

Peptic Ulcer and Mental Disorders Among Adults in the Community: The Role of Nicotine and Alcohol Use Disorders

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Objective: Previous studies have documented links between peptic ulcer disease (PUD) and mood and anxiety disorders among adults in the community. Several substance use disorders (e.g., nicotine and alcohol dependence) are highly comorbid with mood/anxiety disorders and have been also linked with PUD. No previous study has examined the potentially explanatory role of substance use disorders in the link between mood and anxiety disorders and PUD. The objective of the study is to examine relationships between a range of mental disorders and PUD among adults in the United States and to examine the potentially explanatory role of substance use disorders in these links. **Methods:** Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative sample of US adults 18 years of age and over ($n = 43,098$). Diagnostic and Statistical Manual for Mental Disorders IV diagnoses of mood, anxiety, and substance use disorders were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV, and PUD status was assessed via self-report. **Results:** Findings show that mood/anxiety disorders were associated with PUD. Specifically, generalized anxiety disorder (GAD) (Odds ratio (OR) = 3.43) was most strongly associated with PUD, followed by panic disorder (OR = 3.11), dysthymia (OR = 3.59), and bipolar disorder (OR = 2.91). The relationships between most mood/anxiety disorders and PUD were substantially attenuated after adjusting for nicotine and alcohol dependence. **Conclusions:** Mood/anxiety disorders are associated with increased rates of PUD; nicotine and alcohol dependence seems to play a substantial role in explaining the link with PUD. **Key words:** peptic ulcer, nicotine, alcohol, mental disorders, mood disorders, anxiety disorders.

PUD = peptic ulcer disease; **NESARC** = National Epidemiologic Survey on Alcohol and Related Conditions; **NIAAA** = National Institute on Alcohol Abuse and Alcoholism; **AUDADIS-IV** = Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV; **DSM-IV** = Diagnostic and Statistical Manual for Mental Disorders IV; **GAD** = generalized anxiety disorder.

INTRODUCTION

In recent years there has been growing interest in the link between chronic peptic ulcer disease (PUD) and mood and anxiety disorders (1–4). Evidence of this link comes from three main sources. First, data from clinical studies suggest higher rates of anxiety and neurotic personality traits among adult patients with PUD (5). Second, studies that have included patients with anxiety and mood disorders have found significantly high rates of gastrointestinal problems than the general population (6). Third, community-based studies have demonstrated an association between PUD and mood disorders among adults (5–7). There is also substantial literature showing that substance use disorders, such as nicotine and alcohol dependence, are associated with increased risk of PUD (8).

Cigarette smoking and alcohol consumption are both thought to be etiologic factors for the development of PUD. Although evidence on the mechanism and effects of alcohol consumption alone on ulcer formation remain unclear, studies have repeatedly shown that cigarette use is associated with

increased risk of ulcer (9). Specifically, data have suggested that cigarette smoking has a direct impact on ulcer formation, severity, and relapse. Retrospective studies have also indicated that cigarette smoking is a key risk factor in inducing ulcers (8). Moreover, according to the Surgeon General's report (10), ulcers are more likely to occur, less likely to heal, and more likely to cause premature mortality among smokers than nonsmokers. In addition, smoking has been shown to amplify an individual's risk of infection from an ulcer causing bacterium, *Helicobacter pylori*, and increase the risk of ulceration in combination with over-the-counter pain relievers and alcohol (11). Cigarettes contain nicotine, which may increase the risk of developing an ulcer by causing the stomach to increase its production of gastric acid and reducing the stomach's production of mucus, which decreases the protection of the stomach lining from acid (12).

As such, one potential explanation for the link between mood and anxiety disorders and PUD is the possibility that a causal relationship between mental disorders and ulcers that is mediated by substance use disorders. It is well established that mental disorders are associated with high rates of cigarette use and alcohol dependence (8,11,13–19). Yet previous studies have not examined the potential role of alcohol and cigarette use in the relationship between mood and anxiety disorders and PUD (20).

