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Anxiety disorders and drug dependence: Evidence on sequence and specificity among adults

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Abstract

AIM—The goal of this study was to investigate the relationship between specific anxiety disorders and substance dependence, adjusting for potentially confounding demographic factors (e.g., gender) and comorbidity (e.g., alcohol dependence, major depression), among adults in the United States.

METHODS—Data were drawn from the National Comorbidity Survey (NCS), a nationally representative population sample of the US adult population aged 15–54. The temporal sequence of onset of anxiety and substance dependence disorders was examined.

RESULTS—Substance dependence temporally precedes several anxiety disorders, particularly panic disorder. Specifically, a history of past substance dependence predicts current panic disorder (OR=2.62, 95% CI=1.29, 5.32), social phobia (OR=1.7, 95% CI=1.12, 2.41), and agoraphobia (OR=1.78, 95% CI=1.08, 2.94). Conversely, in more than 50% of substance abuse disorder (SAD) cases, in nearly 40% of post-traumatic stress disorder (PTSD) cases, and in nearly 30% of generalized anxiety disorder (GAD) cases, the anxiety disorder has first onset. Similarly, a lifetime history of social phobia, PTSD, or GAD significantly predicts lifetime substance dependence (OR=1.51 for social phobia, 2.06 for PTSD, 1.45 for GAD).

CONCLUSION—For any particular anxiety disorder, a diagnosis of substance abuse can occur prior to or subsequent to an anxiety disorder. Nevertheless, there is also evidence for the specificity of some associations between anxiety and substance dependence disorders; these are independent of the effects of gender and other comorbid disorders, may be causal in nature, and deserve particular attention in clinical settings. The possibility that within a particular anxiety disorder there are a variety of mechanisms of association with various substances should be addressed in future work.

Keywords

anxiety disorders; comorbidity; depression; epidemiology; substance-related disorders

INTRODUCTION

Substance dependence is a tremendous global public health problem.^{1–4} Substance dependence is associated with occupational disability, increased risk of depressive and

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psychotic disorders, social impairment, incarceration, and physical health problems.⁵⁻⁷ The causes of drug abuse and dependence are not known, though previous data suggest that risk factors may be identifiable relatively early in life, even prior to the initiation of use and abuse.

Previous research has focused on examining the relationship between depressive symptoms, antisocial, oppositional, and disruptive behavior disorders, which are thought to precede and predict onset of substance dependence.⁸⁻¹¹ Other factors such as familial history of mood, alcohol, and drug use disorders are also thought to contribute to the risk of substance use,¹²⁻¹⁵ as do childhood abuse and deviant peer affiliations.^{16, 17} For instance, longitudinal research has shown that deviant peer affiliations are related to persistence and course of cannabis use across the lifespan.¹⁸ Also, Merikangas (1998) has demonstrated links between familial mood disorders and substance dependence.¹⁹ The determining factors that govern the shift from vulnerability to onset of substance dependence remain unknown and there are recent data suggesting an interaction between genetic and environmental influences in comorbid substance use and mood disorders.²⁰

Cross-sectional studies of adults show strong links between anxiety disorders and substance use disorders.^{21, 22} Longitudinal studies have also shown associations between anxiety disorders early in life and the subsequent onset of substance use disorders, such as cigarette smoking.^{23, 24} While results of previous studies consistently show links between anxiety disorders and substance dependence, several questions about the association between anxiety disorders and the onset of substance dependence remain. First, it is not clear whether the association between anxiety disorders and substance dependence applies to any anxiety disorder, or whether it is specific only to some anxiety disorders. Second, it is not known whether the relationship between anxiety disorders and substance dependence persists independent of the effects of comorbid depression and alcohol use disorders. Third, it has not been investigated whether the onset of anxiety disorders tend to precede the onset of substance dependence, whether substance dependence occurs prior to the onset of anxiety disorders in the general population.

Against this background, the goal of the current investigation is to examine the relationship between anxiety disorders and substance dependence among adults in the community. First, the study will determine the cross-sectional association between anxiety disorders and substance dependence (current and lifetime) among adults in the community. Second, the study will examine the relationship between specific anxiety disorders and the odds of substance dependence, adjusting for the effects of depression and alcohol dependence. Third, the study will examine the relationship between a history of anxiety disorders (which are not current) and the odds of current substance dependence in order to identify patterns of the temporal sequence of onset of anxiety disorders and substance dependence. We hypothesized that anxiety disorders would be associated with increased likelihood of substance dependence, independent of the effects of depressive and alcohol use disorders. In addition, we anticipated that the onset of anxiety disorders would precede the onset of substance dependence in the majority of cases.

