

# Role of Self-medication in the Development of Comorbid Anxiety and Substance Use Disorders

## A Longitudinal Investigation

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**Context:** Self-medication of anxiety symptoms with alcohol, other drugs, or both has been a plausible mechanism for the co-occurrence of anxiety disorders and substance use disorders. However, owing to the cross-sectional nature of previous studies, it has remained unknown whether self-medication of anxiety symptoms is a risk factor for the development of incident substance use disorder or is a correlate of substance use.

**Objective:** To examine whether self-medication confers risk of comorbidity.

**Design:** A longitudinal, nationally representative survey was conducted by the National Institute on Alcohol Abuse and Alcoholism. The National Epidemiologic Survey on Alcohol and Related Conditions assessed DSM-IV psychiatric disorders, self-medication, and sociodemographic variables at 2 time points.

**Setting:** The United States.

**Participants:** A total of 34 653 US adults completed both waves of the survey. Wave 1 was conducted in 2001-2002, and wave 2 interviews occurred 3 years later (2004-2005).

**Main Outcome Measures:** Incident substance use disorders in participants with baseline anxiety disorders and incident anxiety disorders in those with baseline substance use disorders.

**Results:** Logistic regression analyses revealed that self-medication conferred a heightened risk of new-onset substance use disorders in those with baseline anxiety disorders (adjusted odds ratios [AORs], 2.50-4.99 [ $P < .01$ ]). Self-medication was associated with an increased risk of social phobia (AOR in baseline alcohol use disorders, 2.13 [ $P = .004$ ]; AOR in baseline drug use disorders, 3.17 [ $P = .001$ ]).

**Conclusions:** Self-medication in anxiety disorders confers substantial risk of incident substance use disorders. Conversely, self-medication in substance use disorders is associated with incident social phobia. These results not only clarify several pathways that may lead to the development of comorbidity but also indicate at-risk populations and suggest potential points of intervention in the treatment of comorbidity.

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**M**ENTAL DISORDER comorbidity is highly prevalent and has been linked to serious negative health consequences.<sup>1-3</sup> The causal pathways to comorbidity, however, are poorly understood and have, thus, been identified as an important focus of research attention.<sup>1</sup> Given the significant consequences of mental illness comorbidity and its high prevalence in the general population,<sup>4,5</sup> clarifying the underlying mechanisms through which comorbidity develops will have considerable implications for prevention and treatment.

The purpose of the present study was to investigate one such potential mechanism, self-medication, and its relation-

ship to the development and persistence of comorbid substance use and anxiety disorders. These 2 disorders frequently co-occur in a variety of different populations,<sup>6-9</sup> and the prevalence of one disorder among those diagnosed as having the other frequently exceeds prevalence rates of the individual disorder in clinical and community samples.<sup>10-13</sup> The self-medication or "tension-reduction" hypothesis states that attempts to reduce anxiety via substance use lead to the development of comorbid substance use disorders.<sup>14,15</sup> Support for the self-medication hypothesis comes from several lines of evidence. First, endorsement of self-medication behavior is highly prevalent in comorbid populations.<sup>6,16</sup> Second, studies<sup>17,18</sup> report the onset of anxiety as occurring before sub-

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stance use in comorbid individuals. Third, the anxiolytic properties of alcohol and some drugs have been well established, providing a theoretical basis for the argument that substance use can ameliorate anxiety symptoms.<sup>19,20</sup> Moreover, individuals commonly report that alcohol use is effective in reducing anxiety.<sup>16,21,22</sup>

Conversely, other researchers suggest that primary substance use is responsible for the development of secondary anxiety disorders. These researchers point out not only that substance use worsens psychiatric symptoms<sup>23,24</sup> but also that withdrawal from substances can mimic anxiety disorders through effects on neurotransmitters.<sup>25</sup> Moreover, a “protracted abstinence syndrome” has been associated with anxiety disorders and symptoms and can last up to 10 years.<sup>26,27</sup> In such cases, individuals experiencing withdrawal symptoms may self-medicate with alcohol or other substances to relieve the anxiety that accompanies withdrawal, thereby increasing substance use (via self-medication) and anxiety symptoms (via the effects of the substance itself on anxiety).<sup>28</sup> To our knowledge, this hypothetical model, although discussed in the literature, has not yet been tested empirically.

