseling can improve other health outcomes.

ADDICTION PHARMACOTHERAPY

Pharmacotherapy for Smoking Cessation Treatment

Gunnell D and colleagues. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. British Medical Journal.2009;339:b3805.[41]

Pharmacotherapy is an important tool in helping smokers quit, and varenicline is an effective option.[42,43] However, reports of depression and suicidal thoughts have raised concerns about its safety.[44,45] Gunnell and colleagues investigated whether varenicline is associated with an increased risk of suicide and suicidal behavior when compared with other smoking pharmacotherapy. They evaluated fatal and non-fatal self-harm, suicidal thoughts, and depression among 80,660 patients in the UK who were prescribed a new course of a smoking cessation product; hazard ratios were adjusted for a number of factors, including current or previous psychiatric history. Those who received varenicline, when compared with nicotine replacement, had an adjusted hazard ratio (HR) for fatal or non-fatal self-harm of 1.17 with a 95% confidence interval of 0.59–2.32; the HR for suicidal thoughts was 1.43 (CI=0.53–3.85), and for start of antidepressant therapy, it was 0.88 (CI=0.77–1.00). There likewise was no significant difference in the adjusted hazard ratios associated with bupropion for any of these outcomes.

IMPLICATIONS FOR PRACTICE

While it is reasonable to warn patients of the potential for psychiatric side effects when prescribing varenicline, patients and providers can be reassured that the risk appears to be fairly low. Based on these data, approximately one out every 750 smokers who take varenicline for 3 months may experience an episode of self-harm. There is a possibility that all smoking pharmacotherapy, and perhaps smoking cessation itself, are associated with a modestly increased risk of self-harm and other psychiatric problems.

Office-Based Opioid Agonist Therapy

Walley AY and colleagues. Office-based management of opioid dependence with buprenorphine: clinical practices and barriers. J Gen Intern Med. 2008;23(9):1393–8.[46]

Office-based opioid-agonist therapy (OBOT) was made possible by the Drug Addiction Treatment Act of 2000, allowing physicians to prescribe approved medications (buprenorphine and buprenorphine/naloxone).[47] However, adoption by primary care physicians has been slow. Walley and colleagues assessed buprenorphine clinical practices and barriers in a survey mailed to all 225 office-based physicians in Massachusetts who were waivered to prescribe buprenorphine.[47] Prescribing physicians reported treating a median of ten patients; most non-prescribers (54%) reported they would prescribe if barriers were reduced. Factors associated with prescribing included being a primary care physician compared to a psychiatrist (AOR: 3.02; CI=1.48–6.18) and solo compared to group practice (AOR: 3.01; CI=1.23–7.35). On the other hand, reporting low patient demand (AOR: 0.043, CI=0.009–0.21) and insufficient institutional support (AOR: 0.37; CI=0.15–0.89) were associated with not prescribing.

Barry DT and colleagues. Integrating buprenorphine treatment into office-based practice: a qualitative study. Journal General Internal Medicine.2008;24(2):218–25.[48]

In a qualitative study, Barry and colleagues used semi-structured interviews of 23 office-based physicians in New England to identify physician, patient, and logistical factors that would either facilitate or serve as a barrier to OBOT.[48] Facilitators included promoting continuity of care, positive perceptions of buprenorphine, and viewing buprenorphine as a positive alternative to methadone. Physician barriers included competing activities, lack of interest, and lack of expertise in addiction treatment. Physicians' perceptions of patient-related barriers included concerns about confidentiality and cost, and low motivation for treatment. Perceived logistical barriers in-

cluded lack of remuneration for OBOT, limited ancillary support, time limitations, and a perceived low prevalence of opioid dependence.

