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A Research Agenda for Gender and Substance Use Disorders in the Emergency Department

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Abstract

For many years, gender differences have been recognized as important factors in the etiology, pathophysiology, comorbidities, and treatment needs and outcomes associated with the use of alcohol, drugs, and tobacco. However, little is known about how these gender-specific differences affect ED utilization; responses to ED-based interventions; needs for substance use treatment and barriers to accessing care among patients in the ED; or outcomes after an alcohol-, drug-, or tobacco-related visit. As part of the 2014 *Academic Emergency Medicine* consensus conference on “Gender-Specific Research in Emergency Care: Investigate, Understand and Translate How Gender Affects Patient Outcomes,” a breakout group convened to generate a research agenda on priority questions related to substance use disorders.

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Use of alcohol, illicit and prescription drugs, and tobacco are the most prevalent risky health behaviors of individuals visiting the emergency department (ED) and are more prevalent in this setting than in the general population or other health care settings.¹ In recent multistate ED data from the National Institute on Drug Abuse (NIDA) Clinical Trials Network, 45% of patients reported past-year at-risk alcohol use, 30% reported past-year drug use, and 47% reported current tobacco use.² Substance use among ED patients is associated with violence, all forms of injury, ED recidivism, and high health care costs.³ As an ED visit may be the only point of contact in the health care system for many individuals with high-risk behaviors, it offers an ideal opportunity to prevent and treat substance use disorders. A variety of terms have been used to describe the continuum of substance disorders from misuse to addiction. For the purposes of this document, we will primarily use the term “substance use disorders.”

Gender differences are recognized as influential factors in almost every aspect of substance use, including risk factors; initiation, progression, and maintenance of use; treatment needs; and health sequelae.^{4–6} However, little is known about how these gender-specific differences may affect use of acute health services, including any differences in presentation to the acute care setting; responses to brief ED-based interventions; needs for outpatient substance use treatment and barriers to accessing treatment among ED patients; outcomes after alcohol-, drug-, or tobacco-related visits; or related ED recidivism.

The ED has been proposed as an opportune place for screening, brief intervention, and referral to treatment (SBIRT), as well as treatment initiation for substance use disorders. Not only does a significant proportion of the population make contact with the health care system through the ED, but a disproportionately large number of ED visits are associated with the negative health consequences of substance use. The visit itself, then, may become a “teachable moment,” when patients may be more receptive to behavior change messages or interventions. While study outcomes have been mixed,⁷ there is modest evidence that brief interventions are effective in reducing unhealthy alcohol use^{8–12} or alcohol-related consequences^{7,8} for less severe alcohol use disorders and in reducing smoking among patients with tobacco-associated visits.¹³ Conflicting evidence has been presented regarding the use of SBIRT for drug use.^{14–17}

There is evidence that the efficacy of brief motivational interventions for alcohol, drug, and tobacco interventions may vary by sex.¹⁸ Gentilello et al.¹⁹ found that with patients hospitalized after a serious alcohol-related injury, a brief motivational intervention was effective in men, but not women. They attributed the difference to female drinkers' higher rates of psychosocial and relationship problems, specifically recent intimate partner violence. The authors recommended that brief alcohol intervention programs need to have the capacity to address these co-occurring issues in women. In contrast, Blow et al.²⁰ found that a subgroup of college-age women who received brief advice were the most likely to reduce their binge drinking. Madras et al.,¹⁴ in a large multicenter trial of SBIRT for drug use, found that men with illicit drug use at baseline increased their alcohol use at follow-up; this was not true for women. Choo et al.²¹ found that male gender was associated with receptivity to ED-based smoking cessation counseling. Gender and substance disorders

researchers have suggested the need to design and test gender-specific screening and interventions to improve the ability of SBIRT to have a positive clinical effect on the ED population.

Consensus Process

Through a consensus process, the authors sought to identify research questions that could improve our current knowledge of gender differences in substance use relevant to the ED setting, focusing on the questions with highest potential to improve emergency care. We used a modified nominal group technique to identify the highest priority questions in this area. After initial development of a broad range of possible research questions, we refined and narrowed the list iteratively through discussion by the breakout group, solicited expert review, and conducted online polling of conference participants before the event and in-person voting on the day of the consensus conference. The final voting was done by having participants manually rank questions posted on the conference room wall using colored stickers representing a scale of 1 (low priority, red), 2 (moderate priority, yellow), or 3 (high priority, green). After voting was complete, all questions with average scores greater than 2 were included. Thirty participants attended the substance use breakout session and voted on final questions (see footnote for a full list of participants).

Consensus Research Agenda

Alcohol

Epidemiology, Risk Factors, Presentation, and Comorbidities—The lifetime prevalence of alcohol use disorders is greater in men than in women.^{22,23} However, in more recent years the gender gap in unhealthy alcohol use appears to be closing due to growing use among younger women.²⁴ The Drug Abuse Warning Network (DAWN) reported a 38% increase in alcohol-related ED visits by female young adults, from 37,218 visits in 2005 to 51,464 in 2009, while alcohol-related ED visits by male young adults remained stable.²⁵ Sex-specific thresholds for detecting problem alcohol use should be used with any screening tests; failure to do so may underestimate prevalence of alcohol disorders among women, for whom lower thresholds are more appropriate.²⁶

In general, women progress more rapidly from onset of initial drinking to development of problem drinking than do men, a phenomenon called “telescoping.”^{23,27} Telescoping may make the opportunity for intervention between progressive stages of drinking shorter for women than for men;²⁸ identifying and intervening in early unhealthy alcohol use patterns during the ED visit—and providing accessible referral resources—may be particularly urgent in women.