A major methodological constraint to date has been the lack of available longitudinal data needed to examine the development of comorbidity.<sup>29,30</sup> Previous cross-sectional investigations<sup>11-16,20,28</sup> have also been limited by focusing on the use of alcohol for self-medication rather than other substances and by using clinical rather than population samples, limiting generalizability. The present study uses data from a recently available, longitudinal, nationally representative data set to examine the role of self-medication with alcohol and other drugs on the development and persistence of comorbid anxiety and substance use disorders.

## METHODS

### SAMPLE

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is a longitudinal, nationally representative survey conducted by the National Institute on Alcohol Abuse and Alcoholism. Wave 1 surveys were conducted between January 1, 2001, and December 31, 2002, and consisted of 43 093 respondents from the US adult noninstitutionalized population. A total of 36 356 respondents who completed the wave 1 survey also participated in wave 2, which was conducted between January 1, 2004, and December 31, 2005. The overall response rate was 70.2%, which is based on the response rate of 81.0% at wave 1 and 86.7% at wave 2. The sampling frame of the NESARC was based on US Census Bureau Supplementary Survey data and has been described in greater detail elsewhere.<sup>17</sup>

Respondents were contacted in writing, informed of the nature of the survey and its potential uses, ensured of confidentiality, and told that participation was voluntary. The US Census Bureau and the US Office of Management and Budget reviewed and approved the ethics protocol. Data were weighted to account for sampling biases and to ensure representativeness of the US population based on the 2000 Census. Further information about the NESARC sampling design and methods is available elsewhere.<sup>31</sup>

## MEASURES

### Sociodemographic Variables

The following 8 sociodemographic variables were assessed at wave 1 of the NESARC: sex, income, race/ethnicity, age, region, marital status, education, and urban status (urbanicity). Income was divided into 4 categories (\$0-\$19 999, \$20 000-\$34 999, \$35 000-\$59 999, and  $\geq$ \$60 000), as were race/ethnicity (white, black, Native American or Asian, and Hispanic), age (18-29, 30-44, 45-64, and  $\geq$ 65 years), and region (Northeast, Midwest, South, and West). Marital status was defined as married/cohabitating, divorced/separated/widowed, or never married. Education was similarly trichotomized into less than high school, high school, and some college or higher. Urbanicity dichotomized participants into urban or rural.

### Clinical Disorder Assessment

The Alcohol Use Disorders and Associated Disabilities Interview Schedule IV<sup>32</sup> was used to make *DSM-IV* diagnoses. The reliability and validity of this measure range from good to excellent depending on the diagnosis in question and have been described in detail elsewhere.<sup>33</sup> Lifetime and past-year diagnoses consisted of mood (dysthymia, mania, hypomania, and depression), anxiety (panic disorder, social phobia, specific phobia, and generalized anxiety disorder), personality (histrionic, schizoid, obsessive compulsive, antisocial, dependent, avoidant, borderline, schizotypal, narcissistic, and paranoid), and substance use (alcohol and other drug abuse and dependence) disorders. Diagnoses were categorical; to receive a particular diagnosis, participants must have endorsed the minimum number of symptoms required by the *DSM-IV*. For personality disorder diagnoses, at least 1 of the symptoms must have caused either social or occupational interference. The wave 1 interview measured the presence of Axis I disorders at any point in the participant's lifetime and in the past year. Interviews at wave 2 measured the presence of Axis I disorders in the past year and at any point in the 3-year interval between surveys. New-onset (incident) disorders were defined by excluding those who met the criteria for the disorder at any point in their lifetime (at the wave 1 interview) and including those who met the criteria for the disorder in the wave 2 three-year interval. In defining “any” incident disorder, those who met the criteria for any 1 of the individual disorders assessed at baseline (eg, any of the 4 anxiety disorders: panic, social phobia, specific phobia, and generalized anxiety) were excluded.

### Self-medication

Self-medicating behavior was assessed at the wave 1 survey in 4 different anxiety disorder categories (panic, social phobia, specific phobia, and generalized anxiety). Specifically, participants who endorsed a minimum number of anxiety symptoms (eg, “Did you ever have a strong fear or avoidance of any social situation because you were afraid of being embarrassed by what you might say or do around other people?”) were asked if at any time in the past they had used alcohol or other drugs for the purpose of reducing their fear, anxiety, or avoidance (of a feared object or situation). To clarify, the self-medication question was asked to 2 groups of respondents: those who endorsed anxiety symptoms without meeting the criteria for an anxiety disorder and those who endorsed anxiety symptoms and met the full criteria for an anxiety disorder. In analyses that examined incident anxiety disorders, only the former group was included in the analysis. Use of alcohol for self-medication was differentiated from use of drugs for the same purpose. For ex-