Soeffing JM and colleagues. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. Journal Substance Abuse Treatment.2009;37(4):426–30.[49]

In clinical trials, buprenorphine has been shown to be efficacious at reducing illicit opioid use and improving other clinical outcomes.[50] The effectiveness has been supported by a number of recent observational studies in a variety of settings.[51,52] However, subjects in these studies were not treated in a manner typical of other chronic conditions in primary care practice, where the effectiveness of buprenorphine is less clear, particularly when onsite psychosocial services are not available. Soeffing and colleagues sought to investigate this question by assessing the 12-month outcomes of 255 patients given at least one prescription for buprenorphine in a primary care practice in Baltimore.[49] Patients were classified as "opioid-positive" or "opioid-negative" each month based on patient report, urine toxicology, and provider assessment. After 12 months, 145 (56.9%) patients remained in treatment, and the percentage who were opioid negative increased from 49% in the first month to 76% by month 12. These results are comparable to those reported in the landmark clinical trial of office-based buprenorphine, in which the percentage of opiate negative urine rose from 35% to 64% over a year.[53]

IMPLICATIONS FOR PRACTICE

The adoption of OBOT has the potential to expand treatment availability for opioid-dependent patients, particularly where methadone maintenance therapy is unavailable.[54] There are concerns and barriers that have limited the use of buprenorphine by physicians, even those who have undergone the required training and obtained a waiver.[55] Although not expressed in these studies, there is also a stigma associated with addiction and addiction treatment at a physician and institutional level that needs to be overcome.[56] Physicians who are interested in providing this treatment should be given institutional support and encouragement.

Observational studies support the effectiveness of office-based buprenorphine treatment for opioid dependence. There are a variety of approaches and treatment protocols, but providing this treatment in a setting where opioid dependence is incorporated into primary care and treated like other chronic illnesses appears to be effective. However, there are still unanswered questions about the optimal treatment approach, including intervals for visits, toxicology testing, and “dose” of counseling. It is likely that treatment needs to be individualized, and some patients will require a more intensive approach with closer monitoring and additional psychosocial support.

Acknowledgements: *We acknowledge the editorial assistance of Margaret Krumm in preparation of this manuscript. No financial support was received by the authors for the work represented in this manuscript. This work was presented in an invited oral presentation at the 2010 Annual meeting of the Society of General Internal Medicine. Minneapolis, Minneapolis, May 1, 2010.*

Conflict of Interest: *None disclosed*

Corresponding Author: *Adam J. Gordon, MD, MPH; Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, 7180 Highland Drive (151-C-H), Pittsburgh, PA 15206, USA (e-mail: adam.gordon@va.gov).*

