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Intersection of Stress and Gender in Association With Transitions in Past Year DSM-5 Substance Use Disorder Diagnoses in the United States

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Abstract

Background: Stress contributes to the development and maintenance of substance use disorders, with some research suggesting that the impact of stress on substance use disorders is greater in women. However, this has yet to be evaluated in a national dataset, across major substances of abuse.

Methods: Using data from the newly available U.S. National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Wave 3; $n = 36{,}309$), we evaluated relationships among past year stressful life events (0 or 1 vs. 2+ events, range 0–16) and gender, and their association with transitions (new vs. absent cases; ongoing vs. remitted cases) in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition alcohol use disorder, tobacco use disorder, cannabis use disorder, and nonmedical prescription opioid use disorder diagnoses.

Results: Having two or more stressful life events in the past year increased the odds of having a new alcohol use disorder, tobacco use disorder, cannabis use disorder, and opioid use disorder (OR = 3.14, 2.15, 5.52, and 3.06, respectively) or ongoing alcohol use disorder, tobacco use disorder, and cannabis use disorder (OR = 2.39, 2.62, and 2.95, respectively) compared to zero or one stressful life event. A stress by gender interaction for new vs. absent alcohol use disorder demonstrated that having two or more stressful life events was associated with increased odds of new alcohol use disorder in men (OR = 2.51) and even greater odds of new alcohol use disorder in women (OR = 3.94).

Conclusions: Results highlight that stress is a robust factor in both men and women with new or ongoing substance use disorders, and that effective treatments for substance use should consider the role of stress in addiction etiology and maintenance. There was little evidence for gender differences in the role of stress on transitions in substance use disorders, except for the onset of alcohol use disorders. Given that rates of alcohol use disorders are increasing in women, the impact of stress needs to be considered.

Keywords

substance use disorders, alcohol, tobacco, cannabis, opioid, stress, gender

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Introduction

Substance use disorders (SUDs) are highly prevalent in the United States, contributing to the global burden of disease and increases in morbidity and mortality.[1,2] Twelve-month and lifetime prevalence of Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) alcohol use disorder (AUD) are 13.9% and 29.1%,[3] respectively. Twelve-month and

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lifetime prevalence of DSM-5 tobacco use disorder (TUD) and cannabis use disorder (CUD) are 20.0% and 27.9%[4] and 2.5% and 6.3%,[5] respectively. Twelve-month and lifetime prevalence of DSM-5 non-medical prescription opioid use disorder (OUD) are 0.9% and 2.1%,[6] respectively. With a large proportion of individuals never receiving addiction-specific treatment and with treatments that are only modestly efficacious,[7–11] it is of the utmost importance to understand the factors contributing to substance use development and maintenance, across all major classes of substances, in order to identify novel mechanisms and treatment approaches that facilitate better clinical outcomes in individuals with SUD.

One of the principal mechanisms associated with the maintenance of and relapse to substance use is stress. Preclinical models demonstrate that acute and chronic exposure to stress increases the initiation, escalation, and reinstatement of drug-seeking and self-administration behavior.[12,13] This has been found in animal models using neonatal stress, social defeat stress, social isolation, footshock, pharmacologic stress, restraint stress, and novelty stress, as well as in animals with varying genetic backgrounds (e.g., the alcohol-preferring (P) rat).[12] In humans, laboratory studies demonstrate that stress increases drug craving, decreases the ability to resist drug use, and increases self-administration behavior.[12,14,15] In alcohol-dependent individuals, stress exposure has been found to induce an enhanced and persistent alcohol craving state and increased anxiety and negative emotions.[16,17] Likewise, smokers (35%–100%) often cite stress as a major factor contributing to relapse episodes,[18,19] and individuals report heightened tobacco craving, smoke more intensely, and report greater satisfaction and reward from smoking following stress exposure in the human laboratory.[14] Similar human laboratory studies have examined the effects of stress on cannabis and opioid craving and self-administration behavior, finding that cannabis is often used to cope with stress and negative life events[20] and that stress exposure increases opioid craving in opioid-dependent individuals.[21] It should not be surprising then that AUD/SUD and posttraumatic stress disorder (PTSD) are highly comorbid, and individuals with this comorbidity often have worse outcomes related to social and psychological problems and poorer treatment responses.[22]