Against this background, the goal of the current study is to begin to answer these questions by meeting two main objectives. First, we aimed to determine the association between PUD and the range of mental disorders among adults in the United States. Second, we aimed to examine the role of alcohol and nicotine dependence in the link between ulcer and mood and anxiety disorders. On the basis of the previous findings, we hypothesized that there would be a significant association between mood and anxiety disorders and PUD, and that alcohol and nicotine dependence would play a significant role in explaining the observed link between mood/anxiety disorders and PUD.

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METHODS

Sample

The cross-sectional sample was drawn from participants in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative US survey of 43,093 civilian noninstitutionalized participants aged 18 and older. Details of the sampling frame are described elsewhere (21–23). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored the study and supervised the fieldwork, conducted by the US Bureau of the Census. Young adults, Hispanics, and African-Americans were oversampled, and the study achieved an overall response rate of 81%. To adjust for nonresponse and selection probability, the sample was weighted and adjusted to reflect the US population from the 2000 Decennial Census in terms of age, race, sex, and ethnicity. The research protocol, including informed consent procedures, received full ethical review and approval from the US Census Bureau and US Office of Management and Budget. Demographic characteristics of the NESARC sample has been described elsewhere (22).

Interviewers, Training, and Field Quality Control

A total of 1800 professional interviewers from the Census Bureau using computer-assisted software conducting built-in skip, logic, and consistency checks conducted interviewing. All of the interviewers had experience with other national health-related surveys with an average of 5 years of experience and were further trained for 10 days under the direction of NIAAA. Verification of the interviewer was conducted by regional supervisors who recontacted a random 10% of all respondents for quality control purposes. In addition, a randomly selected subset of respondents was reinterviewed with 1 to 3 complete sections of the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV (AUDADIS-IV). This served as a test-retest reliability study of NESARC measures (24). In the few cases when accuracy was uncertain, the data were discarded and a supervising interviewer repeated the interview.

Measures

The NIAAA AUDADIS-IV was used to assess independent mood and anxiety disorders as well as alcohol and drug use disorders according to Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) criteria (25). This instrument was specifically designed for experienced lay interviewers and was developed to advance measurement of substance use disorders and other mental disorders in large-scale surveys.

Mood and Anxiety Disorders

Mood and anxiety disorders assessed by the AUDADIS-IV included primary major depression, dysthymia, bipolar, generalized anxiety disorder (GAD), panic disorder with or without agoraphobia, social phobia, and specific phobia. Diagnoses were assessed in two timeframes: last 12 months and before the last 12 months. These were combined to create “lifetime” diagnoses for the present analysis. Diagnoses included a requirement of distress and/or social or occupational dysfunction (as per DSM-IV requirement). Rule outs included substance-induced disorders or those because of bereavement. The reliability and validity of mood and anxiety disorder diagnoses and symptom items were fair to good (kappas 0.42–0.64), (26,27) including test-retest and clinical reappraisal studies. Each mood and anxiety disorder has been further validated by showing highly significant associations with disability (15,18,28). Details of the depression, generalized anxiety (28), bipolar (29), social anxiety (29), and panic (30) diagnoses have been described in detail elsewhere.

Substance Use Disorders

Over 40 AUDADIS-IV questions are used to diagnose DSM-IV criteria for alcohol abuse and dependence. Consistent with DSM-IV, lifetime diagnoses of alcohol abuse required ≥ 1 of the 4 abuse criteria in the 12-month period preceding the interview or previously. AUDADIS-IV alcohol dependence diagnoses required ≥ 3 of the 7 DSM-IV dependence criteria in the last 12 months, or during any previous 12-month period. For prior diagnoses of

alcohol dependence, ≥ 3 criteria must have occurred within a 1-year period, after the DSM-IV clustering criterion. Substance and illness-induced disorders were ruled out. Test-retest reliability of the alcohol dependence diagnosis in the AUDADIS-IV have ranged from good to excellent ($K = 0.70$ – 0.84); details of the diagnoses and reliability and validity have been documented elsewhere (20,26,27,31,32–40).