REFERENCES

1. **Robins LN, Helzer JE, Weissman MM, et al.** Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry. 1984;41(10):949–58.
2. Institute of Medicine. Improving the quality of healthcare for mental and substance-use conditions: The quality chasm series. Washington, DC: The National Academies Press; 2005.
3. Institute of Medicine. Crossing the quality chasm: A new health system for the 21st century. Washington, DC: The National Academies Press; 2001.
4. **Mokdad AH, Marks JS, Stroup DF, Gerberding JL.** Actual causes of death in the United States, 2000. JAMA. 2004;291(10):1238–45.
5. **Gordon AJ, Sullivan LE, Alford DP, et al.** Update in addiction medicine for the generalist. J Gen Intern Med. 2007;22(8):1190–4.
6. **Gordon AJ, Fiellin DA, Friedmann PD, et al.** Update in addiction medicine for the primary care clinician. J Gen Intern Med. 2008;23 (12):2112–6.
7. **Dunn KM, Saunders KW, Rutter CM, et al.** Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152 (2):85–92.
8. **Hall AJ, Logan JE, Toblin RL, et al.** Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300 (22):2613–20.
9. **Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H.** Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction. 2009;104(6):993–9.
10. **Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE.** A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. Addiction. 2009;104(9):1541–8.
11. **Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC**. QTc Interval Screening in Methadone Treatment: the CSAT Consensus Guideline. Ann Intern Med. 2008.
12. **Gourevitch MN.** First do no harm…Reduction? Ann Intern Med. 2009;150(6):417–8.
13. **McLellan AT, Turner BJ.** Chronic noncancer pain management and opioid overdose: time to change prescribing practices. Ann Intern Med. 2010;152(2):123–4.
14. **Solberg LI, Maciosek MV, Edwards NM.** Primary care intervention to reduce alcohol misuse ranking its health impact and cost effectiveness. Am J Prev Med. 2008;34(2):143–52.
15. **D'Amico EJ, Paddock SM, Burnam A, Kung FY.** Identification of and guidance for problem drinking by general medical providers: results from a national survey. Med Care. 2005;43(3):229–36.
16. **Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R.** Primary care validation of a single-question alcohol screening test. J Gen Intern Med. 2009;24(7):783–8.
17. **Friedmann PD, McCullough D, Chin MH, Saitz R.** Screening and intervention for alcohol problems. A national survey of primary care physicians and psychiatrists. J Gen Intern Med. 2000;15(2):84–91.
18. **Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M.** Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption–II. Addiction. 1993;88(6):791–804.
19. **Allen JP, Litten RZ, Fertig JB, Babor T.** A review of research on the Alcohol Use Disorders Identification Test (AUDIT). Alcoholism: Clinical & Experimental Research. 1997;21(4):613–9.
20. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction. 2002;97 (9):1183-94.
21. **Vinson DC, Kruse RL, Seale JP.** Simplifying alcohol assessment: two questions to identify alcohol use disorders. Alcohol Clin Exp Res. 2007;31(8):1392–8.
22. **Dawson DA, Grant BF, Stinson FS, Zhou Y.** Effectiveness of the derived Alcohol Use Disorders Identification Test (AUDIT-C) in screening for