**Table 1. Wave 1 Sociodemographic Characteristics and Wave 2 Incident Mental Disorders in the Entire NESARC Sample**

Sociodemographic Variables	NESARC Sample, No. (%) <sup>a</sup> (N=34 653)
Sex	
Male	14 564 (47.9)
Female	20 089 (52.1)
Age, y	
18-29	6 719 (21.8)
30-44	11 013 (30.9)
45-64	10 917 (31.1)
≥65	6 004 (16.2)
Race/ethnicity	
White	20 174 (70.9)
Black	6 577 (11.0)
American Indian/Alaskan	580 (2.2)
Asian/Hawaiian	966 (4.3)
Hispanic	6 356 (11.6)
Marital status	
Married	18 413 (63.1)
Widowed/separated/divorced	8 564 (16.5)
Never married	7 676 (20.5)
Region	
Northwest	6 444 (19.7)
Midwest	7 540 (23.1)
South	12 833 (35.2)
West	7 836 (22.0)
Income, \$	
0-19 999	8 959 (20.3)
20 000-34 999	7 309 (19.6)
35 000-59 999	8 812 (26.3)
≥60 000	9 573 (33.8)
Education	
Less than high school	5 744 (14.6)
High school	9 955 (29.0)
Some college or more	18 954 (56.3)
Urbanicity	
Urban	11 672 (28.9)
Rural	22 981 (71.1)
Incident disorders	
Anxiety disorder	2 906 (9.7)
Alcohol use disorder	1 366 (5.9)
Other drug use disorder	586 (2.0)

Abbreviation: NESARC, National Epidemiologic Survey on Alcohol and Related Conditions.

<sup>a</sup>Percentages are weighted to account for sampling biases.

ample, individuals who initially endorsed several panic symptoms were subsequently asked the following 2 questions: (1) “Did you ever drink alcohol to keep from having panic attacks?” and (2) “Did you ever take any medicines or drugs on your own, that is, without a prescription or in greater amounts or more often or longer than prescribed to keep from having panic attacks?” Responses to both self-medication questions were coded dichotomously as either “yes” or “no,” and all responses were collapsed across anxiety disorders.

Because most individuals who endorsed self-medication with drugs also reported self-medication with alcohol,<sup>34-36</sup> a self-medication variable with the following 3 categories was created for use in these analyses: (1) no self-medication, (2) those who self-medicated with alcohol only, and (3) those who self-medicated with drugs (with or without the use of alcohol also). “No self-medication” (in those who endorsed enough anxiety symptoms to warrant asking this question) was set as the reference category in logistic regression analyses.

Appropriate statistical weights were applied to ensure representativeness of the NESARC data. Owing to the complex sampling design of the NESARC, SUDAAN’s Taylor Series Linearization was used to obtain standard error calculations.<sup>37</sup>

Cross-tabulation and frequency calculations were undertaken to determine descriptive information on sociodemographic and incident mental disorder variables for the entire NESARC sample. Prevalence rates were also calculated for those who used any alcohol or drugs in the past year and reported self-medication.

Descriptive statistics, multiple logistic regressions, and population-attributable fractions (PAFs) were calculated to present information on self-medication in each subpopulation of interest in the present study. In each regression analysis performed in the present study, self-medication was set as the dependent variable, and models were adjusted for sociodemographics and wave 1 lifetime comorbidity (Axis I and II disorders).

First, in participants who had received a diagnosis of anxiety disorder at wave 1, regression analyses were computed to examine the impact of the endorsement of self-medication (with alcohol or other drugs) on incident substance use disorders. All 4 substance use disorders (alcohol abuse and dependence and other drug abuse and dependence) were examined in separate analyses, as were 2 summary “any alcohol/drug use disorder” variables. The proportion of incident disorders that could be attributed to self-medication in anxiety disorders was calculated using PAFs. The following equation was used to calculate all the PAFs in accord with population health and biostatistics research<sup>38,39</sup>:

$$PAF = p(AOR - 1) / [p(AOR - 1) + 1]$$

where *p* is the proportion of individuals in the baseline population of interest who met the criteria for the particular incident disorder in question and AOR refers to the previously calculated adjusted odds of incident disorders in those who self-medicated.

Second, in those who had received a diagnosis of substance use disorder at wave 1, regression analyses were computed to examine the impact of self-medication on incident anxiety disorders. In participants with alcohol use disorders at baseline, separate models were tested with each individual incident anxiety disorder as the independent variable. An “any incident anxiety disorder” model was also tested. The same analyses were then conducted using those with any drug use disorder as the baseline population. The PAFs were calculated to determine the proportion of incident anxiety disorders attributable to self-medication in those with substance use disorders at baseline.