Recent research has highlighted the importance of examining gender differences in substance use and associated gender-sensitive mechanisms. Epidemiologic findings suggest that SUD is more prevalent in men compared to women,[3,23,24] with women being less likely than men to develop an initial or persistent SUD.[25] However, recent findings suggest that the prevalence of drinking has increased in women over the past decade, including drinking volume and frequency.[26] Further, women may be more likely to use substances to manage stress and negative affective states compared to men. Women with AUD often report heightened anxiety, are more likely to experience an anxiety disorder,[27] and are more likely to ascribe their drinking behavior to a stressor compared to men.[28] Women are also more likely to report smoking to reduce negative affect and to improve mood compared to men.[29–31] Human laboratory studies demonstrate that following negative mood induction, women have shorter latencies to smoking than men.[32] Other studies show that opioid-dependent women are 2 to 3 times more likely to have a mood and anxiety disorder compared to men.[33] While it is relatively unknown whether stress differentially affects the development vs. maintenance of SUD in women vs. men, one study demonstrated that the onset of affective or anxiety disorders preceded the onset of SUD more often in women compared to men,[34] suggesting that anxiety and/or stress may be an important factor contributing to the development of SUD, particularly in women. Indeed, women also have higher rates of PTSD than men.[35]

The aim of this study was to examine the intersection of stress and gender in association with *transitions* in DSM-5 SUD diagnoses (AUD, TUD, CUD, and OUD), across all major classes of substances, using newly available data from a nationally representative sample of adults living in the United States (National Epidemiologic Survey on Alcohol and Related Conditions (NESARC); Wave 3). We first examined whether stressful life events in the past 12 months and gender were related to (1) new vs. absent cases of AUD, TUD, CUD, and OUD in the past 12 months and (2) ongoing vs. remitted cases of AUD, TUD, CUD, and OUD in the past 12 months. We then examined two-way interactions in relation to AUD, TUD, CUD, and OUD diagnoses (new vs. absent; ongoing vs. remitted) between stressful life events and gender. We predicted that individuals who experienced stressful life events in the past 12 months would be more likely to also have new or ongoing SUD in the past 12 months, and that this effect would be stronger for women compared to men. It is important to note that, due to the cross-sectional nature of the NESARC, causal or temporal relationships between stressful life events and transitions in SUD diagnoses cannot be addressed in the present investigation.

Methods

Data Source

Data for this study were drawn from the cross-sectional NESARC study (Wave 3, 2012–2013) carried out by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The sample consisted of 36,309

noninstitutionalized men and women aged 18 years and older living in the United States. Informed consent was obtained for all participants, and all individuals who agreed to participate completed an in-person computer-assisted interview consisting of the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5), a reliable and valid measure of DSM-5 Alcohol Use Disorder, nicotine use disorder, and other specific drug use disorders.[36] Hispanic, African American, and Asian respondents were oversampled. Data were adjusted for oversampling and nonresponse and then weighted to represent the U.S. civilian population. Methodology used in the Wave 3 NESARC survey is detailed elsewhere.[3,36]

Stressful Life Events

The Wave 3 of the NESARC survey included questions regarding the presence of 16 stressful events occurring in the last 12 months prior to the Wave 3 interview. Items assessed whether participants experienced stress related to moving, job loss or instability, loss of relationships (divorce and death), interpersonal conflict, financial difficulties, legal difficulties, or being a victim of a crime (e.g., *During the last 12 months, did you move or have anyone new come to live with you?; During the last 12 months, were you fired or laid off from a job?; During the last 12 months, have you been homeless?*). The total number of stressful life events was calculated based on answers to the 16 stressful event questions (see Table 1 for the full list of questions included in the NESARC survey to assess the presence of stressful life events). Given that the distribution of stressful life events was positively skewed, we used a median split to create two groups (zero or one event vs. two or more events). Prior work assessing stressful life events has utilized a median split to characterize stressful life events with this scale.[37–39]

Table 1. Full list of the 16 questions included in the NESARC survey to assess the presence of past year stressful life events.