Women with unhealthy alcohol use demonstrate a higher prevalence of mental health disorders, including depression, anxiety, phobias, and posttraumatic stress disorder (PTSD), compared to men.⁴ Prior experiences of victimization, whether in childhood or in adult partner abuse (or both), are also more common in women than men and have been linked to high-risk alcohol use.²⁹ Overall, women appear to experience more serious medical and psychiatric consequences from unhealthy alcohol use than men.^{19,27,30} Although alcohol-

related visits—many of which involve traumatic injuries—are costly to the health care system,^{3,31} how health care utilization and overall health care burden differs by sex is unknown.

Pharmacology, Neuroendocrinology, and Toxicity—Women achieve higher blood alcohol concentrations than do men after consuming equivalent amounts of alcohol, for reasons that include sex-based differences in total body weight, body composition, and alcohol metabolism.^{32,33} Currently most clinical research involving alcohol use disorders is based on the self-reported amount of alcohol intake; however, report of consumption alone may under represent the magnitude of the problem in women.

In addition, sex-based differences influence neurochemical and behavioral responses to alcohol. Overall, women exhibit an increased sensitivity to alcohol-induced organ pathology, including effects on the heart, brain, and liver; this may be related to sex-specific differences in body weight and body composition or an additive effect of estrogen in augmenting alcohol-related damage.^{34–38} However, there is little research on the biochemical basis for these differences, how these differences may manifest in the acute care setting, or how sex differences in susceptibility to alcohol-related disease may inform sex-specific treatment approaches.³⁹

Responses to ED-based SBIRT for Alcohol—Overall, there is a paucity of literature examining the role of gender in responsiveness to brief interventions in the ED.^{20,40,41} Studies in non-ED settings have had mixed results in terms of sex differences in response to brief interventions. Several studies found no difference in outcomes after brief interventions in the ED when stratified by sex^{42–44} or found that alcohol consumption in brief intervention and control groups declined to the same (nonstatistically significant) extent at follow-up. However, a 2007 Cochrane review and meta-analysis of 22 randomized controlled trials of brief alcohol interventions with 7,619 participants from primary care populations demonstrated the effectiveness of SBIRT in men, but not women, at 1 year follow-up.¹⁸ The Cochrane review stated that the benefit of brief interventions for problem drinking in women is not clear, and recommended “future trials should focus on women and on delineating the most effective components of interventions.”¹⁸ Whether the disparate results by sex found with brief interventions are due to unmeasured abuse histories and other complex gender-based psychosocial dynamics among women drinkers remains unanswered. Appropriately powered studies are needed to see the effect of ED-based brief intervention on alcohol-related outcomes by gender and by other important patient characteristics that may have an interaction with gender.

Regardless of sex differences in response to existing, largely non–sex-specific interventions, a separate question is whether interventions tailored by sex might yield improved outcomes. Sex-specific approaches might include substance-only interventions versus those integrating mental health or other problems,⁴⁵ such as violence involvement or sexual risk behaviors;⁴⁶ different styles of brief interventions, e.g., confrontational versus nonconfrontational;⁴⁷ or targeting specific periods of receptivity to behavior change messages, e.g., during pregnancy for women.⁴⁸ Digital technologies for delivering SBIRT in the ED are increasingly being

studied;^{49,50} further work is needed to see how these might optimize the gender-specific approach to alcohol interventions.

Women face specific barriers to divulging alcohol and drug use, including fear of social service involvement and loss of their children or of public housing. Women are also more likely to face barriers to accessing alcohol treatment programs compared to men and have specific programming needs: they are often in abusive relationships, have greater parenting and child care responsibilities, lack transportation and financial independence, and may benefit from women-only treatment facilities.^{51–54} There is little information available on how existing ED referral resources might be modified, augmented, or revolutionized to lower the threshold for following up (e.g., by providing digital recovery support services or applying integrated approaches).⁵⁵

Drugs

Epidemiology—In 2011, approximately 2.5 million ED visits were related to illicit drug use and misuse of prescription drugs, with approximately half of these visits relating to prescription drugs.⁵⁶ The number of illicit drug-related visits per 100,000 people in the United States rose from 339 to 402 from 2004 to 2011,⁵⁶ while the number of ED visits for nonmedical use of opioids increased 111% from 2004 to 2008; the number of ED visits for nonmedical use of benzodiazepines increased 89% from 2004 to 2008.¹ The true extent of drug use among women, however, is likely to be obscured by provider biases in screening and testing for drug use;⁵⁷ the extent of this bias in the ED, and how provider biases may affect interventions and referrals, is not known.