In participants with both anxiety and substance use disorders in the past year at baseline, the effect of self-medication on persistence of each disorder (anxiety and either alcohol or other drug use) was calculated using logistic regression analyses.

Similar regression and PAF analyses were also conducted in individuals who did not meet the criteria for an anxiety disorder at wave 1 to determine the effect of self-reported self-medication on the development of incident substance use and anxiety disorders.

## RESULTS

**Table 1** gives information on the sociodemographic characteristics and rates of incident disorders in the total NESARC sample. Almost 10% of the population developed an incident anxiety disorder in the 3-year interval

**Table 2. Effect of Self-medication on the Development of Incident Substance Use Disorders in Those With a Lifetime Anxiety Disorder at Baseline**

Incident Substance Use Disorder	No Self-medication, No. (%) <sup>a</sup> (n=5278)	Self-medication With Alcohol (n=558)			Self-medication With Other Drugs (n=237)		
		No. (%) <sup>a</sup>	AOR (95% CI) <sup>b</sup>	PAF, % (95% CI)	No. (%) <sup>a</sup>	AOR (95% CI) <sup>b</sup>	PAF, % (95% CI)
Alcohol abuse (n=774)	78 (2.4)	6 (6.3)	2.24 (0.88 to 5.72)	7.2 (-0.8 to 22.9)	4 (13.2)	<sup>c</sup>	<sup>c</sup>
Alcohol dependence (n=592)	77 (2.5)	10 (7.1)	2.63 (1.04 to 6.67) <sup>d</sup>	10.4 (0.3 to 28.7)	3 (7.0)	<sup>c</sup>	<sup>c</sup>
Any alcohol use disorder (n=1366)	155 (4.7)	16 (12.6)	2.50 (1.26 to 4.97) <sup>e</sup>	15.9 (3.2 to 33.3)	7 (18.6)	2.62 (0.94 to 7.32)	23.2 (-1.1 to 54.0)
Other drug abuse (n=322)	44 (0.9)	5 (1.3)	1.49 (0.51 to 4.37)	0.6 (-0.6 to 4.2)	1 (1.4)	<sup>c</sup>	<sup>c</sup>
Other drug dependence (n=264)	43 (0.9)	9 (1.9)	1.49 (0.58 to 3.84)	0.9 (-0.8 to 5.1)	7 (10.1)	4.99 (1.75 to 14.22) <sup>e</sup>	28.7 (7.0 to 57.2)
Any drug use disorder (n=586)	87 (1.7)	14 (3.0)	1.46 (0.73 to 2.91)	1.4 (-0.8 to 5.4)	8 (10.4)	3.46 (1.26 to 9.49) <sup>d</sup>	20.4 (2.6 to 46.9)

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; PAF, population-attributable fraction.

<sup>a</sup>Percentages are column percentages (eg, of participants who met the criteria for baseline anxiety and did not self-medicate, 2.4% developed incident alcohol abuse) and were weighted to account for sampling biases.

<sup>b</sup>Odds ratios were adjusted for the following sociodemographic variables: sex, age, race/ethnicity, marital status, region, income, educational level, and urbanicity and for any lifetime psychiatric disorder at wave 1.

<sup>c</sup>Analyses were not performed owing to insufficient cell size. Only those who met the criteria for any lifetime anxiety disorder at wave 1 and did not meet the criteria for the substance use disorder in question were included in these analyses.

<sup>d</sup> $P < .05$ .

<sup>e</sup> $P < .01$ .

**Table 3. Relationship Between Self-medication and Incident Anxiety Disorders in Participants With Alcohol Use Disorders at Wave 1**