During the last 12 months...
1. Did you move or have anyone new come to live with you?
2. Were you fired or laid off from a job?
3. Were you unemployed and looking for a job for more than a month?
4. Have you had trouble with your boss or a coworker?
5. Did you change jobs, job responsibilities or work hours?
6. Did you get separated or divorced or break off a steady relationship?
7. Have you had serious problems with a neighbor, friend or relative?
8. Have you declared bankruptcy?
9. Did you have serious trouble with the police or the law?
10. Was something stolen from you, including things that you carry like a wallet, or something inside or outside your home?
11. Has anyone intentionally damaged or destroyed property owned by you or someone else in your house?
12. Did any of your family members or close friends die?
13. Were any of your family members or close friends physically assaulted, attacked or mugged?
14. Did any of your family members or close friends have serious trouble with the police or the law?
15. Have you at any time been homeless?
16. Have you had so much debt that you had no idea how you were going to repay it?

Substance Use Disorders

Wave 3 of the NESARC used DSM-5 criteria to determine diagnostic status.[40] We coded the NESARC data into the following categories for past year (12 months) DSM-5 AUD, TUD, CUD, and OUD diagnoses. *Absent:* no diagnosis in the past year and no diagnosis prior to the past year. *New:* diagnosis in the past year but no diagnosis prior to the past year. *Remit:* no diagnosis in the past year but diagnosis prior to the past year. *Ongoing:* diagnosis in the past year and diagnosis prior to the past year.

Analysis

Data were analyzed using PROC SURVEYLOGISTIC in SAS, version 9.4 (SAS v9.4, SAS Institute Inc., Cary, NC). This procedure allowed for incorporating the stratification, clustering (i.e., primary sampling unit), and unequal weighting of the sampling design. Binary logistic regression analysis was used to examine associations between stressful life events (zero or one event vs. two or more events) and gender with transitions in DSM-5 SUD diagnoses (AUD, TUD, CUD, and OUD; new vs. absent and ongoing vs. remitted). Relationships between stressful life events and gender were assessed in terms of odds ratios and were considered significant at $p < 0.001$. The effects of each variable of interest on any given outcome were interpreted relative to our chosen reference outcome (i.e., zero or one stressful life event, male). Two-way interactions between stressful life events and gender for new vs. absent SUD diagnoses and ongoing vs. remitted SUD diagnoses were performed to investigate whether stress and gender were associated with transitions in DSM-5 SUD diagnoses. Age, race, income, and education were evaluated as potential covariates and were removed from the final models if there was no impact on the pattern of results.

Because the presence of some past year stressful life events overlaps with DSM-5 criteria for SUD, we removed five overlapping stress items from an exploratory analysis (see Table 1: Items 2, 3, 4, 6, and 7). In this exploratory binary logistic regression analysis, we reanalyzed the data with and without these five items added as covariates. Additionally, we explored associations

between specific types of stressful life events, gender, and transitions in past year DSM-5 SUD diagnoses. We collapsed the 16 stressful life events into four categories of stressors: interpersonal problems or loss, job problems or loss, financial problems, and legal- or crime-related stress. These exploratory binary logistic regression analyses included gender as a categorical variable (female vs. male) and each stress category as a categorical variable (zero or one event vs. two or more events) to be consistent with the primary analysis. Both exploratory analyses did not differentially change the pattern of overall results for new vs. absent or ongoing vs. remitted SUD diagnoses or by specific stressor type. However, it should be noted that the financial problems stress category contained only two events so we were unable to evaluate the effect of financial stress on associations with transitions in SUD diagnoses.

Results

Sample characteristics by gender are summarized in Table 2. All chi-square analyses that were performed to examine gender differences in sample characteristics were significant at $p < 0.0001$, except for age ($p = 0.07$), DSM-5 OUD ($p = 0.10$), and stress ($p = 0.65$). New, remitted, and ongoing cases of AUD, TUD, and CUD were each more prevalent in men compared to women. Women were more likely to report having an absent AUD, TUD, and CUD.