Nicotine dependence is assessed in a unique module separate from the assessment of other substance use. Respondents are considered to have ever used cigarettes if they have smoked 100 or more cigarettes during their lifetime. Four other modes of nicotine use are assessed as well: pipe, cigar, snuff, and chewing tobacco. Diagnoses are made explicitly according to DSM-IV guidelines using over 20 symptom items specific to nicotine use to capture each DSM criterion, including a substance-specific nicotine withdrawal syndrome. Good reliability of the current nicotine dependence diagnosis has been documented ($k = 0.63$) (24); further details of the diagnosis as well as reliability and validity have been documented elsewhere (14,17).

Personality Disorders

We controlled for the presence of any measured Axis II personality disorder in multivariable models. AUDADIS-IV diagnostically assesses seven personality disorders: avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial personality disorder. Further details of personality disorder diagnostic sections can be found elsewhere (22,24,29).

Peptic Ulcer Disease

Respondents were asked whether they had experienced a stomach ulcer in the past 12 months. They were subsequently asked whether a doctor had confirmed the diagnosis. Those respondents who reported a physician diagnosed stomach ulcer in the past 12-months were considered for the present analysis ($n = 1101$).

Statistical Analysis

Analyses were conducted using SUDDAN (Software for Survey Data Analysis) to derive standard errors that account for the complex sampling scheme of the dataset (41). Weighted percentages were obtained to describe the demographic characteristics of those with and without an ulcer diagnosis. Statistical associations with demographic characteristics were tested using chi-square test. Odds ratios (ORs) were derived to establish the association between lifetime mental disorders (predictor) and current ulcer (outcome), controlling for demographic characteristics, as well as other mood, anxiety, personality, and substance disorders.

RESULTS

Sociodemographic Characteristics Associated With Ulcer

PUD was significantly associated with being female, older, being widowed, separated or divorced, having less formal education, and lower personal income (Table 1). There were no differences in the prevalence of PUD by race or region of residency (urban versus rural). Alcohol dependence, nicotine dependence, any mood disorder, and any anxiety disorder were significantly more common among those with, compared with those without, PUD.

Association Between Nicotine and Alcohol Dependence With Mood and Anxiety Disorders

All mood and anxiety disorders showed strong and significant associations with alcohol and nicotine dependence. Odds ratios estimating the relationship between mood and anxiety disorders and alcohol dependence ranged from 1.87 (95% confidence interval (CI), 1.66–2.10) (major depression) to 4.07 (95% CI, 3.49–4.74) (bipolar disorder). Odds ratios

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TABLE 1. Demographic Characteristics Associated With Ulcer Prevalence in the United States