Marked differences in the epidemiology of, and ED utilization related to, prescription opioid use have been observed between men and women; this topic is further discussed in the paper of the breakout session dedicated to discussion pain management.⁵⁸ The prevalence of opioid use remains highest in men, but the rate of increase among women has been marked: between 1999 and 2010, opioid overdose deaths increased more than 400% among women, compared to 265% among men.⁵⁹ Women are more likely than men to be prescribed pain medications, are given higher doses, and use them for longer time periods than men,⁶⁰ all factors that may make addressing nonmedical use of opioids in women in the ED particularly challenging.

The ED is often an opportune clinical venue to study the effects of policy changes on human health and health behavior and, likewise, to examine policies that may differentially affect men and women. In the upcoming years, these will include the effect of changing drug policies and laws, including stricter opioid prescribing policies, legalization of medical and recreational marijuana, and family-focused approaches to drug use treatment.

Pharmacology, Neuroendocrinology, and Toxicity—Susceptibility to drug misuse is mediated, in part, by gastric acidity, gastric and intestinal motility, body weight and composition, blood volume, hepatic and renal excretion, plasma drug levels, drug sensitivity, toxicity and side effects, and gene–environment interactions.^{61,62} Sex differences in these mediators, on balance, render female patients more susceptible to the adverse effects

of drugs,⁶³ including liver failure, drug-induced QTc prolongation,⁶⁴ and torsades de pointes.⁶⁵

Women may be at increased risk from both prescription drugs and illicit substances compared to males, may progress to dependence more rapidly (“telescoping” defined above), and have a higher risk of relapse following abstinence.^{27,66,67} Although some of the differences in patterns of use may be related to cultural and societal influences, neuroendocrine differences likely play a role as well.^{68,69} For example, dopamine neurotransmission, which is intimately involved in reinforcing behaviors and drug craving, is different between sexes. This may be partially explained by hormonal differences: estrogen mediates enhancement of dopaminergic transmission, while progestins have been shown to block the reinforcing and other behavioral effects of cocaine in animal models.⁷⁰

Much of the existing pharmacokinetic research focuses on therapeutic dosing of prescription drugs, rather than recreational use or acute overdose of both licit and illicit substances. Of studies on mechanisms of recreational drugs, most focus on stimulants. More research is needed to understand how sex differences in pharmacokinetics and pharmacodynamics affect the development of drug use disorders involving both prescription and illicit substances, as well as sex-specific patterns of adverse outcomes secondary to drug use. Additional investigations should attempt to translate recognized hormonal mechanisms of drug disorders into ED-relevant therapeutic investigations.

Responses to ED-based SBIRT—Although there is a significant body of literature around the use of SBIRT in the ED for the entire spectrum of alcohol use disorders, from at-risk to dependency, much less is known about the effectiveness, utility, and outcomes of SBIRT programs aimed at illicit and prescription drug use and even less about sex-specific enrollment and outcomes.⁷¹ There is some evidence for a sex-specific response to brief interventions: for example, a large multicenter trial of SBIRT for drugs and alcohol in both primary care and in hospital settings demonstrated overall increased abstinence across sites and substance types, but in results stratified by sex, only men reduced cocaine use after the intervention in one of the two sites that included EDs.¹⁴ Among adolescents, ED SBIRT has been shown to be effective for decreasing drug use, and in two studies, that effect was greater in males compared to females.^{16,72} Other drug SBIRT studies have not shown sex differences.⁷³ However, in general, studies of drug interventions in the ED have not been powered to examine differences between sexes and do not examine potential interaction effects involving sex, and many still do not provide sex-stratified adjusted analyses. Further, it remains unclear whether abstinence or reduced consumption has an effect on health consequences or risk behaviors (overall or by sex).

Sex-specific interventions for drug use have not been tested in the ED. A review of published studies from the NIDA National Drug Abuse Treatment Clinical Trials Network between 2000 and 2010⁷⁴ found four with a focus on sex-specific treatment protocols for substance use disorders, including trials evaluating substance use treatment approaches in pregnant women and in women with concomitant substance use disorders and PTSD and using sex-specific HIV risk reduction programs among those with substance use disorders. These studies, which generally had positive intervention effects, provide valuable sex-

specific data around prevalence of health problems related to drug use and justification for sex-specific assessments and interventions (such as trauma-informed care for women with substance use disorders) that might be incorporated into drug interventions in the ED.⁵⁵

Even after accounting for the prevalence of drug use disorders, women remain underrepresented in drug treatment programs. Despite evidence for tailoring of treatment approaches to sex-specific issues, few programs address women's needs for child care, perinatal care, or job and life-skills training. Whether these differences may be addressed through the development of sex-specific intervention and referral strategies remains to be seen.² As noted for alcohol treatments, more research is needed about any sex-specific barriers to accessing necessary drug treatments after ED referral and how to best overcome them.

More knowledge about relevant and influential sex-specific factors among patients in the ED may help providers identify those at increased risk of drug use disorders, including sex-specific patterns and comorbidities associated with unhealthy drug use and barriers to successful utilization of referral resources.