Incident Anxiety Disorder	No Self-medication, No. (%) <sup>a</sup> (n=5009)	Self-medication With Alcohol (n=602)			Self-medication With Other Drugs (n=259)		
		No. (%) <sup>a</sup>	AOR (95% CI) <sup>b</sup>	PAF, % (95% CI)	No. (%) <sup>a</sup>	AOR (95% CI) <sup>b</sup>	PAF, % (95% CI)
Panic	129 (2.8)	28 (5.7)	1.67 (0.91 to 3.07)	3.7 (-0.5 to 10.6)	11 (8.0)	1.76 (0.75 to 4.11)	5.7 (-2.0 to 19.9)
Social phobia	131 (2.9)	30 (6.6)	2.13 (1.28 to 3.55) <sup>c</sup>	6.9 (1.8 to 14.4)	21 (11.3)	3.27 (1.79 to 5.97) <sup>d</sup>	20.4 (8.2 to 36.0)
Specific phobia	361 (8.9)	41 (9.9)	1.00 (0.64 to 1.55)	0.0 (-3.7 to 5.2)	21 (13.5)	1.38 (0.76 to 2.51)	4.9 (-3.3 to 16.9)
GAD	231 (5.0)	30 (8.4)	1.51 (0.88 to 2.61)	4.1 (-1.0 to 11.9)	16 (9.6)	1.25 (0.64 to 2.41)	2.3 (-3.6 to 11.9)
Any anxiety disorder	420 (13.3)	29 (18.8)	1.47 (0.88 to 2.46)	8.1 (-2.3 to 21.5)	11 (24.2)	1.76 (0.74 to 4.20)	15.5 (-6.7 to 43.6)

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; GAD, generalized anxiety disorder; PAF, population-attributable fraction.

<sup>a</sup>Percentages are column percentages and were adjusted to account for sampling biases.

<sup>b</sup>Odds ratios were adjusted for the following sociodemographic variables: sex, age, income, marital status, educational level, race/ethnicity, region, and urbanicity and for any lifetime psychiatric disorder at wave 1. Only respondents who met the criteria for any lifetime alcohol use disorder at wave 1, but not the anxiety disorder in question, were included in the analysis.

<sup>c</sup> $P < .01$ .

<sup>d</sup> $P < .001$ .

between the surveys; 5.9% of the wave 2 sample met the criteria for new-onset alcohol use disorders and 2.0% for other drug use disorders.

Cross-tabulations were calculated in participants with anxiety disorders and substance use to determine the prevalence of self-medication. Of those who endorsed any substance use in the past year, 12.5% reported self-medicating with alcohol and 24.4% with other drugs. Of participants with diagnosable substance use disorders, 23.3% self-medicated with alcohol and 32.7% with drugs.

The prevalence and adjusted odds of incident substance use disorders in the 3 previously defined self-medication categories are given in **Table 2**. Of individuals who met the criteria for a baseline anxiety disorder and reported self-medication with alcohol, 12.6% developed an incident alcohol use disorder. Of those who self-medicated with drugs, 10.4% developed an incident drug use disorder. Conversely, of those who did not self-medicate, only 4.7% and 1.7% developed incident alcohol use and drug use disorders, respectively.

Regression analyses revealed that reported self-medication with alcohol in participants with anxiety disorders at baseline was associated with increased risk of in-

cident alcohol dependence (AOR, 2.63; 95% confidence interval [CI], 1.04-6.67;  $P = .41$ ). In fact, PAF analyses suggested that 15.9% of incident alcohol disorder diagnoses in this population can be attributed to self-medication with alcohol. Similarly, self-medication with drugs was associated with increased odds of incident drug dependence (AOR, 4.99; 95% CI, 1.75-14.22;  $P = .003$ ) and contributed to 20.4% of new-onset drug use disorders. When cell sizes consisted of fewer than 5 respondents, regression analyses were not performed. Therefore, the effect of self-medicating with drugs could not be interpreted with respect to certain incident disorders.

**Table 3** and **Table 4** provide the prevalence rates, AORs, and PAFs of incident anxiety disorders in participants who met the criteria for baseline alcohol use and other drug use disorders, respectively. In participants with a baseline diagnosis of an alcohol use disorder, the prevalence of incident anxiety disorders ranged from 5.7% (panic disorder) to 9.9% (specific phobia) for those who self-medicated with alcohol (Table 3). In participants who self-medicated with other drugs, incidence rates ranged from 8.0% (panic disorder) to 13.5% (specific phobia). Regression analyses showed that endorsement of self-

**Table 4. Relationship Between Self-medication and Incident Anxiety Disorders in Participants With Other Drug Use Disorders at Wave 1**