METHODS

Sample

The National Comorbidity Survey is based on a national probability sample (n=5, 788) of individuals age 15 to 54 in the noninstitutionalized United States population.²⁵ Fieldwork was carried out between September 1990 and February 1992. There was an 82.4% response rate. The data were weighted for differential probabilities of selection and non-response. A weight was also used to adjust the sample to approximate the cross-classification of the

population distribution on a range of sociodemographic characteristics. Weighting and a full description of study methodology are described in detail elsewhere.^{26, 25}

Diagnostic Assessment

Psychiatric diagnoses were generated from a modified version of the World Health Organization (WHO) Composite International Diagnostic Interview,²⁷ a structured interview designed for use by trained interviewers who are not clinicians. WHO field trials (WHO 1990) and National Comorbidity Survey clinical reappraisal studies^{28–30} documented acceptable reliability and validity of all the diagnoses. Psychiatric disorders included in the current investigation were DSM-III-R major depression, generalized anxiety disorder (GAD), simple phobia, social phobia, panic attacks, panic disorder, post-traumatic stress disorder (PTSD), alcohol dependence, and substance dependence. Written informed consent was obtained from each participant after the survey had been fully explained.

Analytic strategy

Logistic regression analyses were used to investigate the association between anxiety disorders and substance dependence (past 12-month and lifetime). First, analyses were adjusted for differences in sociodemographic characteristics (age, gender, race, marital status, income, education). Next, sociodemographic characteristics and comorbid alcohol dependence and major depression were included in the model. The same procedure was used to examine the association between history of anxiety disorders (having lifetime anxiety disorders, but not current) and risk of current drug dependence, and between history of drug dependence and risk of current anxiety disorders. Adjusted odds ratios with 95% confidence intervals were computed.

RESULTS

Association between Anxiety Disorders and Substance Dependence

Association between lifetime anxiety disorders and lifetime drug dependence

—Each anxiety disorder was associated with a significantly increased likelihood of drug dependence, which persisted after adjusting for differences in sociodemographic characteristics, alcohol dependence and major depression (see Table 1).

Sequence of onset of drug dependence and anxiety disorders—Onset of substance dependence occurred sequentially prior to the onset of anxiety disorder in a majority of cases among those with panic attacks, agoraphobia, GAD, and PTSD (see Table 2). Among those with specific phobia and drug dependence, there seemed almost an equal distribution of first onset, and social phobia appeared to have onset prior to drug dependence in the majority of cases. In more than 50% of social phobia cases, in nearly 40% of PTSD cases, and in nearly 30% of GAD cases, the onset of the anxiety disorder was first.

Association between history of anxiety disorders and current drug dependence

Past history of each anxiety disorder, with the exception of panic disorder, was associated with a significantly increased likelihood of current drug dependence (see Table 3). After further adjustment for alcohol dependence, only the links with panic attacks and PTSD remained. Although the pattern of results remained the same, with additional adjustment for comorbid major depression, only the link between history of agoraphobia and substance dependence remained statistically significant.

Association between history of drug dependence and current anxiety disorders

History of drug dependence was associated with a significantly increased likelihood of current panic attacks, agoraphobia, panic disorder, and social phobia (see Table 4). These associations persisted after adjusting for demographic characteristics, alcohol dependence and major depression. The association was strongest for panic disorder. History of drug dependence did not appear to be associated with increased likelihood of specific phobia or GAD.

DISCUSSION

The community data here confirm clinical impressions and previous findings that the relationship between anxiety disorders and substance dependence are complex. These results suggest that for any particular anxiety disorder, comorbid substance use disorders may have an earlier onset and possibly contribute to the pathogenesis of anxiety symptoms, or comorbid substance dependence can have a later onset perhaps reflecting the outcome of behaviors associated with an attempt to self-medicate anxiety symptoms. The data here also provide evidence for (1) strong lifetime associations between specific anxiety disorders and substance dependence among adults in the community; (2) associations between specific disorders are independent of the influence of demographic characteristics and comorbid major depression and alcohol dependence; and (3) specificity of associations between particular anxiety disorders and substance dependence disorders.