Research Questions for Alcohol and Drug Use Disorders in the ED

1. How do the patterns and severity of harmful use differ between genders among ED patients?
2. What are gender-specific risk factors for substance use disorders among patients in the ED?
3. What are the gender-specific health consequences of alcohol and drug use among those presenting to the ED?
4. Do provider gender biases affect screening, interventions, and referrals to treatment for unhealthy alcohol and drug use? If so, how?
5. What are effective gender-specific approaches to alcohol and drug screening in the emergency setting?
6. How does the effectiveness of existing SBIRT protocols differ by gender for improvement 1) in alcohol and drug use, 2) in health consequences, and 3) in associated risk behaviors?
7. How do alcohol and drug interventions with gender-specific content (including gender-specific information about health consequences) perform in the emergency setting?
8. How should ED SBIRT for alcohol and drug use be individualized not only to gender but to gender subgroups (such as adolescents, pregnant women, and lesbian, gay, bisexual, and transgender individuals), to be more effective?
9. Given that many high-risk health conditions coexist with, and play a role in, alcohol and drug use disorders, including mental health problems, violence and injury involvement, and risky sexual behaviors, which should receive priority in ED interventions, and how does this differ by gender?

10. To what extent are problem disclosure and potential entry into treatment negatively influenced by a patient's concern that identification may prompt social service action that could result in removal of children from the home? What are best practices for handling the obligation to record and the obligation to report?
11. How can digital technologies be used in the ED to provide interventions tailored by gender? How do men and women differ in their receptivity to such interventions? How does treatment effectiveness of such technologies differ between men and women?
12. How might gender-based factors be used to strengthen referrals to community-based treatment, especially for women, who face numerous, gender-specific barriers to accessing substance use treatments?
13. What are the gender-specific issues related to initiating or helping patients gain access to pharmacologic therapies for severe alcohol disorders and for drug use (buprenorphine, naloxone, naltrexone) in the ED, in conjunction with appropriate referrals?
14. What are the pharmacokinetic differences in individual drugs of abuse between men and women, and what are the implications for clinical manifestations of drug disorders (overdose, etc.) and for potential novel therapies?
15. What is the role of gender in identifying patients at-risk for drug use and primary prevention or education (e.g., upon prescribing opioids) in the ED?
16. Further exploration is needed of sex-specific effect of opioids on cardiac conduction and clinical significance of this observed difference.
17. What are the effects of marijuana policies on ED use for marijuana-related illnesses, and how does this vary by gender?
18. Which opioid prescribing policies, and which means of disseminating and enforcing the policies, are most effective in reducing prescription drug disorders for each gender?

Tobacco

Epidemiology—The few studies that have reported ED tobacco use prevalence show great variability, with estimates ranging from 21% to 48%.^{75–78} Despite this variability, tobacco use prevalence among ED patients is higher than in the general population. Tobacco use prevalence by sex is not well established in the ED population. In the general population, smoking prevalence historically has been lower among women than men; however, quit rates for women are typically lower than for men,⁷⁹ and women are less likely than men to be prescribed pharmacotherapy for nicotine dependence.⁸⁰

Pharmacology, Neuroendocrinology, and Toxicity—Sex differences in drug efficacy have been reported for common cessation treatments. For instance, quit rates are generally lower in women compared to men treated with nicotine patches, suggesting that increasing the quit rates of women smokers may require supplementing patch treatment with

a rapid-acting form of nicotine replacement, such as gum or nasal spray.^{81–83} Understanding the physiologic basis for these differences could allow pharmacotherapy treatments administered at discharge (if appropriate) to be tailored based on sex and could potentially lead to the development of further treatments specific to sex.

Responses to ED-based SBIRT—Emergency departments should develop and validate brief and practical screening instruments for tobacco use and determine the optimal method for the administration of screening instruments.^{84–86} Research suggests that low-intensity screening, counseling, and referral can prompt ED smokers to quit or attempt to quit.¹³ Although Bernstein et al.¹³ found that no statistical difference existed between the proportion of males and females who wanted to quit smoking in the ED setting, sex differences related to quitting attempts have been noted. Females report more reasons for initiating smoking; are more likely to be motivated to quit by major life changes, such as moving to a new home or pregnancy; and are more likely to use medications or counseling to assist smoking cessation than males.⁸⁷ This may be related to the gender differences in perceived risks and perceived benefits of smoking cessation that have been found, as well as gender differences in the predictors of motivation to quit. Women indicate greater likelihood of perceived risks (weight gain, negative affect, etc.) and benefits (health, well-being, finances, etc.) of smoking cessation and perceived risks negatively predicted pretreatment motivation and treatment success.⁸⁸

Sex-specific changes in smoking in response to illness have also been observed. For example, adolescent girls with asthma, compared to girls without asthma, have been observed to have high dependency scores and continue smoking despite respiratory symptoms, an association that was not observed among boys.⁸⁹ Women are less likely than men to quit smoking after a major health event like a heart attack.⁹⁰ A better understanding of the potential differences in perceptions and experiences of males versus female patients who smoke who present to the ED is needed to determine the need and utility of sex-specific smoking cessation interventions.⁸⁴

Research Questions for Tobacco Use in the ED

1. What are differential motivators for quitting among men and women presenting to the ED?
2. Are gender-tailored interventions, including pharmacologic treatments, more effective for tobacco cessation?
3. Are there counseling styles or message-framing strategies that are more effective for men vs. women?
4. Because counseling in the ED is necessarily brief, are there sex-specific topics that should be broached first, such as negative affective states or fear of weight gain for women or sexual potency for men?
5. What is the most effective tobacco cessation intervention for women, including pregnant women?
6. What is the most effective tobacco cessation intervention for men?