Incident Anxiety Disorder	No Self-medication, No. (%) <sup>a</sup> (n=1728)	Self-medication With Alcohol (n=210)			Self-medication With Other Drugs (n=267)		
		No. (%) <sup>a</sup>	AOR (95% CI) <sup>b</sup>	PAF, % (95% CI)	No. (%) <sup>a</sup>	AOR (95% CI) <sup>b</sup>	PAF, % (95% CI)
Panic	57 (3.8)	5 (2.9)	0.72 (0.21 to 2.51)	-0.8 (-2.3 to 4.2)	9 (5.6)	1.21 (0.38 to 3.88)	1.2 (-3.6 to 13.9)
Social phobia	50 (3.4)	10 (5.9)	1.81 (0.74 to 4.44)	4.6 (-1.6 to 16.9)	20 (11.6)	3.17 (1.70 to 5.92) <sup>c</sup>	20.1 (7.5 to 36.3)
Specific phobia	140 (11.2)	14 (8.4)	0.66 (0.32 to 1.39)	-2.9 (-6.1 to 3.2)	24 (16.2)	1.55 (0.86 to 2.79)	8.2 (-2.3 to 22.5)
GAD	95 (5.6)	13 (8.7)	1.38 (0.64 to 2.95)	3.2 (-3.2 to 14.5)	14 (8.4)	0.98 (0.46 to 2.05)	-0.2 (-4.8 to 8.1)
Any anxiety disorder	151 (15.3)	9 (15.3)	1.10 (0.40 to 3.00)	1.5 (-10.1 to 23.4)	10 (23.9)	1.66 (0.66 to 4.18)	13.6 (-8.8 to 43.2)

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; GAD, generalized anxiety disorder; PAF, population-attributable fraction.

<sup>a</sup>Percentages are column percentages and were adjusted to account for sampling biases.

<sup>b</sup>Odds ratios were adjusted for the following sociodemographic variables: sex, age, income, marital status, educational level, race/ethnicity, region, and urbanicity and for any lifetime psychiatric disorder at wave 1. Only respondents who met the criteria for any lifetime drug use disorder at wave 1, but not the anxiety disorder in question, were included in the analysis.

<sup>c</sup>*P* < .001.

medication with alcohol and other drugs was associated with incident social phobia (self-medication with alcohol: AOR, 2.13; 95% CI, 1.28-3.55; *P* = .004; self-medication with drugs: 3.27; 1.79-5.97; *P* < .001). Just 6.9% (95% CI, 1.8%-14.4%) of new-onset social phobia was attributable to self-medication with alcohol in this population, and 20.4% (8.2%-36.0%) was attributable to self-medication with drugs.

In participants with drug use disorders at baseline, the prevalence of incident anxiety ranged from 2.9% (panic disorder) to 8.7% (generalized anxiety disorder) for those who reported self-medication with alcohol and from 5.6% (panic disorder) to 16.2% (specific phobia) for those who reported self-medication with drugs (Table 4). Regression analyses revealed that self-medication with drugs was significantly associated with new-onset social phobia in this population (AOR, 3.17; 95% CI, 1.70-5.92; *P* < .001). Results for all other analyzed disorders were not statistically significant. A total of 20.1% (95% CI, 7.5%-36.3%) of incident social phobia in participants with drug use disorders could be attributed to self-medicating with drugs.

In participants with comorbid anxiety and alcohol use disorders in the past year at baseline, reported self-medication was not associated with the persistence of anxiety but was associated with persistent alcohol use disorder (AOR, 2.69; 95% CI, 2.06-3.51; *P* < .001). In participants with comorbid anxiety and drug use disorders, self-medication was significantly associated with persistence of other drug use disorder (AOR, 2.67; 95% CI, 1.65-4.31; *P* < .001) but not with anxiety.

Among participants who did not meet the criteria for any lifetime anxiety or substance use disorder at baseline but reported having self-medicated for anxiety, cell sizes for incident substance use disorders were too small for regression analyses to be performed. However, risk of incident anxiety disorders in this population were calculated. Self-medication with alcohol was associated with incident panic disorder (AOR, 1.68; 95% CI, 1.02-2.77; *P* = .41) and social phobia (2.33; 1.54-3.51; *P* < .001) and accounted for 3.9% (95% CI, 0.1%-9.6%) and 8.4% (3.6%-14.8%) of each, respectively. Self-medication with drugs also predicted incident social phobia (AOR, 2.76; 95% CI, 1.61-4.37; *P* < .001), and 16.2% (95% CI, 6.3%-29.1%) of new-onset cases could be attributed to the behavior.

## COMMENT

The present study is the first, to our knowledge, to longitudinally examine the role of self-reported self-medication in the development of comorbid substance use and anxiety disorders. Although it is well established that each of these disorders confers significant risk for development of the other,<sup>40</sup> the underlying mechanisms responsible for this relationship have been less frequently examined. The findings from this study are novel because they identify a risk behavior that stratifies the probability of developing a comorbid disorder in the future. The results identify specific populations in which self-medication confers significant risk for future disorders. This has important implications in the assessment of clinical populations and provides a target for intervention efforts that may prevent future psychiatric morbidity.