By controlling for the effects of gender and comorbid disorders we were able to demonstrate that the association between anxiety and substance dependence is not simply a methodological artifact. While there is growing awareness amongst clinicians of obtaining an alcohol history in all patients with anxiety disorders, and of determining a history of mood and anxiety disorders in all patients with alcohol dependence, there is perhaps less focus on other substances in clinical assessment of patients presenting with anxiety disorders. Substance abuse and dependence are stigmatized conditions, and may be underreported especially upon initial presentation as well as being overshadowed by more clinically obvious comorbid mood symptoms. As such, this may contribute to the relative underdiagnosis and undertreatment of anxiety disorders among persons with comorbid substance dependence, despite its prevalence. In fact, reviewing literature on treatment of patients with comorbid anxiety and substance use disorders shows that there is little evidence of treatment for both disorders or observations of comorbidity.

The strongest association between past substance dependence and current anxiety disorder was observed in panic disorder. This finding is consistent with the frequent observation that panic disorder can be precipitated or exacerbated by substance use or withdrawal.^{31–33} It is also consistent with current understandings of the neurobiology of panic attacks. This theory suggests that panic attacks are underpinned by a distributed neurocircuitry involving the amygdala that may be sensitized or activated by a range of different stressors, including changes in either the external or internal milieu.^{34, 35} While data here cannot be used as evidence to confirm this pathway, these results may be useful in pointing to patterns of specificity that may be fruitfully investigated in future, more detailed studies.

Results also showed associations between past substance and other current anxiety disorders, such as social phobia. Withdrawal from regular social activities is commonly seen in subjects who spend significant amounts of their time and effort on drug seeking and drug taking. There may also be more direct relationships between substance abuse and social anxiety; for example, withdrawal of a range of substances leads to decreased levels of striatal D2 receptors, a finding that is also seen in social anxiety disorder patients.^{36, 37} Speculatively, there may be overlaps between the neurobiological sequelae of substance use

or withdrawal, and the neural substrate of social anxiety. In addition, it is conceivable that use of substances may begin as an attempt to self-medicate feelings of isolation and distress related to lack of social relationships associated with social anxiety.^{38, 39} While only a minority of instances of substance use lead to the development of dependence, it has been shown that social phobia is associated with increased risk of development of substance dependence, once substance use is initiated. For instance, one study⁴⁰ showed very high rates of nicotine dependence among those with social phobia who initiated nicotine use (31.5%), compared with rates of nicotine dependence among those without social phobia (15.4%). As such, it may be that exposure to some substances and learning (through exposure) of the anxiety-relieving effects may lead to the onset of substance use among those with social phobia.

Our findings also indicated that anxiety disorders may contribute to the onset of substance dependence. While the cross-sectional nature of these data and lack of more detailed information on factors influencing onset do not permit conclusions based on these data alone, the persistence of these associations after adjusting for differences in comorbid depressive and alcohol use disorders suggest that the link is not purely attributable to comorbidity. This is consistent with a growing range of evidence emphasizing the relatively early onset of anxiety disorders and associated vulnerability to later comorbid disorders. In more than 50% of social phobia cases, in nearly 40% of PTSD cases, and in nearly 30% of GAD cases, anxiety disorders had first onset. Similarly, a lifetime history of social phobia, PTSD, or GAD significantly predicted lifetime substance dependence, an association that was strongest for PTSD. Furthermore, the greater the number of lifetime anxiety disorders, the higher the risk for past and for current substance dependence.

Several limitations of this study should be emphasized. First, as noted above, the cross-sectional nature of the dataset does not allow inferences about the causality or mechanisms of these observed associations. Second, participants were ages 15–54 only, therefore these results are not generalizable to other age groups. Third, we were unable to analyze the data according to different substance use disorders with confidence in which specific substance was used (mainly due to small cell size; e.g., benzodiazepines); future work needs to explore also the specific relationships between specific substance use disorders and the range of anxiety disorders. Replication in a larger national dataset, such as the NESARC, may be informative. Fourth, while these results are generalizable to the US, they may not be relevant to other countries.

Nevertheless, these data are important in providing preliminary evidence on the potential significance in emphasizing specific associations between particular anxiety disorders and substance dependence. These findings have clear clinical implications, including the need to maintain a reasonable level of suspicion for anxiety disorders in patients with substance use disorders, and the need for early detection and robust intervention for anxiety disorders in order to help prevent subsequent morbidity. Further research is needed to investigate the precise mechanisms, which account for the temporal relationships apparent in this dataset, and to extend the work to include the range of specific substance dependence disorders.