	Ulcer (<i>n</i> = 1101), % (SE)	No Ulcer (<i>n</i> = 41,992), % (SE)
Sex		
Male	41.0 (1.9)	48.1 (0.3)*
Female	59.1 (1.9)	51.9 (0.3)*
Age		
18–29	16.9 (1.6)	21.9 (0.4)*
30–44	26.1 (1.7)	31.0 (0.3)*
45–64	34.0 (1.7)	31.0 (0.3)*
65+	22.9 (1.4)	16.1 (0.3)*
Race		
White	67.6 (2.2)	71.0 (1.6) [†]
Black	11.7 (1.3)	11.1 (0.6) [†]
Native American	4.1 (0.8)	2.1 (2.2) [†]
Asian or Pacific Islander	3.3 (0.9)	4.4 (0.5) [†]
Hispanic	13.3 (2.1)	11.5 (1.2) [†]
Marital status		
Married or living with someone as if married	57.2 (1.8)	61.7 (0.5)*
Widowed, separated, or divorced	29.0 (1.7)	17.2 (0.2)*
Never married	13.9 (1.2)	21.1 (0.5)*
Education		
Less than high school	30.2 (1.7)	15.3 (0.5)*
High school	30.7 (1.9)	29.3 (0.6)*
Some college or higher	39.1 (1.9)	55.4 (0.6)*
Personal income		
0–19,999	60.9 (1.9)	46.9 (0.6)*
20,000–34,999	22.8 (1.6)	22.6 (0.4)*
35,000–69,999	12.8 (1.3)	22.2 (0.4)*
≥70,000	3.5 (0.8)	8.3 (0.4)*
Urbanicity		
Urban	27.8 (2.6)	29.6 (2.2), NS
Rural	72.2 (2.6)	70.4 (2.2), NS
Region		
Northeast	17.2 (3.5)	19.7 (3.4), NS
Midwest	23.0 (2.9)	23.2 (3.2), NS
South	38.2 (3.3)	35.1 (3.3), NS
West	21.6 (3.3)	22.0 (3.5), NS
Alcohol dependence		
Yes	19.0 (1.5)	12.3 (0.4)*
No	81.0 (1.5)	87.7 (0.4)*
Nicotine dependence		
Yes	30.5 (1.8)	17.4 (0.5)*
No	69.5 (1.8)	82.6 (0.5)*
Any mood disorder		
Yes	38.4 (2.0)	19.1 (0.4)*
No	61.6 (2.0)	80.9 (0.4)*
Any anxiety disorder		
Yes	31.4 (1.7)	15.8 (0.4)*
No	68.6 (1.7)	84.2 (0.4)*

NS = not significant.

* *p* < .01.

[†] *p* < .10.

estimating the relationship between mood and anxiety disorders and nicotine dependence ranged from 2.06 (95% CI, 1.88–2.25) (major depression) to 3.48 (95% CI, 3.00–4.03) (bipolar disorder).

Association Between Ulcer and Mood and Anxiety Disorders

PUD was significantly more common among adults with all mood and anxiety disorders measured, compared with those without (Table 2). Before adjustment, odds ratios illustrated that PUD was most strongly associated with dysthymia, GAD, and panic disorder, followed by bipolar disorder, any mood disorder, major depression, any anxiety disorder, social phobia, and specific phobia (Table 2). After adjusting for demographics and nicotine dependence as well as demographics and alcohol dependence, these associations were substantially attenuated but remained statistically significant. After additional adjusting for other mood and anxiety disorders and any personality disorder along with demographics, nicotine dependence, and alcohol dependence, the associations between ulcer and social phobia and specific phobia were no longer statistically significant, yet all other associations remained. Although adjustment for differences in demographics, alcohol dependence, nicotine dependence, and other mood and anxiety disorders were associated with considerable attenuation of the strength of these links, they did not fully explain the relationship. In the final model, the strongest association was between PUD and panic disorder, followed by any mood disorder, bipolar disorder, any anxiety disorder, dysthymia, GAD, and major depression.

DISCUSSION

We will first highlight the main findings of this article, and then discuss implications of these results for clinical work and future research. First, consistent with previous findings (42–44), our results showed an association between the range of mental disorders and increased odds of PUD among adults in the United States. Second, we found that dependence on nicotine and alcohol were associated with substantial attenuation of the link between ulcer and mental disorders yet did not fully explain these links.

Our findings of a link between PUD and the range of mental disorders are consistent with and extend previous findings on the relationship between PUD and mental disorders among adults in the population (45). Specifically, this is the second population-based study of adults that has examined the link between PUD and mental disorders with fairly consistent results. Previously, Goodwin and Stein found a link between PUD and a range of mental disorders in the National Comorbidity Survey (1,46), and found that the strongest link after adjustment for demographic characteristics and other mental disorders was between PUD and GAD. The results of these two population-based studies are generally consistent and our results build on previous studies by providing initial investigation into one possible pathway to explain the observed link.