The present results indicate that endorsement of self-medication is an important risk factor for the development of substance dependence in participants who met the criteria for anxiety at baseline. Compared with people with anxiety disorders who did not self-medicate, self-medication predicted incident alcohol and other drug dependence even after adjusting for a multitude of potentially confounding variables. Furthermore, approximately 10% of incident alcohol dependence and more than one-quarter of new drug dependence diagnoses were attributable to self-medicating at baseline. These findings corroborate and extend theoretical and empirical claims made by several researchers. For example, many study participants claim that anxiety preceded the onset of substance use problems and also report high rates of self-medication.<sup>6,17,41</sup> Theories regarding the development of comorbidity made by many researchers<sup>14,15,34-36,42</sup> are also substantiated by the present findings. For example, the self-medication hypothesis predicts that the specific substance used for anxiety-reducing purposes will tend to be the one on which the individual later becomes dependent or abuses. The findings showing that self-medication with alcohol was associated with incident alcohol use disorders and self-medication with drugs led to the development of other drug use disorders are consistent with these theories.

The considerable proportion of incident alcohol and other drug use disorders attributable to self-medication is an important finding for physicians to bear in mind when designing treatment plans for at-risk patients. The PAFs are most useful when the risk factor is modifiable; therefore, it will be important for future studies to design experiments capable of determining whether the reduction in self-medication leads to a corresponding reduction in incident drug and alcohol dependence. It is, however, important to keep in mind that PAF analyses can provide only an estimate of the maximal effect of eliminating the particular risk factor and that these analyses assume complete causality between the risk factor and outcome. The design of the present study precludes claims about causality among the variables. It is likely that many factors contribute to the development of incident disorders in the populations under examination, and PAF calculations do not account for these. Therefore, the actual reduction in incidence may be somewhat smaller than the reduction reported herein. Much existing literature on comorbidity has focused on disorders as treatment targets rather than on self-medication. Recent findings<sup>43</sup> have shown that treating the underlying symptoms of posttraumatic stress disorder (PTSD) is associated with a reduction in substance use, providing evidence for the self-medication hypothesis and the importance of treating index anxiety disorders. These findings are counterbalanced by those of a study<sup>44</sup> showing that the treatment of primary anxiety disorders is not a feasible or cost-effective route to prevent the development of secondary substance use disorders. Future researchers may, therefore, want to examine whether targeting self-medication specifically is an effective and cost-efficient method for the prevention of substance use disorders.

Interesting results regarding social phobia emerged from this study. Specifically, self-medication with alcohol and other drugs robustly predicted incident social phobia in a variety of baseline populations. First, in participants with subclinical anxiety at baseline, endorsement of self-medication with alcohol or other drugs was associated with incident social phobia 3 years later. This result was maintained after adjusting for sociodemographics and comorbid disorders. Also, in participants with preexisting alcohol use or other drug use disorders, self-medication was associated with incident social phobia. Evidence suggests that social phobia may have its onset in early childhood and is exhibited as behavioral inhibition during the early stages of life.<sup>45,46</sup> In this regard, it is surprising that of all the anxiety disorders, social phobia developed in adults who engaged in self-medication. One explanation may be that these individuals had preexisting subthreshold social phobia that was exacerbated by other drug use. Substance use may, therefore, cause existing social anxiety symptoms to reach clinically significant levels in self-medicating individuals. Another possibility is that the social unacceptability of substance use may create a desire to avoid social contact in those who actively use other drugs. This hypothesis is in line with Stockwell and Bolderston's 1987 outline of "abstinence phobias." They suggested that phobias in individuals with comorbid substance use disorders may be what they termed *abstinence phobias*, meaning that fear is related

to the cessation of substance use.<sup>47</sup> An individual who avoids social contact to maintain his or her other drug use (whether consciously or subconsciously) may present as socially phobic. The genuine fear experienced in the presence of others may be more related to the possibility of getting caught, ostracized, or otherwise coerced into substance use cessation.

The only other anxiety disorder predicted by self-medication was panic disorder, and only in populations that endorsed self-medicating with alcohol (not other drugs) and did not meet the criteria for any baseline substance use or anxiety disorder. This corroborates research by George et al<sup>48</sup> that suggested that the use of alcohol may kindle and condition panic attacks in certain individuals. Note that the etiology of anxiety disorders may not be solely related to self-medication of subclinical anxiety symptoms. Withdrawal from substances also causes symptoms of anxiety, which then may be self-medicated. The apparent incident anxiety may, therefore, represent substance withdrawal and persistent substance use.