Limitations

This paper focused on gender and substance use in the ED. Although there is a complex interplay between gender and other important individual factors (such as race, ethnicity, country of origin, and age) in determining risk for substance use, ED utilization, treatment, and referral needs, and clinical outcomes, an in-depth exploration of these themes was beyond the scope of this paper.

Summary

Gender's role in screening, interventions, and referrals to treatment for substance use disorders is underexplored. Through a consensus process, we identified priority areas for future emergency medicine research that may enable us to develop gender-specific approaches that are more effective in reducing substance use and its harmful health sequelae.

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References

1. D'Onofrio G, Becker B, Woolard RH. The impact of alcohol, tobacco, and other drug use and abuse in the emergency department. *Emerg Med Clin North Am.* 2006; 24:925–67. [PubMed: 16982347]
2. Sanjuan PM, Rice SL, Witkiewitz K, Mandler RN, Crandall C, Bogenschutz MP. Alcohol, tobacco, and drug use among emergency department patients. *Drug Alcohol Depend.* 2014; 38:32–8. [PubMed: 24594289]
3. Rockett IRH, Putnam SL, Jia H, Chang CF, Smith GS. Unmet substance abuse treatment need, health services utilization, and cost: a population-based emergency department study. *Ann Emerg Med.* 2005; 45:118–27. [PubMed: 15671966]
4. Brady KT, Randall CL. Gender differences in substance use disorders. *Psychiatr Clin North Am.* 1999; 22:241–52. [PubMed: 10385931]
5. Walitzer KS, Dearing RL. Gender differences in alcohol and substance use relapse. *Clin Psychol Rev.* 2006; 26:128–48. [PubMed: 16412541]
6. Zilberman M, Tavares H, el-Guebaly N. Gender similarities and differences: the prevalence and course of alcohol- and other substance-related disorders. *J Addict Dis.* 2003; 22:61–74. [PubMed: 14723478]
7. Havard A, Shakeshaft A, Sanson-Fisher R. Systematic review and meta-analyses of strategies targeting alcohol problems in emergency departments: interventions reduce alcohol-related injuries. *Addiction.* 2008; 103:368–76. [PubMed: 18190671]
8. Nilsen P, Baird J, Mello MJ, et al. A systematic review of emergency care brief alcohol interventions for injury patients. *J Subst Abuse Treat.* 2008; 35:184–201. [PubMed: 18083321]
9. Academic ED SBIRT Collective. The impact of screening, brief intervention, and referral for treatment on emergency department patients' alcohol use. *Ann Emerg Med.* 2007; 50:699–710. [PubMed: 17870206]

10. D'Onofrio G, Fiellin DA, Pantalon MV, et al. A brief intervention reduces hazardous and harmful drinking in emergency department patients. *Ann Emerg Med.* 2012; 60:181–92. [PubMed: 22459448]
11. Monti PM, Barnett NP, Colby SM, et al. Motivational interviewing versus feedback only in emergency care for young adult problem drinking. *Addiction.* 2007; 102:1234–43. [PubMed: 17565560]
12. Neumann T, Neuner B, Weiss-Gerlach E, et al. The effect of computerized tailored brief advice on at-risk drinking in subcritically injured trauma patients. *J Trauma.* 2006; 61:805–14. [PubMed: 17033544]
13. Bernstein SL, Bijur P, Cooperman N, et al. A randomized trial of a multicomponent cessation strategy for emergency department smokers. *Acad Emerg Med.* 2011; 18:575–83. [PubMed: 21676054]
14. 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; 99:280–95. [PubMed: 18929451]
15. Woodruff SI, Clapp JD, Eisenberg K, et al. Randomized clinical trial of the effects of screening and brief intervention for illicit drug use: the life shift/shift gears study. *Addict Sci Clin Pract.* 2014; 9:8. [PubMed: 24886786]
16. Bernstein E, Edwards E, Dorfman D, Heeren T, Bliss C, Bernstein J. Screening and brief intervention to reduce marijuana use among youth and young adults in a pediatric emergency department. *Acad Emerg Med.* 2009; 16:1174–85. [PubMed: 20053238]
17. Bogenschutz, MP.; Donovan, DM. [Accessed Sep 20, 2014] Screening Motivational Assessment and Referral to Treatment in Emergency Departments (SMART-ED): Evaluation of Screening, Brief Intervention, Referral to Treatment (SBIRT) and Booster Session for Drug Use Patients Presenting for Treatment in the Emergency Department. Available at: <http://ctndisseminationlibrary.org/protocols/ctn0047.htm>
18. Kaner EF, Beyer F, Dickinson HO, et al. Effectiveness of brief alcohol interventions in primary care populations. *Cochrane Database Syst Rev.* 2007; 18(2):CD004148. [PubMed: 17443541]
19. Gentilello LM, Rivara FP, Donovan DM, et al. Alcohol problems in women admitted to a level I trauma center: a gender-based comparison. *J Trauma.* 2000; 48:108–14. [PubMed: 10647574]
20. Blow FC, Barry KL, Walton MA, et al. The efficacy of two brief intervention strategies among injured, at-risk drinkers in the emergency department: impact of tailored messaging and brief advice. *J Stud Alcohol.* 2006; 67:568–78. [PubMed: 16736077]
21. Choo EK, Sullivan AF, LoVecchio F, Perret JN, Camargo CA Jr, Boudreaux ED. Patient preferences for emergency department-initiated tobacco interventions: a multicenter cross-sectional study of current smokers. *Addict Sci Clin Pract.* 2012; 7:4. [PubMed: 22966410]
22. Khan S, Okuda M, Hasin D, et al. Gender differences in lifetime alcohol dependence: results from the national epidemiologic survey on alcohol and related conditions. *Alcohol Clin Exp Res.* 2013; 37:1696–705. [PubMed: 23763329]
23. Nolen-Hoeksema S, Hilt L. Possible contributors to the gender differences in alcohol use and problems. *J Gen Psychol.* 2006; 133:357–74. [PubMed: 17128956]
24. Nolen-Hoeksema S. Gender differences in risk factors and consequences for alcohol use and problems. *Clin Psychol Rev.* 2004; 24:981–1010. [PubMed: 15533281]
25. Center for Behavioral Health Statistics and Quality. [Accessed Sep 20, 2014] The DAWN Report: Trends in Emergency Department Visits Involving Underage Alcohol, 2005 to 2009. Available at: http://www.samhsa.gov/data/2k11/WEB_DAWN_020/WEB_DAWN_020_HTML.pdf
26. Geneste J, Pereira B, Arnaud B, et al. CAGE, RAPS4, RAPS4-QF and AUDIT screening tests for men and women admitted for acute alcohol intoxication to an emergency department: are standard thresholds appropriate? *Alcohol Alcohol.* 2012; 47:273–81. [PubMed: 22414922]
27. Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug Alcohol Depend.* 2004; 74:265–72. [PubMed: 15194204]