The second main goal of this study was to examine whether and to what degree nicotine and alcohol use problems play a role in the link between mental disorders and PUD. We found that adjusting for nicotine dependence substantially attenuated the link between each mental disorder and PUD, suggesting that nicotine dependence may contribute to vulnerability to

TABLE 2. Prevalence and Odds of Ulcers Among Those With Psychiatric Disorders Compared with Those Without

	Prevalence % (SE) of Ulcers Among Those Without Psychiatric Disorder (in Lifetime Timeframe) (Reference Group)	Prevalence % (SE) of Ulcers Among Those With Psychiatric Disorder	OR (95% CI) Unadjusted	OR (95% CI) Adjusted for Demographics ^a	OR (95% CI) Adjusted for Demographics ^a and Nicotine Dependence	OR (95% CI) Adjusted for Demographics ^a and Alcohol Dependence	OR (95% CI) Adjusted for Demographics ^a Other Mood and Anxiety Disorders, Any Personality Disorder, Nicotine Dependence, and Alcohol Dependence
Full sample	2.3 (0.1)	4.6 (0.3)	2.64 (2.24–3.11)	2.82 (2.32–3.43)	2.51 (2.06–3.07)	2.66 (2.18–3.24)	2.18 (1.50–3.16)
Any mood disorder	1.8 (0.1)	4.6 (0.3)	2.49 (2.13–2.92)	2.65 (2.22–3.15)	2.35 (1.98–2.79)	2.48 (2.08–2.96)	1.52 (1.20–1.93)
Major depression	1.9 (0.1)	6.0 (0.6)	2.91 (2.30–3.69)	3.11 (2.30–4.22)	2.57 (1.87–3.54)	2.71 (1.98–3.69)	1.99 (1.40–2.82)
Bipolar disorder	2.2 (0.1)	7.2 (0.8)	3.59 (2.77–4.65)	3.35 (2.46–4.57)	2.89 (2.11–3.94)	3.08 (2.25–4.22)	1.76 (1.25–2.48)
Dysthymia	2.1 (0.1)	4.5 (0.3)	2.44 (2.09–2.84)	2.67 (2.20–3.23)	2.39 (1.96–2.92)	2.51 (2.07–3.05)	1.86 (1.53–2.27)
Any anxiety disorder	1.9 (0.1)	6.9 (0.7)	3.43 (2.70–4.35)	3.64 (2.71–4.89)	3.19 (2.35–4.33)	3.38 (2.51–4.54)	1.67 (1.24–2.25)
GAD	2.1 (0.1)	6.4 (0.7)	3.11 (2.44–3.95)	3.23 (2.45–4.26)	2.81 (2.09–3.77)	2.99 (2.24–3.99)	2.16 (1.61–2.91)
Panic disorder	2.2 (0.1)	4.3 (0.4)	2.07 (1.70–2.51)	2.23 (1.75–2.84)	2.23 (1.64–3.02)	2.32 (1.72–3.13)	1.16 (0.84–1.59)
Social phobia	2.1 (0.1)	4.3 (0.4)	2.07 (1.70–2.51)	2.23 (1.75–2.84)	1.96 (1.54–2.50)	2.08 (1.64–2.66)	1.25 (0.97–1.62)
Specific phobia	2.1 (0.1)	4.3 (0.4)	2.07 (1.70–2.51)	2.23 (1.75–2.84)	1.96 (1.54–2.50)	2.08 (1.64–2.66)	1.25 (0.97–1.62)
No. psychiatric disorders ^a	Mean (SE)	Mean (SE)	1.41 (1.35–1.48)	1.47 (1.39–1.56)	1.40 (1.32–1.49)	1.48 (1.39–1.57)	1.44 (1.35–1.53) ^b
	0.6 (0.0)	1.3 (0.1)					

^a Adjusted for sex, age, education, race/ethnicity, marital status, and urbanicity.

^b Number of psychiatric disorders included as a quantitative variable, thus no control necessary for “other” psychiatric disorders.