New vs. Absent DSM-5 SUD Diagnoses

New cases of SUD were significantly associated with stress and gender (see Table 3). Having two or more stressful life events was associated with greater odds of new AUD, TUD, CUD, and OUD compared to zero or one stressful life event. Females were less likely to have a new AUD, TUD, and CUD compared to males. New AUD demonstrated a significant stress by gender two-way interaction. Males with two or more stressful life events vs. zero or one event had increased odds of new AUD (OR = 2.51, 95% confidence interval (CI) = 2.16, 2.93), while females with two or more stressful life events compared to zero or one event had the greatest odds of new AUD (OR = 3.94, 95% CI = 3.41, 4.54).

Ongoing vs. Remitted DSM-5 SUD Diagnoses

Ongoing cases of SUD were significantly associated with stress and gender (see Table 4). Two or more stressful life events were associated with greater odds of ongoing AUD, TUD, and CUD compared to zero or one stressful life event. Females were less likely to have an ongoing AUD compared to males. Interactions between stress and gender were not significant for ongoing vs. remitted AUD, TUD, CUD, or OUD.

To further evaluate the association of stressful life events and gender with the odds of new vs. absent or ongoing vs. remitted SUDs, we reran analyses using log-transformed stressful life events as a continuous variable and demonstrated similar findings (data not shown).

Discussion

Results from the present investigation provide strong support for the relationship between past year stress and transitions in past year SUD diagnoses, across all major classes of substances. In a nationally representative sample of adults in the United States, we demonstrate that adults with two or more stressful life events were 2 to 5 times more likely to have a new onset alcohol, tobacco, cannabis, or opioid use disorder compared to those with zero or one stressful life event. Similarly, adults with two or more stressful life events were 2 to 3 times less likely to have a remitted alcohol, tobacco, or cannabis use disorder compared to those with zero or one stressful life event. These epidemiological findings identify that stress, experienced as life event stress, is a critical factor associated with substance abuse onset and persistence.[12,14,15,41] Notably, stress played an important role in SUD transitions similarly for both men and women, with the exception of AUD. Men with two or more stressful life events were 2.5 times more likely to have a new AUD compared to men with zero or one event, whereas women with two or more stressful life events were 4 times more likely to have a new onset AUD compared to women with zero or one event. While life event stress is strongly associated with the transition from absent to new AUD diagnoses in both men and women, the association is particularly robust in women. Given that rates of AUDs have increased in women in the past decade,[26] it is especially important to consider the role of stress in substance use in this population.

It is important to note that given the cross-sectional design of the NESARC (Wave 3), it is unclear whether SUD transitions preceded life event stress or vice versa. However, this general pattern of findings is consistent with established literature demonstrating that stress plays an important role in the initiation and maintenance of substance use in both men and women.[12,41] Previous reviews hypothesized that women may be more likely than men to use substances to regulate stress and negative affect.[42,43] The finding that women with two or more life event stressors were at the greatest odds of having a new onset AUD is in agreement with this hypothesis and other work suggesting that women are more likely than men to attribute their drinking to stress.[28] However, the overall pattern of findings suggests few gender differences when considering the impact of life event stress increasing the likelihood of substance use onset and persistence.

Table 2. Sample characteristics by gender (NESARC, Wave 3; $n = 36{,}309$).

