

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

Esther K. Choo MD, MPH

Gillian A. Beauchamp MD
Lehigh Valley Health Network, gillian.beauchamp@lvhn.org

Francesca L. Beaudoin MD, MS

Edward Bernstein MD

Judith Bernstein
RNC, PhD

See next page for additional authors

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Authors

Esther K. Choo MD, MPH; Gillian A. Beauchamp MD; Francesca L. Beaudoin MD, MS; Edward Bernstein MD; Judith Bernstein; Steven L. Bernstein MD; Kerryann B. Broderick MD; Robert D. Cannon DO; Gail D'Onofrio MD, MS; Marna R. Greenberg DO, MPH, FACEP; Kathryn Hawk MD; Rashelle B. Hayes PhD; Gabrielle A. Jacquet MD, MPH; Melanie J. Lippmann MD; Karin V. Rhodes MD, MS; Susan H. Watts PhD; and Edwin D. Boudreaux PhD



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

Esther K. Choo, MD, MPH, Gillian Beauchamp, MD, Francesca L. Beaudoin, MD, MS, Edward Bernstein, MD, Judith Bernstein, RNC, PhD, Steven L. Bernstein, MD, Kerryann B. Broderick, MD, Robert D. Cannon, DO, Gail D'Onofrio, MD, MS, Marna Rayl Greenberg, DO, MPH, Kathryn Hawk, MD, Rashelle B. Hayes, PhD, Gabrielle A. Jacquet, MD, MPH, Melanie J. Lippmann, MD, Karin V. Rhodes, MD, MPH, Susan Watts, PhD, and Edwin D. Boudreaux, PhD

Department of Emergency Medicine, Warren Alpert Medical School of Brown University (EKC, FLB, MJL), Providence, RI; the Department of Emergency Medicine, Oregon Health & Sciences University (GB), Portland, OR; the Department of Emergency Medicine, Boston University School of Medicine (EB, GAJ), Boston, MA; the Department of Emergency Medicine, Yale School of Medicine (SLB, GD, KH), New Haven, CT; the Department of Emergency Medicine, Denver Health, University of Colorado School of Medicine (KBB), Denver, CO; the Department of Emergency Medicine, Lehigh Valley Hospital, University of South Florida Morsani College of Medicine (MRG), Allentown, PA; the Department of Emergency Medicine, University of Pennsylvania School of Medicine (KVR), Philadelphia, PA; the Department of Emergency Medicine, Texas Tech University Health Sciences Center (SW), El Paso, TX; the Department of Emergency Medicine, University of Massachusetts Medical School (EDB), Worcester, MA; the Department of Community Health Sciences, Boston University School of Public Health (JB), Boston, MA; and the Department of Medicine, University of Massachusetts Medical School (RBH), Worcester, MA

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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Address for correspondence and reprints: Esther K. Choo, MD, MPH, esther_choo@brown.edu.

Substance abuse breakout group participants: Fuad Abujarad, Gavin Barr, Helen Barr (FDA), Gillian Beauchamp, Francesca Beaudoin, Steven L. Bernstein, Edwin D. Boudreaux, Kerry Broderick, Robert Cannon, Esther Choo, Gail D'Onofrio, Fiona Gallahue, Marna Greenberg, Kathryn Hawk, Gabrielle Jacquet, Bryan Kane, Anita Kurt, Judy Linden, Melanie Lippmann, Natalie Locci, Elizabeth Nestor, Jonathan Purtle, Megan Ranney, Karin Rhodes, Tyler Robin, Shaheen Shamji, Danica Stone, Susan Watts, Kevin Weaver, and Jessica Weiland.

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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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