alcohol use disorders and risk drinking in the US general population. Alcohol Clin Exp Res. 2005;29(5):844–54.
23. **Gordon AJ, Maisto SA, McNeil M, et al.** Three questions can detect hazardous drinkers. J Fam Pract. 2001;50(4):313–20.
24. **Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA.** alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Arch Intern Med. 1998;158(16):1789–95.
25. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
26. **Cervantes EA, Miller WR, Tonigan JS.** Comparison of Timeline Follow-Back and Averaging Methods for Quantifying Alcohol Consumption in Treatment Research. Assessment. 1994;1(1):23–30.
27. **Maisto SA, Conigliaro JC, Gordon AJ, Mcginnis KA, Justice AC.** An experimental study of the agreement of self-administration and telephone administration of the Timeline Followback interview. J Stud Alcohol Drugs. 2008;69(3):468–71.
28. **Madras BK, Compton WM, Avula D, Stegbauer T, Stein JB, Clark HW.** Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: comparison at intake and 6 months later. Drug Alcohol Depend. 2009;99(1–3):280–95.
29. **Krupski A, Sears JM, Joesch JM et al**. Impact of brief interventions and brief treatment on admissions to chemical dependency treatment. Drug Alcohol Depend. 2010.
30. **Babor TF, McRee BG, Kassebaum PA, Grimaldi PL, Ahmed K, Bray J.** Screening, Brief Intervention, and Referral to Treatment (SBIRT): toward a public health approach to the management of substance abuse. Subst Abus. 2007;28(3):7–30.
31. The impact of screening, brief intervention, and referral for treatment on emergency department patients' alcohol use. Ann Emerg Med. 2007;50 (6):699-710, 710.
32. **Fleming MF, Barry KL, Manwell LB, Johnson K, London R.** Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices. JAMA. 1997;277 (13):1039–45.
33. **Fleming MF, Mundt MP, French MT, Manwell LB, Stauffacher EA, Barry KL.** Brief physician advice for problem drinkers: long-term efficacy and benefit-cost analysis. Alcohol Clin Exp Res. 2002;26(1):36–43.
34. **Otto C, Crackau B, Lohrmann I, et al.** Brief intervention in general hospital for problematic prescription drug use: 12-month outcome. Drug Alcohol Depend. 2009;105(3):221–6.
35. **Zahradnik A, Otto C, Crackau B, et al.** Randomized controlled trial of a brief intervention for problematic prescription drug use in non-treatment-seeking patients. Addiction. 2009;104(1):109–17.
36. **McQueen J, Howe TE, Allan L, Mains D**. Brief interventions for heavy alcohol users admitted to general hospital wards. Cochrane Database Syst Rev. 2009;(3):CD005191.
37. **Guth S, Lindberg SA, Badger GJ, Thomas CS, Rose GL, Helzer JE.** Brief intervention in alcohol-dependent versus nondependent individuals. J Stud Alcohol Drugs. 2008;69(2):243–50.
38. **Stewart SH, Latham PK, Miller PM, Randall P, Anton RF.** Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. Addiction. 2008;103(10):1622–8.
39. **Anton RF, O'Malley SS, Ciraulo DA, et al.** Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295(17):2003–17.
40. **Nordback I, Pelli H, Lappalainen-Lehto R, Jarvinen S, Raty S, Sand J.** The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology. 2009;136(3):848–55.
41. **Gunnell D, Irvine D, Wise L, Davies C, Martin RM.** Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. BMJ. 2009;339:b3805.
42. **Quinn VP, Hollis JF, Smith KS, et al.** Effectiveness of the 5-As tobacco cessation treatments in nine HMOs. J Gen Intern Med. 2009;24(2):149–54.
43. **Cahill K, Stead LF, Lancaster T**. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2008;(3):CD006103.
44. **Kuehn BM.** Studies linking smoking-cessation drug with suicide risk spark concerns. JAMA. 2009;301(10):1007–8.
45. **Kasliwal R, Wilton LV, Shakir SA.** Safety and drug utilization profile of varenicline as used in general practice in England: interim results from a prescription-event monitoring study. Drug Saf. 2009;32(6):499–507.
46. **Walley AY, Alperen JK, Cheng DM, et al.** Office-based management of opioid dependence with buprenorphine: clinical practices and barriers. J Gen Intern Med. 2008;23(9):1393–8.
47. Drug Addiction Treatment Act of 2000, 42 USC§3502a, Drug Addiction Treatment Act of 2000, (2000)
48. **Barry DT, Irwin KS, Jones ES et al**. Integrating Buprenorphine Treatment into Office-based Practice: a Qualitative Study. J Gen Intern Med. 2008.
49. **Soeffing JM, Martin LD, Fingerhood MI, Jasinski DR, Rastegar DA.** Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. J Subst Abuse Treat. 2009;37(4):426–30.
50. **Mattick RP, Kimber J, Breen C, Davoli M**. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2004;(3):CD002207.
51. **Fiellin DA, Moore BA, Sullivan LE, et al.** Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. Am J Addict. 2008;17(2):116–20.
52. **Parran TV, Adelman CA, Merkin B, et al.** Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. Drug Alcohol Depend. 2010;106(1):56–60.
53. **Fudala PJ, Bridge TP, Herbert S, et al.** Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949–58.
54. **Gordon AJ, Trafton JA, Saxon AJ, et al.** Implementation of buprenorphine in the Veterans Health Administration: Results of the first 3 years. Drug Alcohol Depend. 2007;90:292–6.
55. **Gordon AJ, Liberto J, Granda S, Salmon-Cox S, Andree T, McNicholas L.** Outcomes of DATA 2000 certification trainings for the provision of buprenorphine treatment in the Veterans Health Administration. Am J Addict. 2008;17(6):459–62.
56. **Miller NS, Sheppard LM, Colenda CC, Magen J.** Why physicians are unprepared to treat patients who have alcohol- and drug-related disorders. Acad Med. 2001;76(5):410–8.