28. Randall CL, Roberts JS, Del Boca FK, Carroll KM, Connors GJ, Mattson ME. Telescoping of landmark events associated with drinking: a gender comparison. *J Stud Alcohol*. 1999; 60:252–60. [PubMed: 10091964]
29. Pinchevsky GM, Wright EM, Fagan AA. Gender differences in the effects of exposure to violence on adolescent substance use. *Violence Vict*. 2013; 28:122–44. [PubMed: 23520836]
30. Greenfield SF, Brooks AJ, Gordon SM, et al. Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug Alcohol Depend*. 2007; 86:1–21. [PubMed: 16759822]
31. Lee MH, Mello MJ, Reinert S. Emergency department charges for evaluating minimally injured alcohol-impaired drivers. *Ann Emerg Med*. 2009; 54:593–9. [PubMed: 19577334]
32. Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med*. 1990; 322:95–9. [PubMed: 2248624]
33. Baraona E, Abittan CS, Dohmen K, et al. Gender differences in pharmacokinetics of alcohol. *Alcohol Clin Exp Res*. 2001; 25:502–7. [PubMed: 11329488]
34. Becker U, Deis A, Sørensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology*. 1996; 23:1025–9. [PubMed: 8621128]
35. Hommer D, Momenan R, Kaiser E, Rawlings R. Evidence for a gender-related effect of alcoholism on brain volumes. *Am J Psychiatry*. 2001; 158:198–204. [PubMed: 11156801]
36. Lancaster FE. Gender differences in the brain: implications for the study of human alcoholism. *Alcohol Clin Exp Res*. 1994; 18:740–6. [PubMed: 7943685]
37. Schweinsburg BC, Alhassoon OM, Taylor MJ, et al. Effects of alcoholism and gender on brain metabolism. *Am J Psychiatry*. 2003; 160:1180–3. [PubMed: 12777281]
38. Urbano-Márquez A, Estruch R, Fernández-Solá J, Nicolás JM, Paré JC, Rubin E. The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. *JAMA*. 1995; 274:149–54. [PubMed: 7596003]
39. Kimura M, Miyakawa T, Matsushita S, So M, Higuchi S. Gender differences in the effects of ADH1B and ALDH2 polymorphisms on alcoholism. *Alcohol Clin Exp Res*. 2011; 35:1923–7. [PubMed: 21848961]
40. Choo EK, McGregor AJ, Mello MJ, Baird J. Gender, violence and brief interventions for alcohol in the emergency department. *Drug Alcohol Depend*. 2013; 127:115–21. [PubMed: 22818512]
41. Sanchez-Craig M, Leigh G, Spivak K, Lei H. Superior outcome of females over males after brief treatment for the reduction of heavy drinking. *Br J Addict*. 1989; 84:395–404. [PubMed: 2720192]
42. Daepfen JB, Gaume J, Bady P, et al. Brief alcohol intervention and alcohol assessment do not influence alcohol use in injured patients treated in the emergency department: a randomized controlled clinical trial. *Addiction*. 2007; 102:1224–33. [PubMed: 17565563]
43. Voogt CV, Kleinjan M, Poelen EA, Lemmers LA, Engels RC. The effectiveness of a web-based brief alcohol intervention in reducing heavy drinking among adolescents aged 15-20 years with a low educational background: a two-arm parallel group cluster randomized controlled trial. *BMC Public Health*. 2013; 13:694. [PubMed: 23895403]
44. Wilk AI, Jensen NM, Havighurst TC. Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. *J Gen Intern Med*. 1997; 12:274–83. [PubMed: 9159696]
45. Najavits LM, Hien D. Helping vulnerable populations: a comprehensive review of the treatment outcome literature on substance use disorder and PTSD. *J Clin Psychol*. 2013; 69:433–79. [PubMed: 23592045]
46. Edelman EJ, Dinh A, Radulescu R, et al. Combining rapid HIV testing and a brief alcohol intervention in young unhealthy drinkers in the emergency department: a pilot study. *Am J Drug Alcohol Abuse*. 2012; 38:539–43. [PubMed: 22794939]
47. Moyer A, Finney JW, Swearingen CE, Vergun P. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. *Addiction*. 2002; 97:279–92. [PubMed: 11964101]
48. Chang G, McNamara TK, Orav EJ, et al. Brief intervention for prenatal alcohol use: a randomized trial. *Obstet Gynecol*. 2005; 105(5 Pt 1):991–8. [PubMed: 15863535]