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Table 1

Association between lifetime anxiety disorders and drug dependence among adults in the community

	No drug dependence (7469)	Lifetime drug dependence (629)	Model 1 AOR* (95% CI)	Model 2 AOR* (95% CI)	Model 3 AOR* (95% CI)
Lifetime	% (n)	% (n)			
Mood and anxiety disorders					
Panic attacks	6.52% (493)	19.61% (116)	3.86 (2.7, 5.5)	2.73 (1.83, 4.08)	2.21 (1.48, 3.31)
Agoraphobia	6.81% (403)	16.71% (84)	2.8 (2.1, 3.8)	2.35 (1.68, 3.28)	1.98 (1.35, 2.91)
Panic disorder	6.97% (221)	21.25% (53)	4.1 (2.6, 6.4)	3.24 (1.94, 5.42)	2.53 (1.54, 4.17)
Post-traumatic stress disorder	6.40% (469)	20.90% (122)	4.2 (3.2, 5.7)	2.84 (1.9, 4.23)	2.36 (1.52, 3.66)
Specific phobia	6.59% (751)	14.38% (125)	2.6 (2.08, 4.32)	1.81 (1.2, 2.1)	1.49 (.51, 1.73)
Social phobia	6.20% (886)	15.52% (173)	2.7 (2.13, 3.5)	2.06 (1.56, 2.72)	1.8 (1.33, 2.45)
Generalized anxiety disorder	6.78% (336)	20.36% (79)	3.8 (2.8, 5.2)	2.53 (1.83, 3.49)	1.95 (1.4, 2.7)

Bold=p<.05

* AOR = Adjusted odds ratio

Model 1: Adjusted for demographic differences

Model 2: Adjusted for demographic differences and comorbid alcohol dependence

Model 3: Adjusted for demographic differences, comorbid alcohol dependence and major depression

Table 2

Sequence of onset of anxiety disorders and substance dependence among comorbid cases in the community

Anxiety disorder	Substance dependence onset first	Anxiety disorder onset first
Panic attack	61.77%	38.23%
Agoraphobia	67.24%	32.76%
Panic disorder	80.16%	19.84%
Specific phobia	49.24%	50.76%
Social phobia	43.16%	56.84%
Generalized anxiety disorder	71.84%	28.16%
PTSD	61.36%	38.64%

Table 3

Association between history of anxiety disorder and current drug dependence

Lifetime (but not current) anxiety disorders	No drug dependence (7469)		Drug dependence (629)	
	% (n)	Model 1 AOR* (95% CI)	% (n)	Model 2 AOR* (95% CI)
Panic attacks	2.31% (219)	3.4 (1.64, 7.07)	5.32% (37)	2.57 (1.1, 5.98)
Panic disorder	2.60% (90)	2.47 (0.85, 7.22)	4.19% (14)	1.55 (0.46, 5.2)
Agoraphobia	2.59% (182)	3.13 (1.50, 6.53)	8.06% (39)	2.93 (1.32, 6.54)
Specific phobia	2.39% (161)	2.53 (1.06, 6.04)	5.88% (30)	1.79 (0.66, 4.87)
Social phobia	2.23% (349)	2.15 (1.25, 3.69)	4.47% (61)	1.61 (0.88, 2.94)

Bold= $p < .05$

* AOR = Adjusted odds ratio

Model 1: Adjusted for demographic differences

Model 2: Adjusted for demographic differences and comorbid alcohol dependence

Model 3: Adjusted for demographic differences, comorbid alcohol dependence and major depression

Table 4
 Association between history of drug dependence and risk of current anxiety disorders (past 12-months)

History of drug dependence (not current)	Current anxiety disorder					
	Panic attacks	Agoraphobia	Panic disorder	Specific phobia	Social phobia	GAD
	1.79 (1.05, 3.06)	1.78 (1.08, 2.94)	2.62 (1.29, 5.32)	1.24 (0.82, 1.87)	1.7 (1.12, 2.51)	1.19 (0.74, 1.9)

Bold = $p < .05$

* AOR = Adjusted odds ratio; adjusted for differences in demographic characteristics, alcohol dependence and major depression

GAD = Generalized anxiety disorder