PUD among adults with mental disorders. A body of work has shown that smoking reduces the amount of bicarbonate in the duodenum, which causes problems in the neutralization of acid and may help explain the pathogenesis and natural history of duodenal ulcer disease (12,47). In addition, recent evidence indicates that smoking decreases the gastroduodenal mucosal synthesis of prostaglandin, an important factor in regulation of mucosal defense including the stimulation of duodenal mucosal bicarbonate secretion (48). The general health consequences of cigarette smoking to the gastric mucosa, or surface epithelium of the stomach, include a reduction of circulating epidermal growth factor, damage caused by increases in tissue free radical production and the presence of free radicals in smoke in combination with the reduction of mucosal constitutive nitric oxide synthase activity (8). Another possible mechanism explaining a link between smoking and PUD is the detrimental effects of a reduction in mucosal blood flow. Kalra et al. (49) observed a significant increase in the production of oxygen free radicals and a reduction of mucosal blood flow among smokers in comparison with nonsmokers. Oxygen derived free radicals have been shown to be intimately involved in the pathogenesis of gastric mucosal injury including ischemia reperfusion (49). The reduction of mucosal blood flow could contribute to the further production of free radicals increasing cell death in the lining of stomach (49). The alternation of normal gastric mucosal blood flow and angiogenesis and the suppression of cell proliferation caused by smoking probably contribute to delayed healing among PUD patients (49). Of particular interest, the relationship between PUD and social phobia and specific phobia were no longer statistically significant after adjusting for nicotine dependence. It is not clear why the link between PUD and these phobias would be most strongly influenced by nicotine use, compared with other anxiety disorders, although this finding may merit further study as unique relationships between smoking and social phobia have been noted in several studies (50), suggesting that those with social phobia may be particularly vulnerable to nicotine dependence. As previous studies have shown strong links between social phobia and PUD, this result could provide one explanatory factor for this association.

Chronic alcoholism has been previously correlated with an abnormal mucosal barrier (8). Similar to cigarette smoke, alcohol also produces free radicals in the body (8). It has been hypothesized that at higher levels of alcohol consumption, the antimicrobial effects of alcoholic beverages may be opposed by adverse systemic effects of drinking, such as reduced immune defense (51). Alcohol stimulates gastric acid secretion and has strong antimicrobial activity, and therefore, moderate alcohol consumption may also play a preventive role because of the fact that it may compromise the living conditions of *H. pylori*, a bacterium that has been shown to cause stomach ulcers (8). A study by Brenner et al. (52) illustrated a clear inverse dose-response relationship between reported alcohol consumption and *H. pylori* infection. Although heavy alcohol intake clearly damages the stomach lining, preliminary evidence suggests that moderate alcohol consumption, or

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approximately two drinks per day in women and three drinks in men, may actually protect against the development of stomach ulcers by facilitating the elimination of *H. pylori* (52). Our results suggest that alcohol dependence seems to attenuate the relationship between mood/anxiety disorders and PUD.

There are a number of limitations to keep in mind in interpreting these results. First, data on PUD were based on self-report of a physician diagnosis, which is subject to report bias. We were not able to distinguish duodenal from gastric ulcer by this methodology, and lumping these together may have obscured some interactions. A subset of those endorsing an ulcer diagnosis may actually have had nonulcer (or functional) dyspepsia, and it was not possible to tease out these cases here (53). Only past year diagnoses were included, which may limit recall bias, yet future studies that can use biological measures to diagnose disorders within community-based samples would be of a great interest. Second, as these data are cross-sectional, we are unable to make any inferences about the sequence of the onsets of each of these disorders. On the other hand, the study strengths include the large sample size, inclusion of a nationally representative sample, and validated measures of mental disorders.

In sum, our findings are consistent with previous studies that mood and anxiety disorders are associated with PUD, and we have found new evidence to suggest that nicotine and alcohol dependence may play a mediating role in this link. If these results are replicated, it will lead to the understanding of the role of nicotine and alcohol use in PUD and may shed light on etiology of this disease and identify a new pathway for prevention of PUD.

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