49. Trinks A, Festin K, Bendtsen P, Nilsen P. What makes emergency department patients reduce their alcohol consumption? A computer-based intervention study in Sweden. *Int Emerg Nurs*. 2013; 21:3–9. [PubMed: 23273798]
50. Walton MA, Chermack ST, Shope JT, et al. Effects of a brief intervention for reducing violence and alcohol misuse among adolescents: a randomized controlled trial. *JAMA*. 2010; 304:527–35. [PubMed: 20682932]
51. Amaro H, Hardy-Fanta C. Gender relations in addiction and recovery. *J Psychoactive Drugs*. 1995; 27:325–37. [PubMed: 8788689]
52. Beckman LJ, Amaro H. Personal and social difficulties faced by women and men entering alcoholism treatment. *J Stud Alcohol*. 1986; 47:135–45. [PubMed: 3713175]
53. Brady K. Toward optimal health: Kathleen Brady, PhD, MD, discusses challenges of substance abuse in women. Interview by Jodi R. Godfrey. *J Womens Health (Larchmt)*. 2007; 16:163–7. [PubMed: 17388732]
54. Payne RA, Back SE, Wright T, Hartwell K, Brady KT. Alcohol dependence in women: comorbidities can complicate treatment. *Curr Psychiatr*. 2009; 8:52–9. [PubMed: 20676219]
55. Amaro H, Dai J, Arévalo S, et al. Effects of integrated trauma treatment on outcomes in a racially/ethnically diverse sample of women in urban community-based substance abuse treatment. *J Urban Health*. 2007; 84:508–22. [PubMed: 17356904]
56. Substance Abuse and Mental Health Services Administration. [Accessed Sep 20, 2014] Drug Abuse Warning Network (DAWN): Data, Outcomes, and Quality. Available at: <http://www.samhsa.gov/data/DAWN.aspx>
57. Beasley GM, Ostbye T, Muhlbaier LH, et al. Age and gender differences in substance screening may underestimate injury severity: a study of 9793 patients at level 1 trauma center from 2006 to 2010. *J Surg Res*. 2014; 188:190–7. [PubMed: 24370454]
58. Musey PI Jr, Linnstaedt SD, Platts-Mills TF, et al. Gender differences in acute and chronic pain in the emergency department: results of the 2014 Academic Emergency Medicine Consensus Conference pain section. *Acad Emerg Med*. 2014; 21:000–00.
59. Centers for Disease Control and Prevention. Vital Signs: overdoses of prescription opioid pain relievers--United States, 1999-2008. *MMWR Morbid Mortal Wkly Rep*. 2011; 60:1487–92.
60. Centers for Disease Control and Prevention. [Accessed Sep 22, 2014] Vital Signs Prescription Painkiller Overdoses: A Growing Epidemic, Especially Among Women. Available at: <http://www.cdc.gov/vitalsigns/pdf/2013-07-vitalsigns.pdf>
61. Marazziti D, Baroni S, Picchetti M, et al. Pharmacokinetics and pharmacodynamics of psychotropic drugs: effect of sex. *CNS Spectr*. 2013; 18:118–27. [PubMed: 23374978]
62. Nielsen DA, Utrankar A, Reyes JA, Simons DD, Kosten TR. Epigenetics of drug abuse: predisposition or response. *Pharmacogenomics*. 2012; 13:1149–60. [PubMed: 22909205]
63. Amacher DE. Female gender as a susceptibility factor for drug-induced liver injury. *Hum Exp Toxicol*. 2013; 33:928–39. [PubMed: 24299907]
64. Fanoë S, Jensen GB, Sjøgren P, Korsgaard MP, Grønnet M. Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro. *Br J Clin Pharmacol*. 2009; 67:172–9. [PubMed: 19159406]
65. Coker SJ. Drugs for men and women - how important is gender as a risk factor for TdP? *Pharmacol Ther*. 2008; 119:186–94. [PubMed: 18472167]
66. Becker JB, Hu M. Sex differences in drug abuse. *Front Neuroendocrinol*. 2008; 29:36–47. [PubMed: 17904621]
67. Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. *Psychiatr Clin North Am*. 2010; 33:339–55. [PubMed: 20385341]
68. Roth ME, Cosgrove KP, Carroll ME. Sex differences in the vulnerability to drug abuse: a review of preclinical studies. *Neurosci Biobehav Rev*. 2004; 28:533–46. [PubMed: 15527861]
69. Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP. Sex and estrogen influence drug abuse. *Trends Pharmacol Sci*. 2004; 25:273–9. [PubMed: 15120494]
70. Anker JJ, Carroll ME. The role of progestins in the behavioral effects of cocaine and other drugs of abuse: human and animal research. *Neurosci Biobehav Rev*. 2010; 35:315–33. [PubMed: 20398693]