	Men	Women	χ^2	p
Age (%)			5.45	0.07
18–29	22.9	21.9		
30–44	27.5	28.2		
45+	49.5	49.9		
Race/Ethnicity (%)			47.08	<0.0001
Caucasian	53.9	52		
African American	19.9	22.6		
Native American	1.3	1.5		
Asian	5.4	4.6		
Hispanic	19.5	19.3		
Household income (%)			304.42	<0.0001
$9,999 or less	8.7	10.9		
$10,000–$24,999	22.2	27.8		
$25,000–$49,999	27.7	27.7		
Over $50,000	41.4	33.6		
Education (%)			28.09	<0.0001
Less than high school	15.5	14.8		
Completed high school	28.2	26.1		
Some college or higher	56.4	59.1		
DSM-5 alcohol use disorder (%)[a]			838.21	<0.0001
Absent	64.8	78.4		
New	8	4.6		
Remit	16.5	11		
Ongoing	10.6	6		
DSM-5 tobacco use disorder (%)[a]			355.08	<0.0001
Absent	68.3	76.9		
New	9.7	6.3		
Remit	7.7	5.9		
Ongoing	14.3	10.8		
DSM-5 cannabis use disorder (%)[a]			294.19	<0.0001
Absent	91.4	95.7		
New	2.1	0.8		
Remit	4.7	2.6		
Ongoing	1.8	0.9		
DSM-5 opioid use disorder (%)[a]			6.3	0.10
Absent	97.9	98.2		
New	0.6	0.5		
Remit	1.1	0.9		
Ongoing	0.4	0.4		
Stress (%)			0.21	0.65
0 or 1 stressful event	57.8	58.1		
2 or more stressful events	42.2	41.9		

Note: DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.

[a]Past 12 months; *Absent*, no diagnosis in the past 12 months and no diagnosis prior to the past 12 months; *New*, diagnosis in the past 12 months but no diagnosis prior to the past 12 months; *Remit*, no diagnosis in the past 12 months but diagnosis prior to the past 12 months; and *Ongoing*, diagnosis in the past 12 months and diagnosis prior to the past 12 months.

Table 3. Associations of two or more stressful life events and gender with transitions in *new vs. absent* DSM-5 SUD diagnoses.

	Main effects				Two-way interaction
	Stress (2+ events vs. 0 or 1 event)		Gender (female vs. male)		Stress by gender
	OR (95% CI)	Wald χ^2	OR (95% CI)	Wald χ^2	Wald χ^2
Alcohol use disorder	3.14 (2.82, 3.50)	430.7[a]	0.47 (0.42, 0.53)	170.28[a]	19.03[a,b] [b]Males (2+ vs. 0 or 1 event): OR (95% CI) = 2.51 (2.16, 2.93) [b]Females (2+ vs. 0 or 1 event): OR (95% CI)=3.94 (3.41, 4.54)
Tobacco use disorder	2.15 (1.96, 2.35)	268.00[a]	0.59 (0.55, 0.64)	167.9[a]	ns
Cannabis use disorder	5.52 (4.31, 7.08)	181.59[a]	0.37 (0.28, 0.50)	46.18[a]	ns
Opioid use disorder	3.06 (2.10, 4.47)	33.71[a]		ns	ns

Note: DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; SUD: substance use disorder; OR: odds ratio; CI: confidence interval; ns: nonsignificant.
[a]All Walds significant at $p < 0.0001$ unless specified with ns.

Table 4. Associations of two or more stressful life events and gender with transitions in *ongoing vs. remitted* DSM-5 SUD diagnoses.

	Main effects				Two-way interaction
	Stress (2+ events vs. 0 or 1 event)		Gender (female vs. male)		Stress by gender
	OR (95% CI)	Wald χ^2	OR (95% CI)	Wald χ^2	Wald χ^2
Alcohol use disorder	2.39 (2.14, 2.68)	231.22[a]	0.80 (0.71, 0.90)	13.13[a]	ns
Tobacco use disorder	2.62 (2.31, 2.97)	228.02[a]		ns	ns
Cannabis use disorder	2.95 (2.18, 4.01)	48.48[a]		ns	ns
Opioid use disorder		ns		ns	ns

Note: DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; SUD: substance use disorder; OR: odds ratio; CI: confidence interval; ns: nonsignificant.
[a]All Walds significant at $p < 0.001$ unless specified with ns.