In participants with comorbid disorders at baseline, self-medication predicted the persistence of a substance use disorder rather than an anxiety disorder. This finding will be important for physicians attempting to treat comorbid self-medicating patients because it suggests that amelioration of substance use disorders can be more readily achieved by targeting self-medicating behavior.

The present study presents important information on behaviors that put individuals at risk for comorbidity; however, several limitations warrant attention. First, only 1 mechanism explaining the development of comorbidity was examined (self-medication), although other possible mechanisms, such as heredity and shared etiologic factors, may also play a role. Furthermore, self-medication was not directly measured in real time; instead, it was based on self-report and may, therefore, be subject to recall bias. More direct measures, such as the experience sampling method or ecologic momentary assessment,<sup>20,21</sup> would have been better able to examine the dynamic interplay between anxiety and substance use and determine the potential reduction of anxiety immediately after substance use. The lack of experimental design in the present study precludes any inference of causality. Future research should use experimental methods to directly examine the effect of self-medication on the development of comorbidity. The use of a lifetime self-medication variable at baseline rather than a more recent analysis of self-medication is another limiting factor in examining possible causation. Past-year self-medication was available in the NESARC data set, but cell sizes were too small to allow for further analysis. Future studies assessing the frequency of self-medication, and its temporal relationship with subsequent disorder development, are necessary to clarify its potential causal role in comorbidity.

Next, certain populations (ie, those aged <18 years and those currently residing in institutional settings) were excluded from the NESARC survey; therefore, the results may not generalize to these individuals. This is particularly important given findings that suggest that most anxiety disorders have their onset in adolescence, and that anxiety disorders that begin in adolescence confer extremely high

risk of subsequent substance disorders.<sup>49,50</sup> It is, therefore, possible that a significant proportion of incident disorders and comorbidity was not captured with this study population. Furthermore, the amount of the substance used for self-medication was not assessed in the NESARC survey. The amount consumed is an important potential confounder because it is possible that individuals who use substances more frequently or in greater amounts will be more likely to develop incident disorders. It is also possible that greater amounts of substance use could reflect other types of motives in addition to self-medication. Future research should endeavor to account for volume of substance consumption.

Two anxiety disorders, obsessive-compulsive disorder and PTSD, were not assessed at wave 1 of the NESARC and, therefore, could not be included in the present analyses. There has been little work to date on the relationship between obsessive-compulsive disorder and self-medication; thus, it might be an important direction for future research on comorbidity. A recent study<sup>51</sup> on self-medication in PTSD revealed that a large percentage of individuals with PTSD self-medicate and that this behavior is associated with increased suicide attempts and comorbidity and lower quality of life. Therefore, the longitudinal associations between self-medication and the development of PTSD, and the relationships between incident substance use in those with PTSD, should be examined. Finally, individual anxiety disorders were not examined separately owing to insufficient power. It is possible that self-medication may lead only to subsequent substance use disorders among those who meet the criteria for specific anxiety disorders only. Future research should examine the effects of self-medication on substance use disorders in each anxiety disorder separately. At baseline, individual anxiety disorders were not examined separately owing to insufficient power. More information about specific populations in which self-medication is a significant risk factor could be obtained from examining individual baseline anxiety disorders. Also note that results from the present study are conservative owing to small sample sizes and should, therefore, be interpreted with attention to this fact. Moreover, the short interval between the 2 survey periods may not have been sufficient to capture most new-onset disorders that result from self-medicating. Future longitudinal studies may aim to examine self-medication using a longer time frame.

Despite these limitations, this work provides support for the self-medication hypothesis, which predicts that the use of substances to alleviate anxiety underlies the high comorbidity between substance use and anxiety disorders. Specifically, the particular substance chosen for self-medication (whether drugs or alcohol) is the one that self-medicators seem to be at risk for becoming dependent on in the future. This study also illuminates the risk that self-medication confers for the development of social phobia in a variety of populations.

Given the high percentage of incident substance use disorders and social phobia that can be attributed to self-medication, the reduction of self-medicating behavior may lead to a significant decrease in incident comorbidity in the general population. These results, therefore, have substantial relevance for preventive treatment efforts in psychiatry and primary care and provide physicians with cru-

cial information on specific individual characteristics that put patients at risk for mental illness comorbidity. By assessing current and potential self-medication behaviors, physicians can work to prevent the development of comorbidity in certain patients. Future research should examine whether successful treatment of baseline conditions, such as anxiety disorders, reduces the incidence of self-medication and correspondingly reduces the prevalence of incident comorbid conditions.

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