71. Bernstein E, Bernstein JA, Stein JB, Saitz R. SBIRT in emergency care settings: are we ready to take it to scale? *Acad Emerg Med.* 2009; 16:1072–7. [PubMed: 20053225]
72. Tait RJ, Hulse GK, Robertson SI, Sprivilis PC. Emergency department-based intervention with adolescent substance users: 12-month outcomes. *Drug Alcohol Depend.* 2005; 79:359–63. [PubMed: 16102378]
73. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug Alcohol Depend.* 2005; 77:49–59. [PubMed: 15607841]
74. Greenfield SF, Rosa C, Putnins SI, et al. Gender research in the National Institute on Drug Abuse National Treatment Clinical Trials Network: a summary of findings. *Am J Drug Alcohol Abuse.* 2011; 37:301–12. [PubMed: 21854272]
75. Smith PM. Tobacco use among emergency department patients. *Int J Environ Res Public Health.* 2011; 8:253–63. [PubMed: 21318027]
76. Boudreaux ED, Baumann BM, Friedman K, Ziedonis DM. Smoking stage of change and interest in an emergency department-based intervention. *Acad Emerg Med.* 2005; 12:211–8. [PubMed: 15741583]
77. Lowenstein SR, Tomlinson D, Koziol-McLain J, Prochazka A. Smoking habits of emergency department patients: an opportunity for disease prevention. *Acad Emerg Med.* 1995; 2:165–71. [PubMed: 7497028]
78. Richman PB, Dinowitz S, Nashed A, Eskin B, Cody R. Prevalence of smokers and nicotine-addicted patients in a suburban emergency department. *Acad Emerg Med.* 1999; 6:807–10. [PubMed: 10463552]
79. Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. *J Consult Clin Psychol.* 1999; 67:555–62. [PubMed: 10450626]
80. Steinberg MB, Akincigil A, Delnevo CD, Crystal S, Carson JL. Gender and age disparities for smoking-cessation treatment. *Am J Prev Med.* 2006; 30:405–12. [PubMed: 16627128]
81. Perkins KA, Scott J. Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine Tob Res.* 2008; 10:1245–50. [PubMed: 18629735]
82. Cepeda-Benito A, Reynoso JT, Erath S. Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: differences between men and women. *J Consult Clin Psychol.* 2004; 72:712–22. [PubMed: 15301656]
83. Anthenelli RM, Blom TJ, McElroy SL, Keck PE. Preliminary evidence for gender-specific effects of topiramate as a potential aid to smoking cessation. *Addiction.* 2008; 103:687–94. [PubMed: 18339115]
84. Cunningham RM, Bernstein SL, Walton M, et al. Alcohol, tobacco, and other drugs: future directions for screening and intervention in the emergency department. *Acad Emerg Med.* 2009; 16:1078–88. [PubMed: 20053226]
85. Bernstein SL, Boudreaux ED, Cydulka RK, et al. Tobacco control interventions in the emergency department: a joint statement of emergency medicine organizations. *Ann Emerg Med.* 2006; 48:e417–26. [PubMed: 16997678]
86. Bernstein SL, D'Onofrio G. The clinical impact of health behaviors on emergency department visits. *Acad Emerg Med.* 2009; 16:1054–9. [PubMed: 20053222]
87. Reid RD, Pipe AL, Riley DL, Sorensen M. Sex differences in attitudes and experiences concerning smoking and cessation: results from an international survey. *Patient Educ Couns.* 2009; 76:99–105. [PubMed: 19070455]
88. McKee SA, O'Malley SS, Salovey P, Krishnan-Sarin S, Mazure CM. Perceived risks and benefits of smoking cessation: gender-specific predictors of motivation and treatment outcome. *Addict Behav.* 2005; 30:423–35. [PubMed: 15718060]
89. Guo SE, Ratner PA, Okoli CT, Johnson JL. The gender-specific association between asthma and the need to smoke tobacco. *Heart Lung.* 2014; 43:77–83. [PubMed: 24238774]
90. McKee SA, Maciejewski PK, Falba T, Mazure CM. Sex differences in the effects of stressful life events on changes in smoking status. *Addiction.* 2003; 98:847–55. [PubMed: 12780373]