Of particular interest, gender differences in the association of stressful life events and substance use may be related to how stress is characterized. Our results demonstrate that past year stressful life events (e.g., combined interpersonal, job, financial, and legal stressors) increased the odds of new alcohol, tobacco, cannabis, and opioid use disorders for both men and women. However, prior research from our group has demonstrated that women with a history of childhood maltreatment are more vulnerable to escalated time from first use of alcohol to alcohol dependence.[44] Similarly, past year stressful life events were more strongly associated with a decreased likelihood of smoking cessation in women with a history of childhood adversity compared to men.[45] Further, women were more likely to maintain smoking or relapse to smoking in response to a financial stressor compared to men.[46] In the current study, exploratory analyses collapsing total past year stressful life events into four stress categories (interpersonal problems or loss, job problems or loss, financial problems, and legal- or crime-related stress) did not demonstrate a differential pattern of results from our initial analysis. However, the financial problems category contained only two stress items so we lost the ability to detect an association between financial stress and transitions in past year SUD diagnoses. Thus, depending on the characterization and timing of stress, women and men may be differentially vulnerable to the development or maintenance of substance use, and this is important to consider in future studies.

Because stress is robustly associated with new onset and persistent SUDs across all major substances, understanding the behavioral and neurochemical mechanisms underlying stress-precipitated substance use is critical. Specifically, pharmacologic interventions targeting the brain stress systems or behavioral interventions that focus on managing or reducing stress (e.g., mindfulness training) may be of therapeutic benefit for substance use. Indeed, pharmacotherapies targeting the corticotrophin-

releasing factor and norepinephrine stress systems already show promise in reducing stress-precipitated nicotine or smoking and drinking behavior in preclinical and human laboratory studies.[47–53] Similarly, mindfulness-based stress reduction and mindfulness-based relapse prevention have shown promise for alcohol use, smoking cessation, and other SUDs.[54–57]

Finally, in the present investigation, women were less likely overall to have a new onset alcohol, tobacco, or cannabis use disorder or an ongoing AUD compared to men. This result is largely consistent with literature demonstrating that males have a higher prevalence of SUDs compared to females,[3–6,24] and that men are generally more likely to have a drug use disorder overall.[23] Further, women may be less likely than men to develop an initial or persistent SUD,[25,58] consistent with the present findings. It is only in women with two or more stressful life events that the odds of new onset AUD increase by 4 times that of women with zero or one stressful life event, further identifying the importance of stress in the initiation of problematic alcohol use.

Limitations

First, stressful life events were only assessed in the 12 months prior to the NESARC Wave 3 interview and do not account for stressful life events outside of this period. Thus, the present investigation cannot address the causal or temporal relationship between stressful life events and SUDs examined in this study. It is possible that having a SUD may also increase the odds of higher life event stress. Prospectively designed studies will be an important next step in determining the directionality of the relationship between stress and SUD diagnoses. Relatedly, the assessment of stressful life events relied on retrospective recall by participants and the NESARC survey did not account for the severity of each stressful life event. It is possible that severity ratings may inform whether severe stressors were more strongly associated with AUD, TUD, CUD, or OUD than mild stressors. Similarly, many types of stressful life events were not addressed in the NESARC survey. Individuals may have been misclassified into having had no stressful life events when it is plausible that they could have experienced a stressor(s) not addressed in the NESARC survey. Finally, some stressful life events addressed in the NESARC survey directly overlap with DSM-5 criteria for SUDs. Thus, the data are not entirely independent. However, exploratory analyses removing the five stressful life event items that overlap with DSM-5 criteria did not substantively change the pattern of results.

Conclusions

Results suggest that stress is robustly associated with new and ongoing SUDs for both women and men, across all major classes of substances. The interaction between stressful life events and gender for new vs. absent DSM-5 AUD diagnoses newly identifies that women with two or more stressful life events compared to zero or one event were 4 times more likely to have a new AUD, while men with two or more stressful life events compared to zero or one event were 2.5 times more likely to have a new AUD. While epidemiologic findings from the present investigation do not imply causal or temporal relationships, the results are consistent with work indicating that stress plays a robust role in the development and maintenance of SUDs, and that both women and men may use substances to regulate stress. Importantly, this study highlights that effective interventions for substance use should consider the role of stress in individuals with new or ongoing SUD diagnoses, across all major substances.

Declaration of Conflicting Interests

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